

Research Review: Do motor deficits during development represent an endophenotype for schizophrenia? A meta-analysis

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Background: Early detection of schizophrenia risk is a critical goal in the field. Endophenotypes in children to relatives of affected individuals may contribute to this early detection. One of the lowest cost and longest theorized domains is motor development in children. **Methods:** A meta-analysis was conducted comparing individuals ≤ 21 years old with affected first-degree relatives (FDR) with (1) individuals from unaffected families (controls), or (2) individuals with FDR having other psychiatric disorders. Studies were classified by motor outcome and separate meta-analyses were performed across six correlated domains, with available N varying by domain. **Results:** Inclusion criteria were met by $k = 23$ independent studies with a total $N = 18,582$, and N across domains varying from 167 to 8619. The youth from affected families had delays in gross and fine motor development in infancy ($k = 3$, $n = 167$, Hedges' $g = 0.644$, confidence intervals (CI) = [0.328, 0.960], $p < .001$), walking milestones ($k = 3$, $n = 608$, $g = 0.444$, CI = [0.108, 0.780], $p = .01$), coordination ($k = 8$, $n = 8619$, $g = 0.625$, CI = [0.453, 0.797], $p < .0001$), and had more abnormal movements such as involuntary movements ($k = 6$, $n = 8365$, $g = 0.291$, CI = [0.041, 0.542], $p = .02$) compared with controls. However, not all effects survived correction for publication bias. Effects for neurological soft signs were small and not reliably different from zero ($k = 4$, $n = 548$, $g = 0.238$, CI = [-0.106, 0.583], $p = .18$). When comparing the FDR group to youth from families with other psychiatric disorders, the FDR group was distinguished by poorer gross and fine motor skills ($k = 2$, $n = 275$, $g = 0.847$, CI = [0.393, 1.300], $p < .001$). **Conclusions:** Motor deficits during development likely represent an endophenotype for schizophrenia, although its specificity is limited in relation to other serious mental disorders. It holds promise as a low cost domain for early risk detection, although it will have to be combined with other indicators to achieve clinically usable prediction accuracy. Impaired coordination was the most robust result with a moderate effect size and lack of heterogeneity and publication bias. **Keywords:** Motor function; endophenotype; early detection; first-degree relatives; schizophrenia.

Introduction

Schizophrenia is considered a neurodevelopmental disorder (Catts et al., 2013; Feinberg, 1982; Lewis & Levitt, 2002; Murray & Lewis, 1987; Weinberger, 1987), and various motor impairments are observed in individuals with schizophrenia even in the medication-naïve state (Walther & Strik, 2012). Such impairments include abnormal involuntary movements (Pappa & Dazzan, 2009; Walther & Strik, 2012), neurological soft signs (NSS), catatonic symptoms, psychomotor slowing, and Parkinsonian signs (Walther & Strik, 2012). Studies investigating birth- and high-risk cohorts document motor impairments before the onset of schizophrenia (Cannon et al., 2002; Jones, Rodgers, Murray, & Marmot, 1994; Marcus, Hans, Lewow, Wilkinson & Burack, 1985; Marcus, Hans, Auerbach & Auerbach, 1993; McNeil,

Harty, Blennow, & Cantor-Graae, 1993; Niemi, Suvisaari, Haukka, & Lonnqvist, 2005; Rosso et al., 2000; Walker, Savoie & Davis, 1994). Impaired motor skills in childhood have been categorized as a biomarker for predicting development of schizophrenia in adulthood (Erlenmeyer-Kimling et al., 2000; Niemi et al., 2005). Several other developmental cognitive disturbances, such as attention- and executive control deficits and lower IQ, are present in first-degree relatives (FDR) of individuals with schizophrenia (Erlenmeyer-Kimling et al., 2000; Seidman et al., 2006).

Motor and cognitive dysfunctions often co-occur in individuals with neurodevelopmental disorders (Diamond, 2000), owing to abundant connections between motor and cognitive systems. Such connections, observed in the thalamo-cortico-thalamic circuits and the cerebellum, facilitate the tight interplay of motor and executive control systems during development (Castellanos et al., 1996; Diamond, 2000; Raichle et al., 1994).

Conflict of interest statement: No conflicts declared.

To our knowledge, this is the first meta-analysis assessing specific motor abilities in young (≤ 21 years), unaffected FDR of individuals with schizophrenia compared with control groups. A previous meta-analysis, restricted to individuals who later developed schizophrenia, revealed impaired motor dysfunction in that population (measured as a composite index) (Dickson, Laurens, Cullen, & Hodgins, 2012). However, no evaluation of specific motor impairments was reported. Furthermore, a review of developmental abnormalities during childhood measured in individuals at high risk of schizophrenia concluded that motor and neurological developmental problems appear to predict schizophrenia (Niemi, Suvisaari, Tuulio-Henriksson, & Lonnqvist, 2003). Our meta-analysis provides new cross-sectional information about which *specific* motor domains are impaired in children and adolescents with a familial risk of developing schizophrenia. This group is clinically identifiable and may have the potential for early intervention to forestall or mitigate the emergence of this disorder.

Here, we aim to investigate the occurrence of deviations in motor function during the development (≤ 21 of age) and the presence of specific motor deficits in unaffected FDR of individuals with schizophrenia (hereafter referred to as FDR) compared with controls. Using a systematic review and meta-analysis, we aimed to test whether children and adolescents with a genetic risk of developing schizophrenia and without manifest symptoms of psychosis display evidence for a motor impairment on a group level, which could represent an endophenotype. More specifically, we examined: Do FDR differ in their motor development or specific motor abilities compared with individuals without a genetic predisposition?

Methods

Study registration

This study adheres to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The protocol for the study was registered at PROSPERO international prospective register of systemic reviews (registration number CRD42012002591), before starting the literature search.

Study selection

Searches were performed in PubMed, PsycINFO, EMBASE, and the Cochrane Library. Search terms used were: ('high risk' OR 'high-risk' OR 'clinical high risk' OR 'schizophrenia'[TIAB] OR 'psychos*'[TIAB] OR 'psychotic'[TIAB] OR 'mental illness'[TIAB]) AND ('child*'[TIAB] OR 'adolescen*'[TIAB] OR 'infan*'[TIAB] OR 'offspring') AND ('motor' OR 'motor abilities' OR 'NSS' OR 'motor milestones' OR 'functional outcome' OR 'movement abnormalities' OR 'developmental abnormalities' OR 'developmental disabilities' OR 'motor skills disorder' OR 'dyskines*' OR 'pandysmatur*'). Further, references were examined for relevance and included if appropriate. No limitations were imposed regarding language, publication date, or country of origin.

Studies were included if they: (a) investigate FDR (offspring or siblings) of individuals with schizophrenia; (b) assess motor abilities or neurodevelopment; (c) include a control group; and (d) include a sample ≤ 21 years of age to investigate motor development in children and adolescents. We chose this age cutoff as we aimed to assess individuals in development. The majority of brain maturation in gray matter is completed at this age, although there is some further white matter development (Lenroot & Giedd, 2006). The peak debut of schizophrenia onset is 22 years, (Thorup, Waltoft, Pedersen, Mortensen, & Nordentoft, 2007). Therefore, young FDR under this age constitute a veritable high-risk group. In this study, motor ability reflects motor system functions, including the motor cortex, pyramidal tract, motor neurons, and cerebellum. Despite evidence for saccadic eye movements as an endophenotype for schizophrenia (Calkins, Iacono, & Ones, 2008; Greenwood et al., 2011), we did not include this function in our study. This was because of its etiologic complexities, involving several domains other than the motor domain (Meyhofer et al., 2015), and because of our restriction to measures obtained in clinical settings. Exclusion criteria were: (a) manifest symptoms of schizophrenia in FDR; (b) ultrahigh-risk status in FDR; and (c) studies not providing data for the actual motor function of the child/adolescent.

Data extraction

Two researchers (BKB, CH) independently screened all records obtained in the literature search, focusing on the relevance of titles to inclusion and exclusion criteria. The records were then entered into a Reference Manager 12 database. The data selection from both researchers was merged into a single database and duplicates were removed. The two researchers independently screened the abstract and full article of all records. Reasons for exclusion were recorded in an Excel database for each researcher: (a) FDR were not at genetic risk of developing schizophrenia; (b) FDR had a psychotic episode or diagnosis of schizophrenia; (c) FDR were at ultra high-risk state; (d) no motor outcomes; (e) included population were older than 21 years; (f) duplicate record; and (g) other, i.e., no motor data available for analysis or review papers. Each included or excluded record was assessed by both researchers until a consensus was reached.

Two authors independently extracted data and agreement statistics were subsequently estimated. Ultimately, consensus was sought in case of disagreement, which was reached in all such cases. Data were extracted manually to a prepiloted data-collection sheet and then entered into a database. Where included studies did not report sufficient statistical information for inclusion in the meta-analysis, the authors of the studies were not contacted for additional data.

Outcome measures

A variety of different motor outcomes were reported in the included studies and studies were classified into six domains of motor function. Meta-analyses were performed for each domain and we report the results within the following categories:

- *Gross and fine motor development*: assessed in infants aged 0–3.5 years using the Psychomotor Development Index (PDI) from the Bayley Scale of Infant Development (Bayley, 1969). Test items for the PDI included motor skills, such as rolling, crawling, grasp, and use of utensils.
- *Delay in walking*: age at which the child reached the milestone of walking. Categories were walking with support at the age of 10 months (Mednick, Mura, Schulsinger, & Mednick, 1971), walking at 12 months (Niemi et al., 2005),

or walking without support at the age of 18 months versus later (Henriksson & McNeil, 2004).

- **Impaired coordination:** several measures of coordination were recorded, including finger opposition, diadochokinesis, rapidly opening and closing the hand (Marcus, Hans, Lewow, et al., 1985), placing matches into a box (Hans et al., 2009), patterned movements of arm and hand, tapping finger and foot, finger following, visual motor coordination (copying of simple geometric figures) (Marcus, Hans, Mednick, Schulsinger & Michelsen, 1985), finger-nose, finger pursuit, heel-knee, rapid alternation, and rapid finger movement. Furthermore, activities such as buttoning, writing (Rosso et al., 2000), or inability to draw (Henriksson & McNeil, 2004) were recorded. Fine motor skills (Bagedahl-Strindlund, Rosencrantz-Larsson, & Wilkner-Svanfeldt, 1989; McNeil et al., 1993) were assessed using the Eye-Hand Coordination subscale of the Griffiths Developmental Scale (Alin-Åkerman & Nordberg, 1980; Griffiths, 1970). Eye-hand coordination and finger dexterity were also assessed using the Lincoln-Oseretsky Motor Development Scale (Myles-Worsley et al., 2007; Sloan, 1955).
- **Abnormal movements:** defined as tremors, tics, spasms, or athetoid movements (Rosso et al., 2000). Mirror movements, associated movements, or involuntary movements were also included (Hans et al., 1999; Marcus, Hans, Lewow, et al., 1985). Furthermore, choreoathetoid movements, abnormal facial movements, repetitive and spastic movements, hyper-/hypotonicity, bradykinesia, abnormal hand posture, abnormal posture (Walker et al., 1994), or motor overflow (Marcus, Hans, Mednick, et al., 1985) were assessed. Finally, studies reporting a composite neuromotor measure, where movement abnormalities were the main contributor (Hans et al., 1999; McNeil et al., 1993; Walker et al., 1994).
- **Neurological soft signs:** assessed using the Neurological Evaluation Scale (NES) (Buchanan & Heinrichs, 1989) or during a general neurological examination (Niemi et al., 2005; Rieder & Nichols, 1979). One study divided the NES into repetitive-motor and cognitive-perceptual subscales (Keshavan et al., 2008). The data from the repetitive motor subscale only were used in this meta-analysis.
- **Fine and gross motor skills:** The Lincoln-Oseretsky Motor Development Scale (Sloan, 1955) was used to assess finger dexterity, eye-hand coordination, and gross activity of hands, arms, legs, and trunk in children 6–14 years old (Erlenmeyer-Kimling et al., 2000). One study (Hanson, Gottesman, & Heston, 1976) assessed gross motor skills, such as hopping, walking in a line, and catching a ball, as well as fine motor skills, such as using pegboards, stringing beads, and the Porteus Maze Test.

Individuals from the same sample could be included in several motor outcome domains. For example, if the study tested coordination and abnormal movements, the sample was included in both domains. Furthermore, if the study had an outcome measure comprising many different motor skills, we chose the most relevant motor outcome group to that specific outcome.

Statistical synthesis and analysis

The meta-analysis compares specific motor abilities in young FDR with controls. The relevant heterogeneous data were synthesized using random effects models. Individual effect sizes [Hedges' g with 95% CI] for each study and an overall effect size were calculated and presented as forest plots. We used Hedges' g because Cohen's d is biased for small study samples (Borenstein, Hedges, Higgins, & Rothstein, 2009). Furthermore, meta-regressions were performed in several motor outcome groups, including age as a moderator in outcome

measures with more than $n = 5$ studies. We assessed heterogeneity with I^2 statistics, using a cutoff for $I^2 > 75\%$ to indicate too high a level of heterogeneity to calculate meaningful overall effect sizes (Higgins, Thompson, Deeks, & Altman, 2003). We assessed the potential for publication bias by using funnel plot asymmetry and Egger's test of intercept in a random effects model (Egger, Davey, Schneider, & Minder, 1997). The funnel plot is a scatter plot of study size (standard error) on the vertical axis as a function of effect size on the horizontal axis. Studies are distributed symmetrically about the combined effect size, if a publication bias is not present. Asymmetry in a funnel plot indicates that studies with nonsignificant results may have remained unpublished. Egger's test of intercept quantifies the degree of asymmetry of the funnel plot by regressing a measure of the observed effect to the study's precision. The size and direction of the effect is captured by the slope of the regression line, whereas bias is captured by the intercept (β_0). The larger the intercepts deviation from zero the more pronounced the asymmetry. Reported p -values are two-sided, with alpha at 0.05 for the null-effect test and 0.10 for the regression-based asymmetry tests (Ioannidis & Trikalinos, 2007; Jennions & Moller, 2002). Finally, a 'Trim and Fill' analysis in the random effects model was conducted to quantify the effect of missing studies on the observed effect size and recalculate the meta-estimate based on hypothetical studies that would have generated a symmetrical funnel plot (Duval & Tweedie, 2000). Analyses were performed in Comprehensive Meta-Analysis (2.0) (Borenstein et al., 2009).

Results

Search results and study characteristics

A total of 13,305 records were identified from the literature search after duplicates were removed (Figure 1). According to the predetermined inclusion and exclusion criteria, records were screened first by title and 12,323 records were excluded. The high number of exclusions based on titles alone was due to articles concerning neonates, also referred to as 'high-risk'. Thereafter, 982 full text articles were assessed, resulting in the exclusion of 961 records. Two further articles were identified from reference lists of the identified articles (Mednick et al., 1971; Ragins et al., 1975).

Twenty-three studies were included in the systematic review (Bagedahl-Strindlund et al., 1989; Erlenmeyer-Kimling et al., 2000; Hans et al., 1999; 2009; Hanson et al., 1976; Henriksson & McNeil, 2004; Keshavan et al., 2008; Marcus, Auerbach, Wilkinson & Burack, 1981; Marcus, Hans, Lewow, et al., 1985; Marcus, Hans, Mednick, et al., 1985; McNeil, Fish & Schubert, 2011; McNeil et al., 1993; Mednick et al., 1971; Myles-Worsley et al., 2007; Niemi et al., 2005; Onal, Demir, & Ceylan, 2002; Ragins et al., 1975; Rieder & Nichols 1979; Rosso et al., 2000; Sameroff, Barocas, & Seifer, 1984; Sohlberg, 1985; Walker et al., 1994; Yoshida, Marks, Graggs, Smith, & Kumar, 1999), of which 20 were included in the meta-analysis (Table 1) (Bagedahl-Strindlund et al., 1989; Erlenmeyer-Kimling et al., 2000; Hans et al., 1999, 2009; Hanson et al., 1976; Henriksson & McNeil, 2004; Keshavan et al., 2008; Marcus et al., 1981; Marcus, Hans, Lewow, et al., 1985; Marcus,

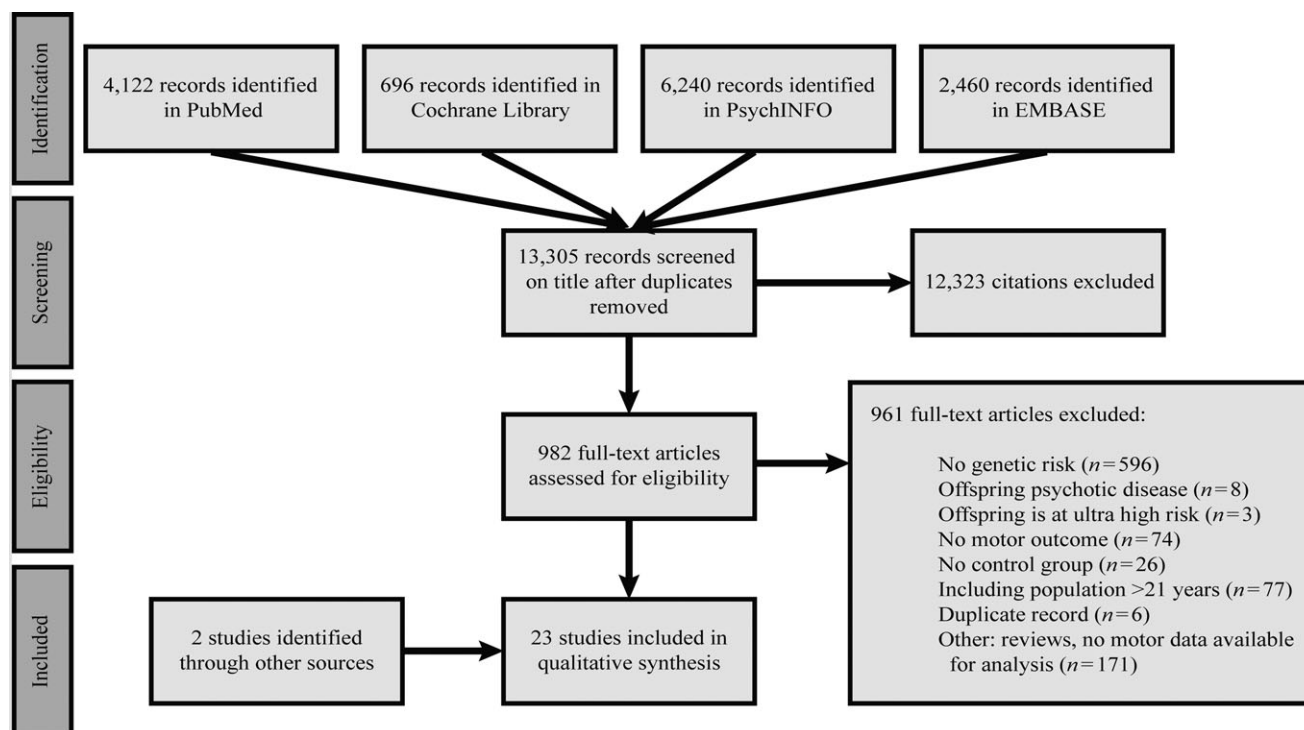


Figure 1 PRISMA flow chart. Note: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (www.prisma-statement.org)

Hans, Mednick et al., 1985; McNeil et al., 1993; Mednick et al., 1971; Myles-Worsley et al., 2007; Niemi et al., 2005; Onal et al., 2002; Rieder & Nichols, 1979; Rosso et al., 2000; Sameroff et al., 1984; Walker et al., 1994; Yoshida et al., 1999). Those not included in the meta-analysis either dealt with follow-up data (McNeil et al., 2011; Sohlberg, 1985) or lacked sufficient information to perform the calculations needed for the meta-analysis (Ragins et al., 1975). Additionally, one article was translated from Turkish (Onal et al., 2002).

Twenty-one studies examined offspring of individuals with schizophrenia, and the two remaining studies were cohort studies that evaluated individuals with schizophrenia and their unaffected siblings (Rosso et al., 2000), and a case-control study (Walker et al., 1994). Populations were assessed in Israel (Hans et al., 1999, 2009; Marcus et al., 1981; Marcus, Hans, Lewow, et al., 1985; Sohlberg, 1985), Europe (Bagedahl-Strindlund et al., 1989; Henriksson & McNeil, 2004; Marcus, Hans, Mednick et al., 1985; McNeil et al., 2011; McNeil et al., 1993; Mednick et al., 1971; Niemi et al., 2005; Onal et al., 2002; Yoshida et al., 1999), the United States (Erlenmeyer-Kimling et al., 2000; Hanson et al., 1976; Keshavan et al., 2008; Ragins et al., 1975; Rieder & Nichols 1979; Rosso et al., 2000; Sameroff et al., 1984; Walker et al., 1994), and the Republic of Palau (Myles-Worsley et al., 2007). All studies included a control group, and two studies also included a nonhealthy control group with psychiatric diagnoses other than schizophrenia assessing a composite motor measure (Erlenmeyer-Kimling et al., 2000; Hanson et al., 1976).

Meta-analyses

Meta-analysis of study results regarding gross and fine motor development suggested that children at high risk performed significantly worse than controls ($g = 0.644$, $p < .001$, $CI = [0.328, 0.960]$) (Figure 2). Moreover, meta-analysis of delayed walking outcomes revealed that infants at high risk for schizophrenia had delayed achievement of walking milestones compared with controls ($g = 0.444$, $p = .01$, $CI = [0.108, 0.780]$). A meta-analysis of impaired coordination demonstrated that FDR were impaired in their motor coordination compared with controls ($g = 0.625$, $p < .0001$, $CI = [0.453, 0.797]$), representing a moderate effect size. Metaregression with age (children vs. adolescents) did not indicate an age-dependent difference in coordination (regression coefficient = -0.0123 , $p = .94$, $CI = [-0.384, 0.360]$). FDR also had a slightly higher risk of abnormal movements compared with controls ($g = 0.291$, $p = .02$, $CI = [0.041, 0.542]$), as revealed by the meta-analysis. Furthermore, the presence of abnormal movements was independent of age (regression coefficient = 0.275 , $p = .25$, $CI = [-0.195, 0.744]$). One study (Rosso et al., 2000) provided data for two age groups (4 and 7 years old). For this study, we included the 7-year-old group to match the ages of children in the other studies in the abnormal movement meta-analysis. However, using the 4-year-old group instead did not influence our estimated effect size ($g = 0.315$, $p = .01$, $CI = [0.066, 0.564]$), $I^2 = 13.2\%$). Meta-analysis of studies investigating NSS revealed no differences between FDR and controls ($g = 0.238$, $p = .18$, $CI = [-0.106, 0.583]$).

Table 1 Characteristics of studies included in the systematic review and meta-analyses of first-degree relatives to individuals with schizophrenia and their motor outcomes

First author (reference)	Country/ town	Type of Study	Sample Size		Female (%)		Motor outcome all	Age (mean or range)	Outcome measure used in meta-analysis
			HR	Control	HR	Control			
Yoshida (1999)	UK	HR	19	24	53	36	Bayley Scale of Infant Development	2 and 7 months	Gross and fine motor development
Sameroff (1984)	Rochester	HR	29	57	NK	NK	Bayley Scales of Infant Development	2.5 years and 4 years	Gross and fine motor development
Marcus (1981)	Israel	HR	19	19	42	NK	Bayley scales of Infant Development	8 months	Gross and fine motor development
Mednick (1971)	Denmark	HR	207	104	NK	NK	Late walking with support and late in holding their heads	4 and 10 months	Delayed walking
Niemi (2005)	Finland	HR	111 & 88	53 & 97	NK	NK	Not able to walk at 1 year. Neurological soft signs.	1 year & childhood or adolescent	Delayed walking
Henriksson (2004)	Sweden	HR	33	100	36	54	Not walking without support, not sitting stable, and coordination/abnormal movements	8 months and 1.5 years.	Delayed walking
Hanson (1976)	US	HR	30	29	NK	NK	Poor motor skills (gross and fine motor, composite measure)	0–4 years	Motor skills compared with other mental diseases
Erlenmeyer-Kimling (2000)	US	HR	79	133	NK	NK	Lincoln-Oseretsky Motor Development Scale, (composite measure).	7–12 years	Motor skills compared with other mental diseases
Keshavan (2008)	US	HR	75	82	54.7	51	NSS [NES scale (repetitive motor)]	Mean age: 15.68 and 15.92	NSS
Rieder (1979)	US	HR	59	59	41	41	Neurological signs	7 years	NSS
Onal (2002)	Turkey	HR	43	45	58.1	55.6	NSS (NES scale)	8–18 years	NSS
Hans (2009)	Israel	HR	20	16	NK	NK	Fine motor dyscoordination	Mean age: 10.35 years	Coordination
Bagedahl-Strindlund (1989)	Sweden	HR	15	17	NK	NK	Griffiths locomotor test and eye-hand coordination test.	5–7.3 years	Coordination
Mytles-Worsley (2007)	Republic of Palau	HR	44	99	52.9	54.5	Lincoln-Oseretsky Motor Development Scale	14–19 years	Coordination
Marcus, Hans, Mednick (1985a)	Denmark	HR	59	59	52.5	52.5	Coordination, laterality, motor impersistence, motor overflow	11–13 years	Coordination
Rosso (2000)	US	Co	63	7941	49.2	49.7	Unusual movements and coordination	4 & 7 years	Abnormal movements
Marcus, Hans, Lewow (1985b)	Israel	HR	46	47	NK	NK	Balance, coordination, and motor overflow	7–14 years	Abnormal movements
McNeil (1993)	Sweden	HR	23 & 23	37 & 38	NK	NK	Griffiths Developmental Scale: eye-hand coordination test and Touwen and Precti's neurological examination.	6 years	Coordination
Walker (1994)	US	CC	28	21	42.9	66.7	Neuromotor abnormalities, motor skills and milestones combined	0–15 years and 0–2 years	Abnormal movements
Hans (1999)	Israel	HR	24	16	54	31	Neurobehavioral functioning (coordination and abnormal movements)	14–21 years	Abnormal movements
Sohlberg (1985)	Israel	HR	50	50	NK	NK	Bender-gestalt test	8.1–14.8 years	Sample already used in coordination (Marcus, Hans, Lewow, et al., 1985) Follow-up data
McNeil (2011)	Sweden	HR	38	91	34.2	52.7	Delayed motor mile stones as part of pandysmaturation	NK	Not enough data provided in the paper for performing meta-analysis
Ragins (1975)	US	HR	10	10	NK	NK	Bayley Scale of Infant Development/Late walking	4–8 months and 1.7 years	Not enough data provided in the paper for performing meta-analysis

HR, high risk study; CC, case-control study; Co, cohort study; NSS, neurological soft signs; NES, neurological evaluating scale; NK, not known.

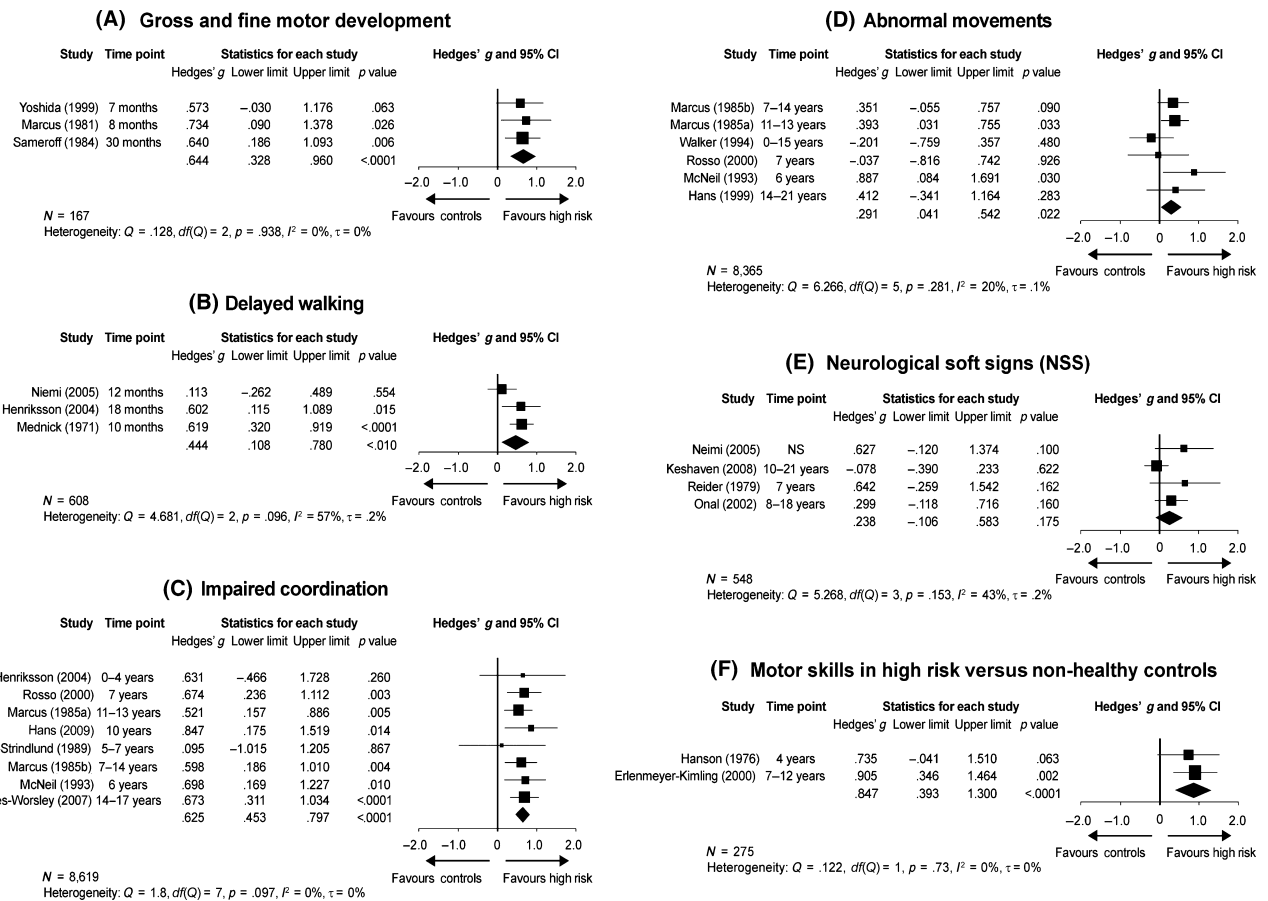


Figure 2 Forest plots with effect size and heterogeneity of the six motor outcome measures: (A) gross and fine motor development, (B) delayed walking, (C) impaired coordination, (D) abnormal movements, (E) neurological soft signs and (F) motor skills in high risk versus non-healthy controls

Assessment of gross and fine motor skills in FDR compared with offspring of parents diagnosed with a mental disorder other than schizophrenia demonstrated that the FDR had poorer motor skills ($g = 0.847$, $p < .001$, $CI = [0.393, 1.300]$), representing a large effect size albeit based on two studies only.

Assessment of publication bias by visually inspecting the funnel plots indicated three asymmetrical funnel plots (coordination, abnormal movement, and NSS) (Figure 3). Egger's regression methods testing for funnel plot asymmetry were conducted (Table 2). For NSS studies, the intercept β_0 , which provides a measure of asymmetry, was 2.703 with a significant two-tailed p -value = .09, implying possible publication bias. The remaining funnel plots were not significant for asymmetry. A Trim and Fill analysis for NSS (Table 2) suggested two missing studies to the left side of the mean effect, suggesting negative results remain unpublished. The imputed point estimate was 0.076 ($CI = [-0.264, 0.417]$), indicating no significant difference between FDR and controls.

A Trim and Fill analysis for the remaining studies (Table 2) showed one missing study for impaired coordination, but the recalculated effect size 0.610 ($CI = [0.443, 0.776]$) still revealed a significant

difference between FDR and controls. In contrast, the Trim and Fill analysis for abnormal movement suggested one missing study and an imputed effect size of 0.229 ($CI = [-0.038, 0.496]$), indicating no difference between FDR and controls when assessing for abnormal movement.

Discussion

Results of the present meta-analysis demonstrated significant impairments in several specific motor outcomes in unaffected FDR of individuals with schizophrenia compared with healthy controls and offspring of parents with other mental disorders. These include impaired coordination which had the most robust estimate owing to the moderate effect size and small 95% CI. Further impairments are seen in delayed gross and fine motor development in infancy, delayed achievement of walking, and the presence of more abnormal movements. However, we did not detect a significant difference in the presence of NSS. Furthermore, gross and fine motor skills in FDR compared with offspring of parents with other mental illnesses revealed a high effect size, but the wide 95% CI makes the estimate more uncertain. Overall, the results of the present meta-analysis

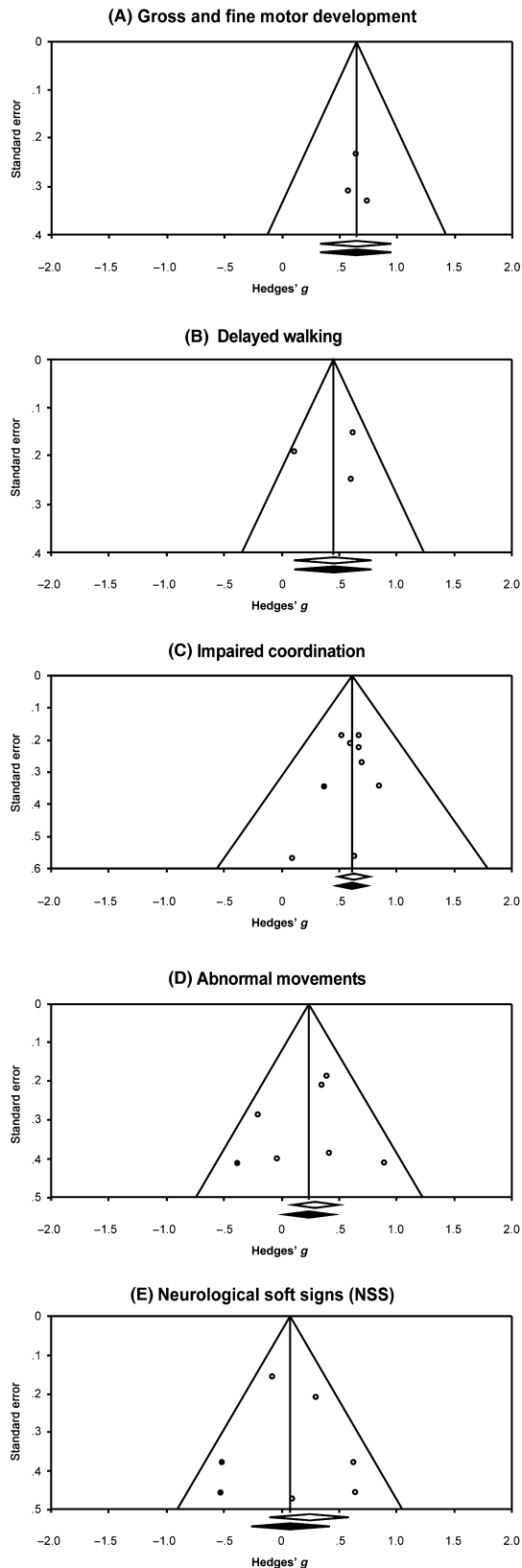


Figure 3 Publication bias. Funnel plots with a Trim and Fill analysis of (A) gross and fine motor development, (B) delayed walking, (C) impaired coordination, (D) abnormal movements and (E) neurological soft signs. The clear dots represent the actual studies, and the clear diamond represents the effect size and CI. The black dots represent the missing studies suggested by the Trim and Fill analysis, and the black diamond represents the recalculated estimated effect size and CI where the potential missing studies are incorporated

demonstrated poorer motor abilities in unaffected FDR compared with controls.

Delayed walking was the only domain with heterogeneity above 50%. However, no evidence of significant between-study heterogeneity was detected in any of the five meta-analyses. This suggests that the estimates of motor abilities are not dependent on the population investigated or reflected by where the study was performed, but was determined by whether the child/adolescent was a FDR or not.

As no large and significant between-study heterogeneity was identified, we applied tests to evaluate potential publication bias (Ioannidis & Trikalinos, 2007). In the domain of NSS, both Egger’s test and the Trim and Fill analysis found significant potential of publication bias. Incorporating the possibility of publication bias for NSS further strengthened the result of the observed meta-analysis, showing no difference between FDR and controls when assessing for NSS.

Neurological soft signs and neurological abnormalities have been reported repeatedly in patients with schizophrenia (Boks, Russo, Knegeting, & van den Bosch, 2000; Bombin, Arango, & Buchanan, 2005; Heinrichs & Buchanan, 1988; Ismail, Cantor-Graae, Cardenal, & McNeil, 1998; Keshavan et al., 2003; Peralta et al., 2011; Quitkin, Rifkin, & Klein, 1976; Rossi et al., 1990; Scheffer, 2004; Woods, Kinney, & Yurgelun-Todd, 1986), in pre-morbid groups (Leask, Done, & Crow, 2002; Walker & Lewine 1990; Cannon et al., 2002), and in adult FDR. However, results from our meta-analysis did not confirm these findings. Subtle neurological impairments, as measured with NSS, typically increase with age (Chen, Lam, Chen, & Nguyen, 1996; Rossi et al., 1990). In contrast to our findings, higher NES scores have elsewhere been detected in individuals with schizophrenia and their relatives, and deviations were positively correlated with age in both groups (Compton et al., 2007). The influence of age could explain why two meta-analyses (Chan, Xu, Heinrichs, Yu, & Gong, 2010; Neelam, Garg, & Marshall, 2011) assessing adult FDR of individuals with schizophrenia reported a significantly higher proportion of NSS in this group, whereas we did not observe any differences across groups in younger individuals. Moreover, the NES was designed to assess adults diagnosed with schizophrenia (Buchanan & Heinrichs, 1989) and may therefore lack sensitivity for the assessment of younger populations without psychosis, where motor and neurological development is ongoing. We suggest that the existing measures may not sufficiently accommodate the inherent characteristics of motor development in children and adolescents and could be considered as possible contributors to the negative findings. There is a need for studies that are either longitudinal or sufficiently broad in age range to enable the evaluation of the effects of age and development on the expression of NSS reported in schizophrenia.

However, the results from each motor domain are not independent of each other, due to both an

Table 2 Assessment of publication bias

	Egger's test of the intercept			Missing studies	Duval and Tweedie's trim and fill			
	β_0	95% CI	<i>p</i> -value (two sided)		Observed effect size	95% CI	Imputed Point estimate	95% CI
Gross and fine motor development	0.316	[-15.975, 16.609]	0.846	0	0.644	[0.328, 0.960]	Unchanged	Unchanged
Delay in walking	-1.246	[-82.430, 79.938]	0.877	0	0.444	[0.108, 0.780]	Unchanged	Unchanged
Impaired coordination	-0.234	[-1.589, 1.122]	0.688	1	0.625	[0.453, 0.80]	0.610	[0.443, 0.776]
Abnormal movements	-0.164	[-4.672, 4.343]	0.924	1	0.291	[0.041, 0.542]	0.229	[-0.038, 0.496]
Neurological soft signs	2.702	[-1.056, 6.462]	0.09	2	0.238	[-0.106, 0.583]	0.076	[-0.264, 0.417]

overlap among individuals in the different motor domains and an overlap among the motor subdomains. Consequently, though the domains represent different aspects of the motor system, they cannot be regarded as specific discrete entities. The domains are connected through circuits and networks within the motor system itself, and via interactions with other functional systems in the brain. Finally, we cannot dismiss the possibility that the deviations reported here in unaffected FDR could be transitory deviations (Gogtay, 2007) that may normalize during development. Only longitudinal studies can address this.

It is notable that none of the motor tests included in the present meta-analysis used more advanced physiological measures, such as actigraphs. This probably reflects the relatively recent attention to the use of these measures. However, future studies assessing motor function in FDR should strive to add digital measures of movement sequences and motor patterns to detect subtle differences in a comprehensive way.

Studies of motor abilities in FDR of individuals with schizophrenia compared with FDR of individuals with bipolar disorder or other neurodevelopmental disorders could further determine the specificity of these motor deviations in relation to schizophrenia. Alternatively, they may suggest a shared biological pathway of neurodevelopmental disorders. Adult psychiatric illnesses may originate from developmental disorders, with different symptom presentations in childhood (Rutter, Kim-Cohen, & Maughan, 2006). Given the status of the field and that children and young people included in this study are in development, caution should be taken when advising about interventions for this FDR group to avoid unnecessary false alarms. Early warning signs may disappear at later stages in FDR, due to minor deviations, resilience factors, or as part of normal development (Gogtay, 2007). Thus, ideally we want to identify specific and early warning markers, characterized by a clinically quantifiable risk factor index such as a composite risk score. This could comprise, for example, a genetic polygenic risk score

(or a family history), early symptoms, environmental components, and other measures of cognition or motor function, which specifically differentiate FDR from controls. Although still not definitive, a composite risk score is probably more accurate with a higher rate of positive and negative predictive values and thus yields a higher sensitivity and specificity than a single test.

Deficits of saccadic eye movements among others are established as valid endophenotypes for schizophrenia (Greenwood et al., 2011). In the present meta-analysis, young FDR showed evidence for group-level motor deficits during development, which could represent a potential endophenotype for a genetic vulnerability to develop schizophrenia.

Strengths and limitations

This is the first meta-analysis to assess specific motor outcomes in young unaffected FDR of individuals with schizophrenia compared with control groups. Our meta-analysis has several strengths including broad search criteria and independent selection of studies by two assessors to minimize the risk of assessor bias. Furthermore, we evaluated different age groups and specific motor functions in a systematic way, which has not been done previously.

Several limitations should be borne in mind. This is a meta-analysis of cross-sectional studies, thus we are unable to determine whether the same individuals show both early and late motor abnormalities – only longitudinal data can address this. In addition, inferences drawn relate to genetic and environmental consequences of having a parent diagnosed with schizophrenia and not necessarily the antecedents of schizophrenia in adulthood. Furthermore, two of the studies included were of siblings rather than offspring. Siblings and offspring differ genetically (siblings share dominance effects, while parents and offspring do not) and environmentally (offspring are typically reared by parents with schizophrenia, siblings are not). Moreover, we divided the included studies into domains of function to compare the same motor outcome measures in a single meta-

analysis. This resulted in fewer studies in each domain, but revealed that FDR and controls did not differ in terms of NSS. This finding may have been veiled in studies reporting profiles or composite measures of motor function. Finally, the variety of instruments and differences in sources of information used in the present studies in addition to the differences for recruiting the cohorts and the limited amount of information concerning the method of recruitment did not allow for a stringent evaluation of the degree of validity of the instruments or the selection bias. Future studies should therefore attempt to use validated instruments and describe the process of recruitment and the composition of their sample, inclusive its representativeness in more detail.

Conclusions

We report specific motor impairments in unaffected FDR of individuals with schizophrenia who are 21 years or younger when compared with controls demonstrating poorer motor abilities in FDR. The effect across studies assessing for impaired coordination may be considered the most robust with a moderate effect size, a narrow confidence interval, and no detected heterogeneity or publication bias. Thus, this domain is worthy of future research. Furthermore, the occurrence of delayed gross and fine motor development in infancy and delayed walking in FDR compared with controls is also supported. Additionally, we observed a significant difference in abnormal movements between the FDR and controls, however, due to a possible publication bias this finding should be interpreted cautiously. Further, no overall differences could be demon-

strated in the assessment of NSS when comparing these groups. The adult measure of NSS may lack sensitivity for age-dependent assessment of soft signs in developing children and adolescents. Individuals at familial risk of schizophrenia had poorer gross and fine motor skills than children of parents with other mental disorders. These motor deficits suggest that delayed motor development may represent a potential endophenotype for schizophrenia, and likely reflect the underlying neurodevelopmental vulnerability. However, the limited amount of accessible studies did not allow the exploration of the specificity of this finding in depth. The fact that motor deficits are present through early childhood and into adulthood reflects the complexity of neuro-motor development and is consistent with the hypothesis that schizophrenia represents a neurodevelopmental disorder.

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Key points

- A meta-analysis demonstrated poorer motor abilities in the unaffected first-degree relatives (≤ 21 years) of individuals with schizophrenia than in the youth from unaffected families, suggesting motor deficits during development may represent a potential endophenotype for schizophrenia.
- Impaired coordination, represented the most reliable finding with a medium effect size.
- In contrast, neurological soft signs did not yield reliable effects.
- Fine and gross motor skills were impaired in relatives of individuals with schizophrenia compared with relatives of individuals with other major psychiatric disorders.

References

- Alin-Åkerman, B., & Nordberg, L. (1980). *Griffiths developmental scales I and II*. Stockholm: Psykologiforlaget.
- Bagedahl-Strindlund, M., Rosencrantz-Larsson, L., & Wilkner-Svanfeldt, P. (1989). Children of mentally ill mothers: Social situation and psychometric testing of mental development. *Scandinavian Journal of Social Medicine*, 17, 171–179.
- Bayley, N. (1969). *Bayley scales of infant development*. New York: Psychological Corporation Bay.
- Boks, M.P., Russo, S., Knegeting, R., & van den Bosch, R.J. (2000). The specificity of neurological signs in schizophrenia: A review. *Schizophrenia Research*, 43, 109–116.
- Bombin, I., Arango, C., & Buchanan, R.W. (2005). Significance and meaning of neurological signs in schizophrenia: Two decades later. *Schizophrenia Bulletin*, 31, 962–977.
- Borenstein, M., Hedges, L., Higgins, J., & Rothstein, H. (2009). *Introduction to Meta-analysis* (1st edn). Chichester, UK: John Wiley & Son Ltd.

- Buchanan, R.W., & Heinrichs, D.W. (1989). The Neurological Evaluation Scale (NES): A structured instrument for the assessment of neurological signs in schizophrenia. *Psychiatry Research*, *27*, 335–350.
- Calkins, M.E., Iacono, W., & Ones, D.S. (2008). Eye movement dysfunction in first-degree relatives of patients with schizophrenia: A meta-analytic evaluation of candidate endophenotypes. *Brain and Cognition*, *68*, 436–461.
- Cannon, M., Caspi, A., Moffitt, T.E., Harrington, H., Taylor, A., Murray, R.M., & Poulton, R. (2002). Evidence for early-childhood, pan-developmental impairment specific to schizophreniform disorder: Results from a longitudinal birth cohort. *Archives of General Psychiatry*, *59*, 449–456.
- Castellanos, F.X., Giedd, J.N., Marsh, W.L., Hamburger, S.D., Vaituzis, A.C., Dickstein, D.P., ... & Rapoport, J.L. (1996). Quantitative brain magnetic resonance imaging in attention-deficit hyperactivity disorder. *Archives of General Psychiatry*, *53*, 607–616.
- Catts, V.S., Fung, S.J., Long, L.E., Joshi, D., Vercammen, A., Allen, K.M., ... & Weickert, C.S. (2013). Rethinking schizophrenia in the context of normal neurodevelopment. *Frontiers in Cellular Neuroscience*, *7*, 60.
- Chan, R.C.K., Xu, T., Heinrichs, R.W., Yu, Y., & Gong, Q. (2010). Neurological soft signs in non-psychotic first-degree relatives of patients with schizophrenia: A systematic review and meta-analysis. *Neuroscience and Biobehavioral Reviews*, *34*, 889–896.
- Chen, E.Y., Lam, L.C., Chen, R.Y., & Nguyen, D.G. (1996). Neurological signs, age, and illness duration in schizophrenia. *Journal of Nervous and Mental Disease*, *184*, 339–345.
- Compton, M.T., Bollini, A.M., Mack, L.M., Kryda, A.D., Rutland, J., Weiss, P.S., ... & Walker, E.F. (2007). Neurological soft signs and minor physical anomalies in patients with schizophrenia and related disorders, their first-degree biological relatives, and non-psychiatric controls. *Schizophrenia Research*, *94*, 64–73.
- Diamond, A. (2000). Close interrelation of motor development and cognitive development and of the cerebellum and prefrontal cortex. *Child Development*, *71*, 44–56.
- Dickson, H., Laurens, K.R., Cullen, A.E., & Hodgins, S. (2012). Meta-analyses of cognitive and motor function in youth aged 16 years and younger who subsequently develop schizophrenia. *Psychological Medicine*, *42*, 743–755.
- Duval, S., & Tweedie, R. (2000). Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*, *56*, 455–463.
- Egger, M., Davey, S.G., Schneider, M., & Minder, C. (1997). Bias in meta-analysis detected by a simple, graphical test. *British Medical Journal*, *315*, 629–634.
- Erlenmeyer-Kimling, L., Rock, D., Roberts, S.A., Janal, M., Kestenbaum, C., Cornblatt, B., ... & Gottesman, I.I. (2000). Attention, memory, and motor skills as childhood predictors of schizophrenia-related psychoses: The New York High-Risk Project. *American Journal of Psychiatry*, *157*, 1416–1422.
- Feinberg, I. (1982). Schizophrenia: Caused by a fault in programmed synaptic elimination during adolescence? *Journal of Psychiatric Research*, *17*, 319–334.
- Gogtay, N.G. (2007). Cortical brain development in nonpsychotic siblings of patients with childhood-onset schizophrenia. *Archives of General Psychiatry*, *64*, 772–780.
- Greenwood, T.A., Lazzeroni, L.C., Murray, S.S., Cadenhead, K.S., Calkins, M.E., Dobie, D.J., ... & Braff, D.L. (2011). Analysis of 94 candidate genes and 12 endophenotypes for schizophrenia from the Consortium on the Genetics of Schizophrenia. *American Journal of Psychiatry*, *168*, 930–946.
- Griffiths, R. (1970). *The abilities of young children*. London: Child Development Research Centre.
- Hans, S.L.M., Marcus, J., Nuechterlein, K.H., Asarnow, R.F., Styr, B., & Auerbach, J.G. (1999). Neurobehavioral deficits at adolescence in children at risk for schizophrenia: The Jerusalem Infant Development Study. *Archives of General Psychiatry*, *56*, 741–748.
- Hans, S.L., Auerbach, J.G., Nuechterlein, K.H., Asarnow, R.F., Asarnow, J., Styr, B., & Marcus, J. (2009). Neurodevelopmental factors associated with schizotypal symptoms among adolescents at risk for schizophrenia. *Development and Psychopathology*, *21*, 1195–1210.
- Hanson, D.R., Gottesman, I.I., & Heston, L.L. (1976). Some possible childhood indicators of adult schizophrenia inferred from children of schizophrenics. *British Journal of Psychiatry*, *129*, 142–154.
- Heinrichs, D.W., & Buchanan, R.W. (1988). Significance and meaning of neurological signs in schizophrenia. *American Journal of Psychiatry*, *145*, 11–18.
- Henriksson, K.M., & McNeil, T.F. (2004). Health and development in the first 4 years of life in offspring of women with schizophrenia and affective psychoses: Well-Baby Clinic information. *Schizophrenia Research*, *70*, 39–48.
- Higgins, J.P., Thompson, S.G., Deeks, J.J., & Altman, D.G. (2003). Measuring inconsistency in meta-analyses. *British Medical Journal*, *327*, 557–560.
- Ioannidis, J.P., & Trikalinos, T.A. (2007). The appropriateness of asymmetry tests for publication bias in meta-analyses: A large survey. *Canadian Medical Association Journal*, *176*, 1091–1096.
- Ismail, B.T., Cantor-Graae, E., Cardenal, S., & McNeil, T.F. (1998). Neurological abnormalities in schizophrenia: Clinical, etiological and demographic correlates. *Schizophrenia Research*, *30*, 229–238.
- Jennions, M.D., & Moller, A.P. (2002). Publication bias in ecology and evolution: An empirical assessment using the ‘trim and fill’ method. *Biological Reviews of the Cambridge Philosophical Society*, *77*, 211–222.
- Jones, P., Rodgers, B., Murray, R., & Marmot, M. (1994). Child development risk factors for adult schizophrenia in the British 1946 birth cohort. *Lancet*, *344*, 1398–1402.
- Keshavan, M., Montrose, D.M., Rajarethinam, R., Diwadkar, V., Prasad, K., & Sweeney, J.A. (2008). Psychopathology among offspring of parents with schizophrenia: Relationship to premorbid impairments. *Schizophrenia Research*, *103*, 114–120.
- Keshavan, M.S., Sanders, R.D., Sweeney, J.A., Diwadkar, V.A., Goldstein, G., Pettegrew, J.W., & Schooler, N.R. (2003). Diagnostic specificity and neuroanatomical validity of neurological abnormalities in first-episode psychoses. *American Journal of Psychiatry*, *160*, 1298–1304.
- Leask, S.J.D., Done, D.J., & Crow, T.J. (2002). Adult psychosis, common childhood infections and neurological soft signs in a national birth cohort. *British Journal of Psychiatry*, *181*, 387–392.
- Lenroot, R.K., & Giedd, J.N. (2006). Brain development in children and adolescents: Insights from anatomical magnetic resonance imaging. *Neuroscience and Biobehavioral Reviews*, *30*, 718–729.
- Lewis, D.A., & Levitt, P. (2002). Schizophrenia as a disorder of neurodevelopment. *Annual Review of Neuroscience*, *25*, 409–432.
- Marcus, J., Auerbach, J., Wilkinson, L., & Burack, C.M. (1981). Infants at risk for schizophrenia. The Jerusalem Infant Development Study. *Archives of General Psychiatry*, *38*, 703–713.
- Marcus, J., Hans, S.L., Auerbach, J.G., & Auerbach, A.G. (1993). Children at risk for schizophrenia: The Jerusalem Infant Development Study: II. Neurobehavioral deficits at school age. *Archives of General Psychiatry*, *50*, 797–809.
- Marcus, J., Hans, S.L., Lewow, E., Wilkinson, L., & Burack, C.M. (1985b). Neurological findings in high-risk children: Childhood assessment and 5-year followup. *Schizophrenia Bulletin*, *11*, 85–100.

- Marcus, J., Hans, S.L., Mednick, S.A., Schulsinger, F., & Michelsen, N. (1985a). Neurological dysfunctioning in offspring of schizophrenics in Israel and Denmark. A replication analysis. *Archives of General Psychiatry*, *42*, 753–761.
- McNeil, T.F., Fish, B., & Schubert, E.W. (2011). Prospective study of pandysmaturation and adult mental disorder in high-risk and normal-risk offspring. *Journal of Psychiatric Research*, *45*, 561–567.
- McNeil, T.F., Harty, B., Blennow, G., & Cantor-Graae, E. (1993). Neuromotor deviation in offspring of psychotic mothers: A selective developmental deficiency in two groups of children at heightened psychiatric risk?. *Journal of Psychiatric Research*, *27*, 39–54.
- Mednick, S.A., Mura, E., Schulsinger, F., & Mednick, B. (1971). Perinatal conditions and infant development in children with schizophrenic parents. *Social Biology*, *18*, S103–S113.
- Meyhofer, I., Steffens, M., Kasparbauer, A., Grant, P., Weber, B., & Ettinger, U. (2015). Neural mechanisms of smooth pursuit eye movements in schizotypy. *Human Brain Mapping*, *36*, 340–353.
- Murray, R.M., & Lewis, S.W. (1987). Is schizophrenia a neurodevelopmental disorder? *British Medical Journal*, *295*, 681–682.
- Myles-Worsley, M., Ord, L.M., Ngiralmu, H., Weaver, S., Blailes, F., & Faraone, S.V. (2007). The Palau Early Psychosis Study: Neurocognitive functioning in high-risk adolescents. *Schizophrenia Research*, *89*, 299–307.
- Neelam, K., Garg, D., & Marshall, M. (2011). A systematic review and meta-analysis of neurological soft signs in relatives of people with schizophrenia. *BioMed Central Psychiatry*, *11*, 139.
- Niemi, L.T., Suvisaari, J.M., Haukka, J.K., & Lonnqvist, J.K. (2005). Childhood predictors of future psychiatric morbidity in offspring of mothers with psychotic disorder: Results from the Helsinki High-Risk Study. *British Journal of Psychiatry*, *186*, 108–114.
- Niemi, L.T., Suvisaari, J.M., Tuulio-Henriksson, A., & Lonnqvist, J.K. (2003). Childhood developmental abnormalities in schizophrenia: Evidence from high-risk studies. *Schizophrenia Research*, *60*, 239–258.
- Onal, O., Demir, C., & Ceylan, M.E. (2002). Soft neurological signs in children of schizophrenic parents: A controlled study. [Turkish]. *Klinik Psikofarmakoloji Bulteni/Bulletin of Clinical Psychopharmacology*, *12*, 78–85.
- Pappa, S., & Dazzan, P. (2009). Spontaneous movement disorders in antipsychotic-naïve patients with first-episode psychoses: A systematic review. *Psychological Medicine*, *39*, 1065–1076.
- Peralta, V., de Jalon, E.G., Campos, M.S., Basterra, V., Sanchez-Torres, A., & Cuesta, M.J. (2011). Risk factors, pre-morbid functioning and episode correlates of neurological soft signs in drug-naïve patients with schizophrenia-spectrum disorders. *Psychological Medicine*, *41*, 1279–1289.
- Quitkin, F., Rifkin, A., & Klein, D.F. (1976). Neurologic soft signs in schizophrenia and character disorders. Organicity in schizophrenia with premorbid asociality and emotionally unstable character disorders. *Archives of General Psychiatry*, *33*, 845–853.
- Ragins, N., Schachter, J., Elmer, E., Preisman, R., Bowes, A.E., & Harway, V. (1975). Infants and children at risk for schizophrenia. Environmental and developmental observations. *Journal of the American Academy of Child Psychiatry*, *14*, 150–177.
- Raichle, M.E., Fiez, J.A., Videen, T.O., MacLeod, A.M., Pardo, J.V., Fox, P.T., & Petersen, S.E. (1994). Practice-related changes in human brain functional anatomy during nonmotor learning. *Cerebral Cortex*, *4*, 8–26.
- Rieder, R.O., & Nichols, P.L. (1979). Offspring of schizophrenics III. Hyperactivity and neurological soft signs. *Archives of General Psychiatry*, *36*, 665–674.
- Rossi, A., De, C.S., Di, M., Manna, V., Ceccoli, S., & Stratta, P., & Casacchia, M. (1990). Neurological soft signs in schizophrenia. *British Journal of Psychiatry*, *157*, 735–739.
- Rosso, I.M., Bearden, C.E., Hollister, J.M., Gasperoni, T.L., Sanchez, L.E., Hadley, T., & Cannon, T.D. (2000). Childhood neuromotor dysfunction in schizophrenia patients and their unaffected siblings: A prospective cohort study. *Schizophrenia Bulletin*, *26*, 367–378.
- Rutter, M., Kim-Cohen, J., & Maughan, B. (2006). Continuities and discontinuities in psychopathology between childhood and adult life. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *47*, 276–295.
- Sameroff, A.J., Barocas, R., & Seifer, R. (1984). The early development of children born to mentally ill women. In N.F.A.E.J. Watt, L.C. Wynne, & J.E. Rolf (Eds.), *Children at risk for schizophrenia, a longitudinal perspective* (pp. 482–514). Cambridge: Cambridge University Press.
- Scheffer, R.E. (2004). Abnormal neurological signs at the onset of psychosis. *Schizophrenia Research*, *70*, 19–26.
- Seidman, L.J., Giuliano, A.J., Smith, C.W., Stone, W.S., Glatt, S.J., Meyer, E., & Cornblatt, B. (2006). Neuropsychological functioning in adolescents and young adults at genetic risk for schizophrenia and affective psychoses: Results from the Harvard and Hillside Adolescent High Risk Studies. *Schizophrenia Bulletin*, *32*, 507–524.
- Sloan, W. (1955). The Lincoln-Oseretsky motor development scale. *Genetic Psychology Monographs*, *51*, 183–252.
- Sohlberg, S.C. (1985). Personality and neuropsychological performance of high-risk children. *Schizophrenia Bulletin*, *11*, 48–60.
- Thorup, A., Waltoft, B.L., Pedersen, C.B., Mortensen, P.B., & Nordentoft, M. (2007). Young males have a higher risk of developing schizophrenia: A Danish register study. *Psychological Medicine*, *37*, 479–484.
- Walker, E., & Lewine, R.J. (1990). Prediction of adult-onset schizophrenia from childhood home movies of the patients. *The American Journal of Psychiatry*, *147*, 1052–1056.
- Walker, E.F., Savoie, T., & Davis, D. (1994). Neuromotor precursors of schizophrenia. *Schizophrenia Bulletin*, *20*, 441–451.
- Walther, S., & Strik, W. (2012). Motor symptoms and schizophrenia. *Neuropsychobiology*, *66*, 77–92.
- Weinberger, D.R. (1987). Implications of normal brain development for the pathogenesis of schizophrenia. *Archives of General Psychiatry*, *44*, 660–669.
- Woods, B.T., Kinney, D.K., & Yurgelun-Todd, D. (1986). Neurologic abnormalities in schizophrenic patients and their families. I. Comparison of schizophrenic, bipolar, and substance abuse patients and normal controls. *Archives of General Psychiatry*, *43*, 657–663.
- Yoshida, K., Marks, M.N., Graggs, M., Smith, B., & Kumar, R. (1999). Sensorimotor and cognitive development of infants of mothers with schizophrenia. *The British Journal of Psychiatry*, *175*, 380–387.

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