

THE PERSISTENCE OF DEVELOPMENTAL MARKERS IN CHILDHOOD AND  
ADOLESCENCE AND RISK FOR SCHIZOPHRENIC PSYCHOSES IN ADULT LIFE.  
A 34-YEAR FOLLOW-UP OF THE NORTHERN FINLAND 1966 BIRTH COHORT.

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THE PERSISTENCE OF DEVELOPMENTAL MARKERS IN CHILDHOOD AND ADOLESCENCE AND RISK FOR SCHIZOPHRENIC PSYCHOSES IN ADULT LIFE. A 34-YEAR FOLLOW-UP OF THE NORTH FINLAND 1966 BIRTH COHORT.

SUMMARY

Childhood precursors of schizophrenia include multiple abnormalities of development. Continuities between early and subsequent deviance are poorly characterised. We studied associations among premorbid developmental deviance using data at ages 1 year (learning to stand, walk, and speak, attainment of bladder and bowel control) and 16 years (success at school). Generalised linear modelling was used to examine differential linear associations and trends across adult psychiatric diagnoses. In babies who, as adults, suffered schizophrenia or any psychosis, those who learned to stand latest were also more likely to perform poorly at school in both motor and theoretical domains at age 16 when compared with earlier learners. The effect was independent of genetic and perinatal factors. We conclude that the early developmental deviation in the first year of life is associated with lower school performance at age 16. Developmental continuity among children who develop psychoses was stronger than among normal controls and those hospitalised for non-psychotic psychiatric disorder. These findings are in line with hypothesis that a neural diathesis is present during postnatal brain development before schizophrenia. This supports the longitudinal dimension and life span models of schizophrenia.

**KEY WORDS:** schizophrenia, psychosis, development, risk, motor, precursors.

## INTRODUCTION

Development may go awry long before schizophrenia begins. Numerous studies of premorbid function have revealed abnormalities or developmental delays in neuromotor, cognitive, language, emotional or social functioning. (McNeil et al., 2000; Isohanni et al., 2000a; Jones, 2001; Fuller et al., 2002; Cannon et al., 2003). Jones et al. (1994) studied the British 1946 birth cohort and found evidence of delayed motor and speech development by the age of 2 years in those children who developed schizophrenia as adults. Isohanni et al. (2001) replicated and extended these findings in the Northern Finland 1966 Birth Cohort using even earlier developmental data (year 1). Ages at learning to stand, walk and become potty trained were related to subsequent risk for schizophrenia and other psychoses (to age 31 years): earlier milestones reduced, and later milestones increased the risk. These results provided evidence that the motor developmental effect inferred by that study is linear, specific to psychosis, and detectable as early as 12 months of age when measures of development have truncated variance due to censoring of temporal milestones. This effect is also apparent in other domains of development e.g. in the same cohort markers of enuresis (development of continence) and bowel control were also associated with adult schizophrenia and other psychoses.

Neuromotor and cognitive markers of risk of schizophrenia have also been found in older children. Crow et al. (1995) studied the UK 1958 birth cohort where pre-schizophrenic children at age 7 had been slower to develop continence and had poor coordination and vision; at age 7, 11 and 16 they had poorer academic performance,

and at age 16 they were rated as clumsy. Findings consistent with abnormal development of motor co-ordination in the non-academic domain during school years at ages 7 to 11 years have also been reported by Cannon et al. (1999) in a large, population-based nested case-control study in Helsinki 1951-1960 Birth Cohort, as well as in a smaller case-control study by Helling et al. (2003). However, in another population based study, the Northern Finland 1966 Birth Cohort, Isohanni and co-workers (2000b) found that poor school performance at age 16 in subjects requiring motor skill (eg. sports and handicrafts) was not a risk factor for later schizophrenia.

Few prospective studies have been able to address hypotheses concerning the *persistence* of developmental deviance and related phenotypic anomalies. This requires prospective data from two time points before onset. The difficulty of obtaining such data mean that currently we know very little about the longitudinal pattern of developmental dysfunction in the early and late premorbid phases of schizophrenia: are early deficits associated with risk for schizophrenia e.g. is delayed attainment of milestones associated with poorer school performance? If so, this would suggest that the same children who exhibit deficits at one time point, also exhibit deficits at other times – thereby defining a longitudinal phenotype at risk for adult psychosis. Most evidence uses information from one source or time-point only or group means in different time points: this makes it difficult to tell whether it is the same children who are deviant, developmentally, on each occasion.

However, we do have some important data from longitudinal studies. Walker's (1994) classic study of "home movies" obtained from families where one child later

developed schizophrenia indicated that gross but transient abnormal motor behaviour was most pronounced during the first two years of life, but found some evidence of “catching-up” in later years of childhood. In the UK 1958 birth cohort (Crow et al., 1995) problems in social adjustment and school performance detected in preschizophrenic children at age 7 were still present (manifest as differences in group means) at follow-up at the age of 11. In the Philadelphia cohort of the National Collaborative Perinatal Project (Rosso et al., 2000) deviance on motor coordination at age 7 as well as unusual movements at ages 4 and 7 predicted adult schizophrenia, but there was no additional predictive value from assessments of motor functioning later in childhood (teenage years). In a prospective longitudinal study in Iowa, test scores in preschizophrenic children dropped significantly between ages 13-16 years (Fuller et al., 2002). Persistent, pan-developmental (neuromotor, language, cognition) impairment specifically associated with schizophreniform disorder was detected in early childhood in the Dunedin Multidisciplinary Health and Developmental Survey (Cannon et al., 2002) where cases performed worse than controls on standard tests of motor skill at ages 3, 5, and 9 years but not at age 7 years.

There is some evidence of persistence of deviance among children at high genetic risk for serious psychopathology (reviewed by Cannon et al., 2003) – a phenomenon that Fish et al. (1992) has labeled pandevelopmental retardation or pandysmaturation. However, early markers for schizophrenia may be more distinguished by variability than constancy (Watt, 1984): little is known about whether the same children show deviancy in multiple areas on multiple occasions pre-morbidly. Some evidence of persistence in deviant neuromotor development in high-risk infants has been reported

in motor skills (Mednick and Schulsinger, 1974), or having high frequencies of soft neurological signs (motor coordination and left-right orientation) during infancy and school age (Marcus et al., 1993). In the New York High-Risk Project, longitudinal stability and persistence was seen in verbal memory, gross motor function and attention (Erlenmeyer-Kimling et al., 2000). However, some studies show normal neurological development in high-risk infants (reviewed by Marcuse and Cornblatt 1986).

As far as we know, the study of Cannon et al. (2002) is the only study analyzing the diagnostic specificity of the continuity: they demonstrated that this phenomenon existed in broad schizophreniform disorder. In addition, none of these studies integrate developmental data from age 1 year through to the end of the teenage years.

We set out to investigate a number of longitudinal aspects of the life-course developmental trajectory to adult psychoses in the Northern Finland 1966 Birth Cohort where investigation of early risk factors for adult disorders has already been informative. Slow motor development (later attainment of milestones: standing and walking without support), measured by parental report at age one year has been linked with mental retardation (von Wendt et al., 1984), twin status (Moilanen and Rantakallio, 1989), the risk of criminal behavior among boys whose mothers smoked during pregnancy (Räsänen et al., 1999), and with the risk of schizophrenia and other psychoses (Isohanni et al., 2001).

In this paper we studied the longitudinal persistence of developmental deviance by examining whether development at age about 1 (using the ages of achievement of developmental milestones) was associated with further markers of ability or performance in school in late adolescence (teacher ratings of school performance recorded at age 16 years). To be more specific, we investigated:

- 1) Whether the same children who achieved developmental milestones later (i.e. did not learn to stand, walk, and speak, and did not attain continence at about age 1) also receive lower marks from teachers when asked to rate their performance at school in motor and academic domains. This would further support our notion of a developmental gradient of risk, and would compare early (quick) with later (slow) learners using data from a later (but still pre-morbid) period more proximal to the onset of illness.
- 2) Does longitudinal persistence, by which we mean the strength of association between early and later developmental markers (operationalised as a linear association in correlation or regression), vary by diagnosis? Here we compare schizophrenia (under two definitions: narrow DSM-III-R, broad DSM-III-R including schizophrenia spectrum cases) and all psychoses and also non-psychotic disorders admitted to hospital with controls having no hospital treated disorders.

- 3) Is the persistence of any developmental deviance general, or specific to the motor domain? We test this by comparing school marks in school subjects involving motor skills, with those that reflect more general academic abilities.
- 4) Are these developmental markers associated with developmental disorders; in particular, with the co-morbidity of mental retardation, as well as genetic and perinatal risk?

## METHODS

### Subjects and data collection

Detailed description and additional information regarding the study variables and methods is available from previous reports (Isohanni et al., 2001). The Northern Finland 1966 Birth Cohort is based upon 12 068 pregnant women and their 12 058 live-born children in the provinces of Lapland and Oulu with an expected delivery date during 1966, representing 96% of all births (Rantakallio, 1969; Isohanni et al., 1997). Data on biological, socioeconomic and health conditions, living habits and family characteristics were collected prospectively from pregnancy up to the age of 31. A total of 284 had died and 757 emigrated, leaving 11 017 eligible individuals in Finland at the age of 16 years.



The Faculty of Medicine Ethics Committee of the University of Oulu keeps the study design of the Northern Finland 1966 Birth Cohort under review. In the field survey conducted in 1997, subjects were given a complete description of the study, its aims and requirements: all subjects had an opportunity to refuse to participate and gave written informed consent. A total of 83 individuals did not consent to the use of their data and were excluded, as well as seven organic mental disorders, leaving 10 927 cohort members for the present study (5 586 boys, 51.1%).

#### Information on childhood development at age 1

Developmental data obtained during children's visits to welfare centers were obtained during a special examination performed at age one year. In 96% of the cases the information was collected at an age of 11.5 months or later (Rantakallio et al., 1985). The following developmental milestones were examined at this 1-year examination:

*Age of standing and walking without support.* Parents were asked the age (in months) that the child learned these skills. We used the following categories for analyses: standing (before 10 months, at 11, or not learned by 12 months); walking (before 10 months, at 11, or not learned by 12 months). Although data were available on standing before 9 months; this category was collapsed with before 10 months due to the low frequency of very early development.

*Potty training.* Whether the child defecated into a potty (always, mostly, sometimes, or never). This variable was dichotomized: at least sometimes vs. never.

*Day/night time wetting.* Parents were asked if the child was dry (mostly dry, always dry, or wet every day/night). The variable was dichotomized: mostly or always dry vs. wet every day/night.

*Talking.* Parents were asked how many words the child spoke: no words, one or two words, three or more words.

#### Information on adolescent development at age 16

We used school performance (teacher rating) as a developmental marker. It was operationalised in two ways, as a motor score (mean of subjects involving activity skills) and theoretical performance (academic score of all other school subjects including languages, which probably reflect general ability).

*Motor score:* the mean score of individual school subjects related to neuromotor development and involving motor coordination: physical education, music, drawing, craft: woodwork/ knitting.

*Theoretical, academic score:* the mean score of all other subjects: Finnish language: reading/literacy; second, third etc. language; mathematics; chemistry; physics; history; biology; geography; religion and civics.

*Mean score* of all (motor and theoretical) subjects was also used.

These school marks, at age 16 have been described in detail by Isohanni et al. (1998). Their range in Finland is from 4 (fail) to 10 (excellent). Although they are scored (by teachers) taking only discrete values (4/5/6/7/8/9/10) individual scores are approximately normally distributed. Averages of scores over subjects e.g. to form motor and academic scores, generates even more normally distributed scores that are suitable for analysis using traditional methods for continuous variables. Our group comparisons are therefore conducted in terms of mean scores on aggregates of school marks (not on each school subject individually). This facilitates interpretations of hypothesis tests involving interactions between developmental group (early/late) and diagnosis and enables us to use a general linear model for analysis (see section below).

#### Information on adult psychiatric morbidity

The nation-wide Finnish Hospital Discharge Register (FHDR) covers all hospitals. All cohort members over 16 years appearing on the FHDR until the end of 1997 for any mental disorder (i.e. ICD-8 290-309, DSM-III-R diagnoses 290-316, and ICD-10 F 00-F69, F99) were identified. All case records were scrutinized and diagnoses were validated for the DSM-III-R criteria (Isohanni et al., 1997; Moilanen et al., 2003). Inter-rater reliability was good with kappa values from 0.6 to 0.9. Finally, altogether 146 patients (84 males) with known psychotic episode before 1998 were invited to participate in a field survey, including two cases not found in the FHDR by the end of year 1997. Of the two cases one was treated in outpatient and the other was inpatient with onset of the illness after 1997. Of the invited index subjects 92 (52 males) participated in the field survey, which took place during 1999-2001. Structural

diagnostic interview for DSM-III-R (Spitzer et al., 1989) and anamnestic information were the main diagnostic instruments. Two cases were excluded as organic etiology was found to be the cause for their psychosis. Additionally two cases were excluded as only developmental disorder was diagnosed. One case was diagnosed as having schizotypal personality disorder. Of the non-participants and twelve deceased subjects only case records were available and the diagnosis was made according to the records.

The following best estimate diagnostic categories were used:

1. Two diagnostic definitions of schizophrenia

1.1. Schizophrenia defined as any individual who at any time met DSM-III-R criteria.

A total of 111 cases (72 men) of “narrow” DSM-III-R schizophrenia arose by end of the 34th year (cumulative incidence 1.0 %; 95% CI 0.8, 1.2).

1.2. Broadly defined schizophrenia or DSM-III-R schizophrenia as above and 22

“schizophrenia spectrum” cases 295.40 (9), 295.70 (7), and 297.70 (6) resulting 133 cases (79 men)

2. All psychoses (n= 159, 93 men); in category 1.2 were added: 269.13 (1), 296.24

(7), 296.34 (4), 296.44 (4), 296.54 (2), 296.64 (2), 298.8 (1), 298.9 (5).

3. Non-psychotic disorders (n = 313, 221 men). Substance use disorders (n = 131);

non-psychotic mood disorders (n = 61); anxiety disorders (n = 51); adjustment

disorders (n= 61); personality disorders (n = 66); other non-psychotic diagnoses (n = 95). Multiple diagnoses were possible in this category, and the number of diagnoses exceeds the number of cases.

4. Cohort members with no psychiatric hospital treatment. A total of 10 453 subjects (5 273 or 50.4% men) without psychiatric hospitalization until the age of 31 represented the unaffected population and served as comparison group.

## Covariates

*Sex.* Initial analyses were performed for boys and girls separately, and then the sexes were pooled.

*Perinatal risk* (present/absent) is related to the development of schizophrenia in this sample (Jones et al., 1998). This was defined as one of low birth weight (<2500g), short gestation (<37 weeks), or perinatal brain damage. Children were considered to have perinatal brain damage if they had an Apgar score of zero at one minute or less than five at 15 minute, convulsions during the neonatal period, or a diagnosis of asphyxia, brain injury, or intraventricular hemorrhage at discharge, but did not have CNS malformation, chromosomal aberrations, or hereditary CNS degeneration.

*School type* at age 14: normal vs. special schools. Special schools are for children with motor handicap, hearing or vision defects, intellectual disability or severe behavioural problems (Rantakallio and von Wendt, 1985; Isohanni et al., 1998).

*School grade level:* in normal, age appropriate grade or above vs. below (Isohanni et al., 1998). These variables (especially school type) reflect mental retardation, low intelligence and educational handicap.

*Genetic risk and familial loading of psychoses.* We used family history of psychoses (FH) as proxy genetic variable and divided schizophrenia patients into two groups: FH positive or not (Mäki et al., 2003). In the case of the cohort members with

schizophrenia, all hospital notes and available outpatient notes were checked to find out whether or not a first degree relative (mother, father, or sibling) had experienced a psychotic episode. Additionally in a field survey during 1999-2001 all of the 60 participating schizophrenia patients underwent the Family Interview for Genetic Studies (FIGS; Maxwell, 1992). In the FIGS procedure the patient and the mother, or if the mother was not willing or able to participate, the father or one of the siblings, were asked whether any first degree relatives had experienced psychotic symptoms. The relationship between development at age 1 and school performance at age 16 was studied stratified by genetic risk: data on familial risk for the cohort members without psychoses were not available.

#### Statistical analysis

Spearman correlation coefficients were calculated to summarise the association between development at age 1 and educational performance at age 16, without assuming linearity of trend.

Analysis of variance (ANOVA) was used to test for differences in group means among the variables of interest (average school marks by developmental group). In this parametric analysis a single degree of freedom F-test was used to examine evidence for a linear trend across (up to three) categories of development. Potential confounding by sex, perinatal risk and school type and grade level (criteria for school marks are not necessary the same in different school types or grades) was controlled.

The interaction of linear trend of school performance across the levels of standing without support by each diagnostic category was examined using an orthogonal contrast in ANOVA. Tests of interaction between trend and diagnostic group compared the slope of lines in the controls to that of each diagnostic group (Figure 1). It is noteworthy that the linear trend component in a given data set may be significant even though a corresponding ANOVA (for differences between means) does not reach conventional significance. This is related to the fact that a specific trend component is tested in the trend analysis, whereas an unspecified effect involving group differences is tested by traditional ANOVA. Orthogonal trend analysis as applied here is a more powerful method than ordinary ANOVA.

The SAS statistical software package (version 8.02) was used for the data management and analysis. Statistical tests were considered significant at  $P < 0.05$  and marginally significant at  $P < 0.1$ . No adjustment for multiple testing was performed. Caution should therefore be exercised over interpretation of marginally significant models.

## RESULTS

### Correlations

Insert Table here!



Table 1 shows the correlations between the age at learning to stand without support and later school performance in motor, theoretical and all domains stratified by the four diagnostic groups.

Developmental continuities in the general (unaffected) population

In the unaffected general population without psychiatric hospital treatment (controls) the developmental gradient at age 1 was related to subsequent function at age 16 as assessed by teachers' ratings of school subjects involving motor and theoretical performance. The magnitude of this long range association was small (-0.05 for theoretical subjects to -0.09 for motor subjects), as might be expected, but highly robust statistically, as revealed by the confidence limits excluding zero values, due to the large sample size in this group which enable very precise statements to be made about even small effects.

#### Developmental continuities in the diagnostic groups

In schizophrenia (with narrow or broad definition) and all psychoses a robust correlation was observed for motor marks, with a similar pattern for theoretical and all subjects (Table 1). The strongest correlation was found between the age at learning to stand and school performance in motor subjects ( $r=-0.30$ ) among narrow DSM-III-R schizophrenia cases. The inclusion of theoretical subjects in the score for all subjects seems to dilute the association observed when only motor subjects are combined (see discussion).

The results for the cases having hospital-treated non-psychotic disorders (not shown in Table 1) were similar to those observed among controls in terms of pattern, but slightly stronger (greater in magnitude): Spearman correlations were -0.124 (-0.243 to -0.002) in the motor domain, -0.081 (-0.202 to 0.042) in the theoretical domain, and -0.090 (-0.210 to 0.032) in combined domains. However, none of these associations statistically are reliable, despite the larger sample size in this group than the two classifications of schizophrenia.

### Linear trend

When associations were examined in terms of linear trends (across the three milestone categories) only a small (but statistically robust) association existed between development at age 1 and 16 years (Table 1) in the unaffected, general population (excluding those hospitalised for non-psychotic psychiatric disorders). In the group hospitalised for non-psychotic disorder no association existed (not shown in Table 1) so linear trends were not relevant.

In narrow and broad schizophrenia and all psychoses the developmental gradient appeared to persist into the teenage years: age at learning to stand was associated significantly (Table 1) with school performance in motor subjects, theoretical subjects and overall score.

### Linear interaction

Tests for linear interaction (trend x diagnosis) were significant in the motor domain in narrow DSM-III-schizophrenia ( $p=0.037$ ), and for broad DSM-III-R schizophrenia ( $p=0.024$ ) and all psychoses ( $p=0.028$ ). This interaction (narrow schizophrenia) is shown graphically in Figure 1. There was no such interaction for non-psychotic disorders (not shown).

Interactions were statistically reliable at the 0.05 level for motor marks, but sample size and limited power meant that similar patterns of effects for theoretical and all subjects returned only marginal (trend) significance levels ( $0.05 < p < 0.14$ ). Nevertheless we remark on the consistency of the trends, not the absolute levels of the p-values alone.

Insert Figure 1 here!

#### Other developmental milestones

The analyses were repeated using age of walking without support by one year, bladder control (urination), potty training (defecation), and age of speaking. There were some sporadic correlations and linear trends linking slow development at age 1 and poor performance scores at age 16 (not shown), but they did not achieve statistical significance.

#### Effect of covariates

When boys and girls were analyzed separately, the results were essentially the same, even though school performance was better at age 16 among girls. When the analyses were repeated selecting by school type and including only those individuals in normal school (and having no mental retardation), the results were nearly identical with those in Table 1 including all cases. This was also the case when the analysis was restricted to only schoolchildren in their normal grade.

The results were also similar as in Table and Figure 1 when the sample was stratified by genetic risk and cases with known familial risk of psychoses were excluded. Spearman correlation coefficients were -0.323 (-0.513 to -0.104) (motor score), -0.247 (-0.449 to -0.021) (theoretical score, and -0.276 (-0.473 to -0.052) (all). Correspondingly, estimates of linear interactions were (F (df=1,df=9233), p-value): motor score 4.38, 0.0365; theoretical score: 3.51, 0.0612, all 4.06, 0.0438.

#### Missing data.

Data on standing, walking, potty training, day wetting or speaking were missing from the 1-year examination in 9% to 12%, and school marks in 2% of cases. There were no significant differences between diagnostic outcome groups in terms of examination age or proportions of missing data.

## DISCUSSION

The main finding was that in the unaffected general population the developmental gradient at age 1, manifest and observed in parents reports of the timing of key milestones had small but robust associations with subsequent functioning in late adolescence as assessed by teachers' ratings of performance in school for subjects involving motor coordination and general academic performance. In schizophrenia (narrowly and broadly defined) and all psychoses gross neuromotor development (age learned to stand) at about age 1 was related to subsequent performance at age 16 in

school subjects in the motor and the theoretical domain. Persistent developmental deviance appears stronger in the motor domain but also extends to theoretical, academic abilities. Regarding diagnostic specificity, linear relationships between the age of learning to stand and adolescent school performance existed both in narrow and broad schizophrenia and all psychoses. When sex, genetic or perinatal risk, or severe handicap (mainly mental retardation) were taken into account the effect persisted and these factors appear not to confound the association.

In other developmental domains (learning to walk, attainment of bladder and bowel control, speech) no consistent persistence was found. It is likely that the examination age at 1-year was too early to detect an effect.

As we have earlier reported (Isohanni et al., 1998), an excess of children destined to develop severe mental disorders were not in normal schools or grades, at least partly due to low intelligence. The criteria of marks are not necessary identical in different schools. However, when only cases in normal school were analyzed or school type and grade level were controlled in analysis of variance, the interaction between diagnosis and development persisted.

Adulthood psychoses seem to be complex in their developmental trajectory. Individual risk markers in neuromotor development are not powerful, and seem to be most detectable and persistent in schizophrenic psychoses and extensively in the motor and theoretical domain, as was demonstrated by Cannon et al, (2002).

## Methodologic discussion

The study had reasonable statistical power for our primary analyses since we were able to exploit the whole cohort. However, the rarity of functional psychoses and small effect sizes means that Type II statistical errors are possible; rejection of the null-hypothesis is not self-evident and large effects are probably worth considering even when results do not reach the threshold of statistical significance. In a population based sample, a non-significant result does not prove the null hypothesis, but it may reflect either small effect size or inadequate power (Kraemer et al., 2001).

The selection of variables to calculate a motor score school was done in an ad hoc manner based on a priori assumptions regarding those school subjects that require motor skills; factor analysis did not identify any “motor factor”, and marks for all subjects were strongly interrelated. We were not able to use any standardized neurological and psychological examinations as did Rosso et al. (2000) or Cannon et al. (2002). In contrast to earlier studies we were able to expand the observation time from age 1 to 16 years and calculate correlations between two time points.

To our knowledge, two general population studies have examined the relationship between development and school performance at younger ages. In a non-selected study population, Werner et al. (1968) indicated that the faster learners during the first year of life were superior to the others in their educational capacity at age 10 and Rantakallio et al. (1985) found out similar associations when children in the Northern Finland 1966 Birth Cohort were 14 of age.

Persistence existed between gross motor development at age 1 and general school performance at 16 although the latter does reflect many other aspects than adolescent's motor and cognitive capacity and environment; that may be one reason why the magnitude of persistence was moderate. In an ideal study, multiple repeated measures of specific neuromotor function would permit time-dependent, longitudinal analyses on the determinants of change in neuromotor areas. As far as we know this kind of study does not exist, and we must rely on data mainly collected for other purposes being more or less valid proxy markers for neuromotor development. In this study data on development at age 1 and performance at school at age 16 were collected to analyse general development. We speculate that our markers only partly reflect neuromotor development, and this may explain why the effects (correlations and trends) were not very robust.

Selection, information and recall bias were minimized by the use of a large, unselected, geographically representative, general population sample with small attrition and high rates of follow-up over three decades combined with use of record linkage; our longitudinal data are unique and extensive. The emigration of 757 cohort members and the death of 284 individuals before age 16 is unlikely to have introduced any systematic bias. Our major results involved standardized childhood data collected prospectively in a special examination near the time point that developmental milestones took place. The case finding procedures were independent of sample attrition.

Theoretical explanation



What underlying biological mechanisms could account for the observed persistence between early development and adolescent performance? Brain growth continues throughout life. It is especially active in the fetus at the age of 1-2 years, during puberty and early adulthood (Goldfield and Wolff, 2002). In infants, the motor region is one of the most myelinated and metabolically active areas of the cerebral cortex, dominated by dopamine metabolism. The feedback circuit linking the motor cortex with subcortical structures is maximally activated in early life, and an abnormality is more likely to be manifested in motor dysfunction (Walker, 1994). Neuronal circuits involving both prefrontal areas and the basal ganglia are critically implicated in movement. As higher cortical areas take over the control of the infant's equilibrium, the infant is enabled to keep its balance and to stand. These brain areas also appear to subserve cognitive-behavioural control processes needed later in many areas at school. Variations in performance of frontal-striatal circuitry could parsimoniously explain how variations in early developmental delay in the motor domain could be related to later performance on some cognitive tasks, as well as aspects of motor control; such processes are known to depend on dopamine-dependent functions of frontal-striatal loops (Haber et al., 2000; Robbins et al., 1998), as is the development of schizophrenia. This hypothesis was supported by our finding that age of achieving developmental motor milestones was associated with adolescent performance in motor but also in other, academic domains. It seems also to be that the persistence we detected is *specific* to all psychoses (although the number of non-schizophrenic psychoses was small) which seem nosologically differ from other, severe non-psychotic disorders.

A neurodevelopmental perspective of schizophrenia provides one major theoretical explanation for these early precursors of the syndrome (Weinberger, 1995). This model suggests that schizophrenia results from abnormalities in early brain development that are manifest in different ways according to the stage of brain maturation; in this context psychosis is an age-dependent manifestation. Rapid development at about age 1 may be a big challenge especially for a person with schizophrenic vulnerability. If later developmental milestones are interpreted as a marker of abnormal early brain development it may be that measurable effects are more likely during phases of critical development, such as occurs in early life for motor systems. This may explain why the persistence of developmental delay appeared limited using the mixed, proxy measures available to us.

High risk studies have indicated that early motor deviance may mark the disorder's hereditary basis. The earliest developmental research of risk markers involved the follow-up of high-risk samples, and most studies showing some persistence of risk markers are high-risk studies (Watt, 1978; Marcus et al., 1993; Erlenmeyer-Kimling et al., 2000). Our results support the hypothesis that in an unselected sample the persistence of developmental delay is independent of known genetic risk of psychoses. When we stratified by genetic risk, motor delay/impairments persisted in pre-schizophrenic subjects without known genetic risk for psychosis. This suggests that the persistence of markers of abnormal neurodevelopment in schizophrenia is not specific for persons at high familial risk. The persistent phenotypic motor deviance we found is thus not necessarily an indicator of susceptibility genes, at least such that are manifested in 1<sup>st</sup> degree relatives with psychosis. One limitation of our approach is that it is unclear

what precise biological factors our epidemiologically rather course definition of genetic risk reflects; e.g. the number of relatives is not taken into account. Familiarity is not necessarily a good proxy of genetic risk although currently there are no better alternatives for use in epidemiological research. The effect of genetic risk on the persistence of motor developmental deviances thus remains open to further investigation but our results support the hypothesis that persistent developmental deviance is not an expression of genetic risk.

To our knowledge this is the fourth study of psychosis where the persistence of risk markers is analyzed in a population sample. Crow et al. (1995) observed some continuity in academic abilities in pre-schizophrenic children at age 7, 11 and 16 years and Cannon et al. (2002) in motor and also other domains between ages 3 and 11. Rosso et al. (2000) demonstrated that deviance on motor coordination at age 7 as well as unusual movements at ages 4 and 7 predicted adult schizophrenia. This study extends some persistence from age 1 to 16 and specifies the continuity to the motor area at age 1 and also to other areas around academic skills at age 16. We could also demonstrate that the persistence is present in all psychoses; Cannon et al. (2002) linked persistent developmental impairment to schizophreniform disorder. Premorbid persistence of these minor, subclinical impairments may be independent of genetic and perinatal exposures.

In summary, the markers of adulthood schizophrenic psychoses appear to have some persistence in their developmental trajectory. Our data identify long range associations among two diverse, prospectively rated markers of vulnerability to schizophrenia that span early childhood through to the end of school age. Is it possible that delay (within

normal limits) in gross motor milestones at age 1 and poor performance at age 16 is a persistent marker of vulnerability to schizophrenia even in a population sample. These findings are in line with hypothesis that a neural diathesis is present during postnatal brain development in the epigenesis of schizophrenia, and also support the longitudinal dimension and life span models of schizophrenia (Isohanni et al., 2000b; Cannon et al., 2003). This early diathesis is subtle, confined to selected domains, and does not lend itself for use in predictive or early intervention purposes. However, in future it may be possible to develop more specific methods than developmental speed at age 1 and performance at school at 16 for identifying persistent deviation as a marker of risk for schizophrenia.

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## Figure legends

Figure 1. Motor performance at the age 16 (mean motor score) in DSM-III-R schizophrenia and persons without hospital treated psychiatric disorder until the age of 34 years in the Northern Finland 1966 Birth Cohort in different categories by age learned to stand without support at the age 1. Test for linear interaction ( $P=0.037$ ) indicates that linear trend across the level of standing without support differs between DSM-III-R schizophrenia cases and those who have not been hospitalised due to psychiatric disorder.

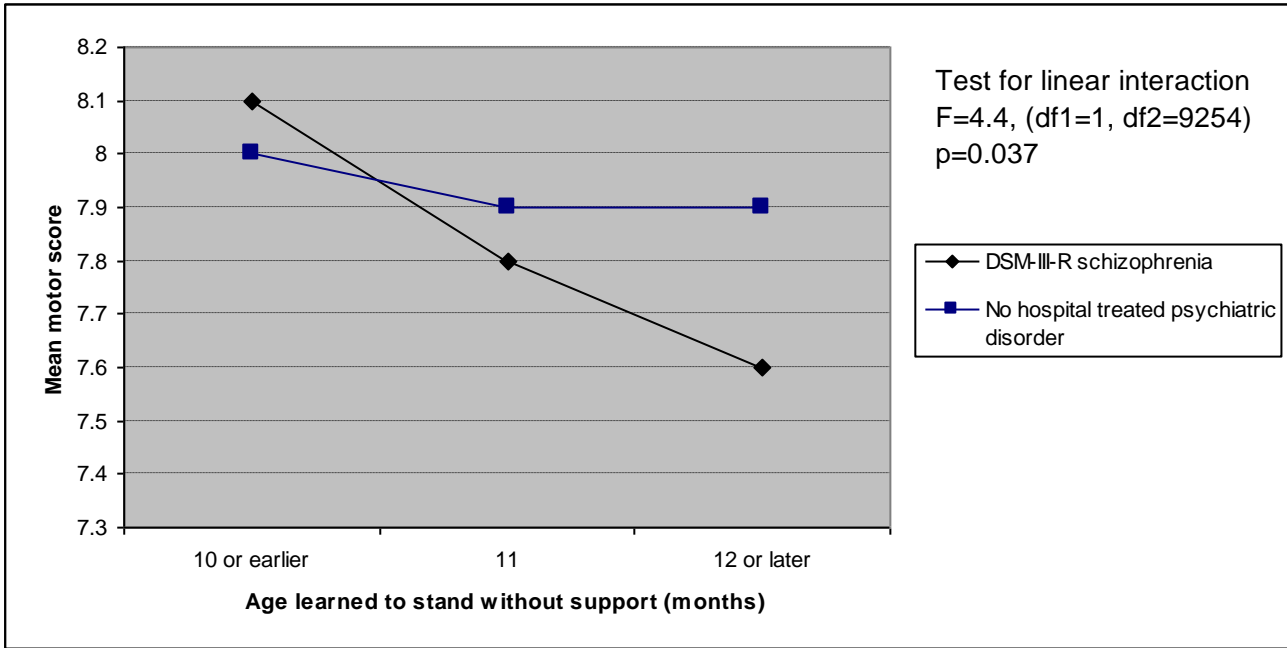


Table 1. The relation between motor development at the age 1 (standing without support) and educational performance at the age 16 assessed using mean scores (motor, theoretical and all subjects) of school subjects.

Diagnosis	Standing without support at age 1		School performance at age 16			Analysis		
	Age at learning	N	Motor <sup>1</sup> mean (sd)	Theoretical <sup>2</sup> mean (sd)	All <sup>3</sup> mean (sd)	Spearman correlations (95% CI)	p-value for linear trend <sup>4</sup>	Test for interaction <sup>5</sup> F, (df1,df2), p-value
All psychoses	before 10	26	8.1 (0.7)	7.7 (1.1)	7.8 (1.0)	<sup>1</sup> -0.30 (-0.47 to -0.10)	<sup>1</sup> 0.006	<sup>1</sup> 4.4, (1,9254) 0.037
	11 months	27	7.8 (0.8)	7.3 (1.2)	7.4 (1.0)	<sup>2</sup> -0.22 (-0.40 to -0.02)	<sup>2</sup> 0.017	<sup>2</sup> 3.3, (1,9254) 0.071
	12 or later	47	7.6 (0.7)	7.1 (1.1)	7.2 (0.9)	<sup>3</sup> -0.25 (-0.43 to -0.05)	<sup>3</sup> 0.010	<sup>3</sup> 4.1, (1,9254) 0.044
	All	100	7.8 (0.7)	7.3 (1.2)	7.4 (1.0)			
	before 10	33	8.2 (0.7)	7.6 (1.1)	7.8 (0.9)	<sup>1</sup> -0.27 (-0.43 to -0.09)	<sup>1</sup> 0.009	<sup>1</sup> 5.1, (1,9274) 0.024
	11 months	33	7.7 (0.8)	7.2 (1.2)	7.3 (1.0)	<sup>2</sup> -0.17 (-0.34 to -0.01)	<sup>2</sup> 0.034	<sup>2</sup> 2.2, (1,9274) 0.138
	12 or later	54	7.6 (0.7)	7.1 (1.1)	7.3 (0.9)	<sup>3</sup> -0.21 (-0.37 to -0.02)	<sup>3</sup> 0.019	<sup>3</sup> 3.2, (1,9274) 0.075
	All	120	7.8 (0.7)	7.3 (1.1)	7.4 (1.0)			
	before 10	41	8.1 (0.7)	7.6 (1.1)	7.7 (0.9)	<sup>1</sup> -0.26 (-0.41 to -0.10)	<sup>1</sup> 0.009	<sup>1</sup> 4.9, (1,9293) 0.028
	11 months	36	7.7 (0.8)	7.3 (1.2)	7.4 (1.0)	<sup>2</sup> -0.19 (-0.35 to -0.02)	<sup>2</sup> 0.033	<sup>2</sup> 3.2, (1,9293) 0.072
	12 or later	62	7.6 (0.7)	7.1 (1.1)	7.2 (0.9)	<sup>3</sup> -0.23 (-0.38 to -0.06)	<sup>3</sup> 0.017	<sup>3</sup> 3.7, (1,9293) 0.042
	All	139	7.8 (0.7)	7.3 (1.1)	7.4 (1.0)			
	before 10	4082	8.0 (0.7)	7.5 (1.1)	7.6 (0.9)	<sup>1</sup> -0.09 (-0.11 to -0.07)	<sup>1</sup> <0.001	
	11 months	2421	7.9 (0.7)	7.4 (1.1)	7.5 (1.0)	<sup>2</sup> -0.05 (-0.07 to -0.03)	<sup>2</sup> 0.003	
	12 or later	2848	7.9 (0.7)	7.3 (1.1)	7.5 (0.9)	<sup>3</sup> -0.06 (-0.08 to -0.04)	<sup>3</sup> <0.001	
	All	9351	8.0 (0.7)	7.4 (1.1)	7.5 (0.9)			

<sup>1</sup>) motor score (physical education, music, drawing, craft; woodwork/knitting).

<sup>2</sup>) theoretical score (native language; reading/literal, second, third, fourth and fifth language; mathematics; chemistry; physics; history; biology; geography; religion and civics).

<sup>3</sup>) mean of all school subjects (motor and theoretical scores).

<sup>4</sup>) Analysis of variance; controlled for sex, perinatal risk, and school type and grade level at the age 14.

<sup>5</sup>) Analysis of variance; linear interaction (trend x diagnosis). Each diagnostic category is contrasted to the category no psychiatric hospital treatment.