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Altered growth trajectory of head circumference during infancy and schizophrenia in a National Birth Cohort

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ABSTRACT

Identification of abnormalities in the developmental trajectory during infancy of future schizophrenia cases offers the potential to reveal pathogenic mechanisms of this disorder. Previous studies of head circumference in pre-schizophrenia were limited to measures at birth. The use of growth acceleration of head circumference (defined as the rate of change in head circumference) provides a more informative representation of the maturational landscape of this measure compared to studies based on static head circumference measures. To date, however, no study has examined whether HC growth acceleration differs between pre-schizophrenia cases and controls. In the present study, we employed a nested case control design of a national birth cohort in Finland. Cases with schizophrenia or schizoaffective disorder (N = 375) and controls (N = 375) drawn from the birth cohort were matched 1:1 on date of birth (within 1 month), sex, and residence in Finland at case diagnosis. Longitudinal data were obtained on head circumference from birth through age 1. Data were analyzed using a new nonparametric Bayesian inversion method which allows for a detailed understanding of growth dynamics. Adjusting for growth velocity of height and weight, and gestational age, there was significantly accelerated growth of head circumference in females with schizophrenia from birth to 2 months; the findings remained significant following Bonferroni correction ($p < 0.0125$). This is the first study to report abnormal HC growth acceleration, a more sensitive measure of somatic developmental deviation of this measure, in schizophrenia.

1. Introduction

Abnormalities in the trajectory of early development during infancy and childhood among individuals who later develop schizophrenia, compared to controls, have supported the neurodevelopmental hypothesis of this disorder (Cannon et al., 1997; Isohanni et al., 2004; Jones et al., 1994; Walker et al., 1994). To date, there is evidence that head circumference (HC) at birth is abnormal in pre-schizophrenia. Small HC was related to an increased risk of later schizophrenia, independent of other factors (Cantor-Graae et al., 1998; Hultman et al., 1997) though other studies found no association, or relationships that were restricted to females (Wahlbeck et al., 2001; Welham et al., 2009). However, in contrast to other indices of development which delineate trajectories, including developmental milestones, neurocognition, and behavior prior to schizophrenia onset (Cannon et al., 1997; Isohanni et al., 2004; Keskinen et al., 2015; Khandaker et al., 2011), the pattern of HC growth among pre-schizophrenia cases following birth has not been well investigated because those studies utilized measures of HC that were isolated to birth. Growth trajectory of HC can more optimally be studied by examining growth velocity, which is defined as the rate of change in HC per unit change in time. The assessment of growth velocity of HC after birth, using frequent, longitudinal measures and a statistical approach developed specifically to calculate growth velocity, provides essential information on cumulative development, thereby addressing the question of whether there are somatic deviations of the growth trajectory of this measure during childhood among individuals who later develop schizophrenia.

We addressed these questions using a powerful new nonparametric Bayesian inversion method for reconstructing growth velocity curves from sparse temporal data (Lopez-Pintado and McKeague, 2013; McKeague et al., 2011). In particular, this approach allows for a detailed

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understanding of growth patterns, taking into account large fluctuations in growth velocity and high between-subject variability.

We applied this method to examine the relationship between growth velocity of HC in pre-schizophrenia cases and controls in a national birth cohort investigation, the Finnish Prenatal Study of Schizophrenia (FiPS-S). We hypothesized that there would be deviations of HC growth velocity during infancy in pre-schizophrenia cases compared to controls.

2. Methods

The Finnish Prenatal Study of Schizophrenia (FiPS-S) is based on a nested case-control design. All offspring were derived from the Finnish Maternity Cohort (FMC), consisting of virtually all pregnancies in Finland beginning in 1983 (total sample size is over 1 million). The computerized nationwide Finnish Population Registry was created in 1971. The registry includes comprehensive data on place of birth, place of residence, and biological parents, including their birth dates. The Finnish Hospital and Outpatient Discharge Registry (FHDR) was used to identify all diagnoses for psychiatric hospital admissions and outpatient treatment visits. The FHDR computerized data are available from 1969 to the present.

The sample of the FiPS-S consisted of all offspring born in Finland from 1983 to 1998, and subjects were followed up until 2009 (see "Case and control identification"). While these birth and follow-up years led to potential inclusion of some relatively young onset cases, childhood/adolescent onset schizophrenia, though rare, has been well described (Rapoport and Gogtay, 2011). To identify the cases, we conducted a registry linkage between the FMC and the FHDR, using personal identification numbers. Cases were defined as having schizophrenia (ICD-10 F20) or schizoaffective disorder (ICD-10 F25) (heretofore, these cases are referred to as "schizophrenia"). This protocol led to the identification of 1514 cases of schizophrenia or schizoaffective disorder (N = 1226 with schizophrenia, 288 with schizoaffective disorder). The age at first treatment was recorded by the first contact for a schizophrenia diagnosis by a psychiatric facility. In a prior study, the validity of schizophrenia diagnoses according to the FHDR was excellent: 93% of subjects with a diagnosis of schizophrenia in the FHDR were assigned a consensus diagnosis of schizophrenia following interview (Mäkikyrö et al., 1998).

The schizophrenia cases in the FiPS-S were matched 1:2 to controls (N = 3028) drawn from the birth cohort who were without schizophrenia, other nonaffective psychotic disorders, and bipolar disorder, by date of birth (within 1 month), sex, and residence in Finland at the time of case diagnosis.

The study was approved by the ethical committees of the hospital district of Southwest Finland, the National Institute for Health and Welfare, and the Institutional Review Board of the New York State Psychiatric Institute.

2.1. Collection of data on head circumference, height, and weight from well baby health clinics

Parents in Finland have their children evaluated with nationally standardized developmental assessments at well baby centers throughout the country at age 1 month and every 1–2 months until 15 months (Ministry of Social Affairs and Health, 2009). Physicians and registered nurses complete a nationally standardized form, including HC, height, and weight measurements at every visit. The examinations are conducted on 99% of all children in Finland. Archived longitudinal data were abstracted manually in record rooms from the well baby centers by public health or research nurses highly trained and experienced in data acquisition. At least one HC measurement was obtained on 2127 subjects (1066 cases and 1061 controls).

2.2. Measures

The primary measure was growth velocity of HC at *a priori* selected time points during the first year of life. The analyses were limited to the first year of life because insufficient HC measurements were available beyond that age (see "Statistical analysis" for criteria of subject selection based on availability of HC measurements).

2.3. Covariates

Covariates, representing potential confounders, consisted of height growth velocity, weight growth velocity, maternal age, paternal age, gestational age at time of birth, maternal education, province of birth, degree of urbanization at birth, and maternal and parental history of schizophrenia spectrum disorders and any psychiatric disorder

Table 1
Demographic characteristics in relation to schizophrenia case-control status.

	Cases (N = 375) Mean (SD)	Controls (N = 375) Mean (SD)	t	p-Value
Gestational age (weeks)[a]	39.4 (1.7)	39.4 (1.5)	0.1	0.92
	N (%)	N (%)	χ^2	p-Value
Sex			N/A	N/A
Females	165 (44)	165 (44)		
Males	210 (56)	210 (56)		
Maternal age (years)			3.6	0.61
19 or less	16 (4.3)	12 (3.2)		
20–24	74 (19.7)	70 (18.7)		
25–29	130 (34.7)	138 (36.8)		
30–34	97 (25.9)	108 (28.8)		
35–39	48 (12.8)	42 (11.2)		
40 or more	10 (2.7)	5 (1.3)		
Paternal age (years)[b]			–	1.00
19 or less	4 (1.1)	4 (1.1)		
20–24	40 (10.8)	44 (11.9)		
25–29	120 (32.5)	122 (32.9)		
30–34	109 (29.5)	105 (28.3)		
35–39	64 (17.3)	65 (17.5)		
40–49	31 (8.4)	29 (7.8)		
50 or more	1 (0.3)	2 (0.5)		
Province of birth			4.2	0.24
Eastern Finland	44 (11.7)	42 (11.2)		
Northern Finland	49 (13.1)	61 (16.3)		
Southern Finland	185 (49.3)	160 (42.7)		
Western Finland	97 (25.9)	112 (29.9)		
Degree of urbanization			2.7	0.26
Rural	83 (22.1)	95 (25.3)		
Semi-Urban	37 (9.9)	46 (12.3)		
Urban	255 (68)	234 (62.4)		
Maternal education[c]			2.2	0.53
Secondary school	92 (24.7)	81 (21.7)		
High-school	218 (58.4)	230 (61.7)		
College/bachelor degree	40 (10.7)	45 (12.1)		
Master/doctoral degree	23 (6.2)	17 (4.6)		
Maternal SSD[d]	42 (11.2)	8 (2.1)	23.3	< 0.001
Maternal any psychiatric disorder[e]	116 (30.9)	57 (15.2)	25.3	< 0.001
Parental SSD[d]	63 (16.8)	11 (2.9)	39.0	< 0.001
Parental any psychiatric disorder[e]	178 (47.5)	92 (24.5)	41.8	< 0.001

Abbreviations: SSD, schizophrenia spectrum disorder.

[a] Missing data for 63 cases and 45 controls.

[b] Missing data for 6 cases and 4 controls.

[c] Missing data for 2 cases and 2 controls.

[d] ICD-10 codes F20–25, F28–29, ICD-9 codes 295, 297, 298.9X, 301.2C, and ICD-8 codes 295, 297, 298.20, 298.30, 298.99, 299.

[e] In addition to the above this includes ICD-10 codes F10–19, F30–34, F38–39, F40–45, F48, F50–53, F55, F59–66, F68–69, F84, F99, ICD-9 codes 296, 298.8A, 299, 300–301.1, 301.2 excluding 301.2C, 301.3–301.9, 302, 307.1A, 307.4A, 307.4F, 307.4H, 307.5A, B, C & E, 307.8A, 307.9X, 309–309.1, 309.2 excluding A&B, 309.2D, E & F, 309.3–309.9 excluding 309.3A & 309.4A, 312.0A, 312.1–312.2, 312.3 excluding 312.3D, 312.4–312.9, 291–292, 303–305, and ICD-8 codes 291, 296, 298.00, 298.10, 303–304, 300.0–302.9, 305, 306.40, 306.50, 306.98, 307.99, and 308.

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