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Early Intermodal Integration in Offspring of Parents With Psychosis

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Identifying early developmental indicators of risk for schizophrenia is important for prediction and possibly illness prevention. Disturbed intermodality has been proposed as one important neurodevelopmental risk for schizophrenia. Early intermodal integration (EII) is the infant's ability to link motility and perception and to relate perception across modalities. We hypothesized that infants of parents with schizophrenia would have more EII abnormalities than infants of healthy parents and that infants of parents with affective psychosis would be intermediate in severity. The New England Family Study high-risk sample, ascertained from community populations, was utilized. Eight-month-old infants of parents with schizophrenia (*n* = 58), affective psychoses (*n* = 128), and healthy controls (*n* = 174) were prospectively assessed. Diagnoses of parents were determined 30 years later blind to offspring data. EII measures were grouped into 3 domains characterizing different aspects of infant development: (1) one's own body, (2) objects, and (3) social interactions. Results demonstrated that body- and object-related EII abnormalities were significantly increased for infants of parents with schizophrenia compared with control infants and not significantly increased for infants of parents with affective psychoses. EII abnormalities in relation to social interactions were significantly increased in infants of parents with schizophrenia and affective psychoses. Thus, body- and object-related EII abnormalities were most severe in infants of parents with schizophrenia, supporting the importance of intermodality dysfunction as an early indicator of the vulnerability to schizophrenia. Future research should evaluate how this dysfunction evolves with development and its associations with other psychopathological and neurodevelopmental deficits in youth at risk for psychosis.

Key words: schizophrenia/high-risk study/developmental psychology

Introduction

Many studies, beginning with Barbara Fish's pioneering work in the 1950s, have shown that offspring of parents with schizophrenia manifest a range of developmental abnormalities beginning in early childhood.[1] These include deficits in social, cognitive, neurological, and brain measures, all supporting a neurodevelopmental basis for schizophrenia.[2,3] In recent years, there has been an increased focus on disturbances of the self in understanding the nature of the psychopathology of schizophrenia. A key question is when do such psychological disturbances begin?[4] The hypothesis of disturbed intermodality was originally proposed by Parnas and colleagues[5] as a neurodevelopmental feature that may be relevant to the self-disorders, emerging in individuals who develop schizophrenia. To our knowledge, this interesting hypothesis has not been tested in young children at risk for schizophrenia. If found in youth prior to schizophrenia, these phenomena can clearly be separated from later confounds such as medications or symptoms and can be attributed to altered early development. Moreover, it would be important to know if the intermodality impairment is a characteristic of vulnerability to psychosis in general or if it is associated with schizophrenia risk per se.

Early intermodal integration (EII) is the infant's ability to link motility and perception and to relate perception across modalities—eg, vision, touch, audition, and proprioception. Intermodal integration occurs from birth on: Infants combine perception and action, eg, when they

explore their body, orient to sounds, and mouth or reach for objects. According to Rochat,[6] an infant's psychological world can be best understood when considered in relation to the self, objects, and people. Therefore, we examined EII in relation to these 3 domains. Although they interact with each other, these domains correspond to different psychological experiences, allowing infants to develop specific skills.

Empirical studies demonstrate that the *development of the self* occurs from birth through multimodal perception and action. The correspondence of visual, tactile, proprioceptive perception, and action allows infants to recognize themselves and distinguish themselves from others.[6,7] For example, when infants open and close their hand, they can simultaneously see and feel the movement of their hand. They tend to explore themselves when placed in front of mirrors, observing their own movements and enjoying the experience of visual-proprioceptive contingency. Infants are capable of self-other discrimination at 4 months.[8,9] Self-awareness is expressed in perception and action and remains implicit until the middle of the second year, when the child develops language and symbolic competencies.[10,11]

EII in relation to an object is linked to the *development of motor functions*. Empirical studies show that following predominantly oral exploration of objects by 2 months, infants develop around 4 months a complex combination of manual, oral, and visual inspection along with systematic eye-hand coordination and reaching behavior.[6,12] The developing eye-hand coordination allows the infant at around 5 months of age to make use of the instrumental and perceptual functioning of the hands.

Rochat[13] describes that early facial imitation might play an important role in the *development of intersubjectivity*, defined as the sense of shared experience that emerges from reciprocity. The sense of shared experience determines the development of social cognition in infancy, which allows individuals to understand, control, and predict the behavior of others. Studies have shown that the early imitative ability of young infants (eg, imitation of tongue protrusion and head and finger movements) is the result of an active intermodal matching between vision and proprioception.[14–17]

Thus, EII is at the basis of the development of the self and complex mental and motor abilities (eg, cognitive, affective, and social abilities) later in life. Based on a growing psychopathology literature, these complex functions are typically disturbed in patients with schizophrenia.[3] The theoretical relationship between intermodal integration and schizophrenia is reflected in the idea that the failure to develop normal EII persists as a trait in the developmental trajectory preceding schizophrenia and may be manifest in the earliest developmental phases of life well before self-disorders are observed in psychosis.

To our knowledge, there is no empirical published study that determines whether EII abnormalities are an indicator of the vulnerability for schizophrenia. First, we will determine if EII abnormalities occur more frequently in offspring of parents with schizophrenia than in offspring of comparison subjects. If they are only found in offspring of persons with schizophrenia vs affective psychosis, we would consider them specific. However, this cannot be predicted a priori as many abnormalities are found in the histories of offspring of both disorders.[18] Importantly, observing EII abnormalities in infancy clearly points to an early developmental origin that is distinguishable from prodromal signs of psychosis, supporting the neurodevelopmental origins of the disorders.[5]

The primary aim of this study was to determine whether EII abnormalities are indicators of the familial vulnerability for schizophrenia by studying young children of parents with schizophrenia enrolled in the New England Family Study (NEFS), a high-risk (HR) study. The HR research method consists of studying enriched samples of individuals with an increased risk of developing a disorder because they have a first-degree, biological relative with the disorder, most commonly a parent.[19] We hypothesized that infants of parents with schizophrenia would have more EII abnormalities than infants of healthy parents and that these abnormalities would be more frequent in infants of parents with schizophrenia compared with infants of parents with affective psychoses.

Methods

Study Population

The Collaborative Perinatal Project Sample. Participants were selected from the Providence and Boston cohorts of the Collaborative Perinatal Project (CPP),[20] also known as the New England Family Study. The NEFS consisted of 17 741 pregnant women (first generation, Generation-1) recruited between 1959 and 1966 at university-affiliated medical centers in Boston and Providence (Harvard Medical School and Brown University). Extensive data on gestation, labor, and delivery were collected. Children (second generation, Generation-2) underwent repeated medical, neurological, and psychological examinations at birth; 4 and 8 months; and 1, 4, and 7 years of age. The psychological investigation conducted at the 8-month visit was used to assess EII. Follow-up rates for survivors were 88% at 1 year of age and 79% at 7 years. The characteristics of the offspring and their parents enrolled in the NEFS are summarized in table 1.

HR Follow-up Study. The details of Generation-1 ascertainment and diagnoses have been described.[21,22] A total of 859 parents with a history of psychiatric treatment and/or hospitalization were identified by maternal report at enrollment during pregnancy in the original CPP and by subsequent record linkage efforts with public psychiatric facilities between 1994 and 2002. Of these parents, 755 were eligible for follow-up and

Table 1. Items of the Bayley Scales in 3 Categories for Early Intermodal Integration

Intermodal Integration in Relation to	
One's own body	• Fingers hand in play; inspects own hands; approaches mirror image; responds playfully to mirror
An object	• Eyes follow pencil; regards cube/pellet; glances from one object to another; follows a vanishing ring/spoon; eyes follow ball across table; sustains inspection of ring
	• Manipulates ring; reaches for ring/cube; carries ring to mouth; closes on dangling ring; retains cube briefly[a]; picks up cube; retains 2 cubes; exploitive paper play; recovers rattle in crib; reaches persistently; lifts cup; reaches for second cube; transfers object from hand to hand; plays with string; pulls string and secures ring; lifts up cup by handle; manipulates the bell with interest in details; attempts to secure 3 cubes; brings 2 objects together[a]; unilateral reaching[a]; secures pellet (rake/ pincer/ neat pincer)[a]; fingers holes in pegboard; puts cube in cup
	• Searches with eyes for sound; plays with rattle; turns head to sound of bell/rattle; enjoys sound production; rings bell imitatively
Social interactions	• Social smiles; visually recognizes mom; vocalizes to social stimulus; reacts to disappearance of face; responds to social play; responds to name/nickname; adjusts to words

[a]Items are from the Bayley motor scale; all other items are from the mental scale.

had at least one Generation-2 offspring assessed after 4 months of age. These parents were located through a variety of methods and invited to participate in a 2-stage screening and diagnostic interview. During stage 1, psychiatric symptoms were assessed using the Quick Diagnostic Interview Schedule[23] to screen for Axis I disorders. The second interview used the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV: SCID)[24] conducted by trained MA-level clinical interviewers and yielded Axis I diagnoses of any form of psychotic, major affective, bipolar, or substance use disorders. Expert diagnosticians reviewed all of the information collected from both interviews and medical records, if available, to determine final best estimate diagnoses (see Goldstein and colleagues).[21] Of the 755 Generation-1 parents, 212 parents (153 mothers and 59 fathers) were identified with DSM-IV psychotic disorders (116 parents with affective and 96 with schizophrenic psychoses).

This approach to grouping of the nonaffective and affective psychoses is based on numerous studies in the literature on the transmission of schizophrenia and affective psychoses.[25–28] Parents with schizophrenia, schizoaffective disorder of depressed type, delusional disorder, brief psychosis, schizophreniform disorder, and psychosis not otherwise specified were classified into one group (schizophrenia psychotic spectrum disorders, or so-called nonaffective psychoses), and parents with schizoaffective disorder of bipolar type, bipolar disorders with psychosis, and major depressive disorder (MDD) with psychosis were classified into a second group (affective psychoses). Parents with a history of psychotic diagnoses that were brief compared with other psychiatric disorders (eg, MDD or substance disorders) were also categorized as a psychotic diagnosis. We have used this categorization in a number of other publications with our NEFS cohort[18,21,22,29] and thus validity of this classification remains consistent with previous work.

Control parents were selected to be comparable with parents with psychotic disorders based on the parent's age, ethnicity, study site, number of offspring enrolled in the National Collaborative Perinatal Project, and patient status (public or private) and on the offspring's age, sex, and history of chronic hypoxia.[21] Eligible control parents included all surviving Generation-1 parents other than the $n = 859$ with a history of psychiatric treatment and/or hospitalization. A sample of 308 potential control parents was identified, relocated, and interviewed with the SCID. Of these, 132 (119 mothers and 13 fathers) were included in the final control group. Exclusion criteria included (1) Axis I psychotic disorder, bipolar disorder, or recurrent major depression (with and without psychosis); (2) Axis II, Cluster A personality disorders; (3) first-degree relative with a history of psychosis, mania, or suicide; (4) genetic disorder with known neurobiological deficits in offspring or parent (eg, Huntington's disease).

Generation-2 Sample. The sample of 212 psychotic and 132 nonpsychotic parents had a total of 467 pregnancies: 167 offspring among parents with affective psychosis, 114 offspring among parents with nonaffective psychosis, and 186 offspring among nonpsychotic parents. Of note, among the 344 final Generation-1 parents, there were 4 "two parent families," in which both parents were diagnosed with some form of psychosis, resulting in a sample size of 340 unduplicated families.

Assessment of EII

We assessed EII abnormalities in the following 3 domains, which describe best the infant development according to Rochat[6]: intermodal experience in relation to (1) one's own body, (2) objects, and (3) social interactions. We chose 54 items from the Bayley scales of mental and motor development that typically assess EII and assigned the selected items to one of the 3 EII domains.

The categories with the corresponding items are listed in table 1. The 4 items in the category "EII in relation to one's own body" measure awareness and exploration of the body and require visual/tactile-proprioceptive correspondence. The 43 items measuring object-oriented EII require eye tracking, visually directed reaching and mouth/eye-hand coordination. The 7 items measuring social response and intersubjectivity involve imitative processes (eg, intermodal matching between vision and proprioception) and affective attunement to others.

The 1960 edition of the Bayley scales[30] was assessed at age 8 months in infants enrolled in the NEFS. Children were tested with 64 items of the mental and 31 items of the motor scale covering the age range 2 months through 11 months. All items were scored pass/fail. The Bayley scales were administered by trained clinical psychologists who had no information on the child's HR status. Data quality was enhanced through systematic training, interrater reliability measures, and monitoring. The psychometric properties of the 1960 edition were tested in 8-month-old infants enrolled in the CPP and yielded good tester-observer and test-retest reliability of the Mental and the Motor Scale (tester-observer reliability: Mental Scale, 0.89 and Motor Scale, 0.93; test-retest reliability: Mental and Motor Scale, 0.75).[31]

Data Analyses

The internal consistency of the items within each of the 3 EII categories was assessed: Cronbach's alphas were .75, .95, and .77, respectively, for body-, object-, and people-oriented EII. An average score was calculated by dividing the number of failed items by the total number of nonmissing items in each EII category and for all items of 3 categories together.

Relationship Between HR Status and Intermodal Integration in Infancy

The relationship between HR status and the intermodal integration scores was assessed using generalized linear models (GLM), accounting for intrafamilial correlation. The distribution of the variable measuring object-oriented EII was skewed to the right. Given that the main conclusions of the analyses with the log-transformed and the untransformed variable were the same, we presented the untransformed results with the advantage of simple interpretation. The normality assumption held for the variable measuring EII in relation to social interactions and for the variable including all EII items. However, we could not assume a normal distribution for the variable measuring body-oriented EII because most of the infants scored zero. Accordingly, this variable was dichotomized in a group of infants scoring zero failed items (93%) and a group of infants with at least one failed item (7%).

The relationship of HR status to the continuous mean score of either social or object-oriented EII was assessed

using linear mixed models (SAS PROC MIXED).[32] The association was summarized in terms of the mean difference and its SE. Logistic regression models (generalized estimating equation approach; SAS PROC GENMOD) were used to estimate the OR and its 95% CI for the association between HR status and the dichotomous variable measuring body-related EII.

We controlled for prematurity by including in the model a variable adding the number of weeks of gestation to age at the 8-month visit. The following potential confounders were examined: ethnicity (Caucasian vs non-Caucasian), child's gender and age at assessment (<8.5, ≥8.5 months), mother's age at birth (<20, 20–34, ≥35), ill parent's gender, study site (Boston vs Providence), birth year (continuous), and family socioeconomic status. Besides the child's age and gender, the final model included confounding covariates that changed the estimate of the association between the exposure and outcome by at least 10%.

Results

Relationship Between HR Status and Intermodal Integration in Infancy

The relationship between HR status and EII was assessed in the offspring included in the HR sample. Table 2 summarizes their characteristics. Compared with the univariate analyses, adjusting for covariates tended to increase the association between HR status and EII abnormalities. All multivariate analyses were adjusted for age and gender of the offspring. Some analyses were also adjusted for the confounding variables mother's age, race, birth year, and the ill parent's gender.

Table 3 presents the results from GLMs testing the association between HR status (group at risk for schizophrenia, nonaffective psychoses, affective psychoses vs control group) and the 3 EII categories. When measuring object-related EII abnormalities, the difference in the mean score of failed items was .039 (beta-estimate; *P* value = .006). On average, the EII mean score of infants whose parents had schizophrenia was 36% higher than the mean score of the control infants when keeping all other covariates constant (see figure 1). Regarding EII abnormalities in relation to social interactions, the estimate of the mean difference was .044 (*P* value = .03) in the offspring of parents with schizophrenia and .033 (*P* value = .04) in the offspring of parents with affective psychoses compared with the control offspring. Thus, the mean score of infants whose parents had schizophrenia was 27% higher than the one of the control infants, and the mean score of infants whose parents had affective psychoses was 21% higher than the one of the control infants when keeping all other covariates constant (see figure 1). Infants of parents with schizophrenia were 3 times more likely than control infants to be in the group of infants who failed at least 1 item measuring body-related EII (*P* value = .04; see figure 2). The results of the

Table 2. Characteristics of the New England Family Study (NEFS) and the High-Risk Sample by Parental Diagnostic Group (Includes Only Offspring Who Contributed to the Analyses)

| | | High-Risk Sample | | | |
| | NEFS (n = 13 323)[a] | Schizophrenia (n = 58) | Nonaffective Psychoses[b] (n = 97) | Affective Psychoses[c] (n = 128) | Control Subjects (n = 174) |
Characteristics					
Male (%)	51	59	56	49	50
Ethnicity (%), Caucasian[d]	86	90	87	92	91
Family socioeconomic status, mean (SD)	5.8 (2.0)	5.6 (1.9)	5.5 (1.9)	5.6 (2.1)	5.7 (2.0)
Boston site (%)	78	76	74	76	76
Mother's age at birth (%)					
<20	16	12	10	9	5
20–34	75	66	74	80	79
≥35	9	22	16	11	16
Offspring of an ill mother (%)	—	67	66	77	—[e]
Offspring per family (%)					
1	7580 (75.0)	42 (85.7)	70 (85.3)	71 (72.4)	90 (72.6)
2	1936 (19.2)	5 (10.2)	9 (11.0)	22 (22.5)	22 (17.7)
3	489 (4.8)	2 (4.1)	3 (3.7)	5 (5.1)	9 (7.3)
4+	97 (1.0)	—	—	—	3 (2.4)

[a]Out of the 17 921 offsprings included in the NEFS, 4598 (25.7%) did not undergo the 8-month examination.
[b]Includes the offspring of parents with schizophrenia (n = 58), schizoaffective disorder depressed type (n = 13), psychosis not otherwise specified (n = 22), and delusional disorder (n = 4).
[c]Includes the offspring of parents with bipolar disorder with psychosis (n = 55), major depressive disorder with psychosis (n = 63), and schizoaffective disorder bipolar type (n = 10).
[d]The other ethnic group was African American, Puerto Rican, Oriental, and other.
[e]Offspring of healthy mothers: 91%.

Table 3. Main Effects of Different High-Risk Groups on Object-Oriented, People-Oriented, Body-Oriented Early Intermodal Integration (EII)

| | | Group at Risk for a Specific Type of Psychosis vs Control Group | | | | | | | |
| | | Schizophrenia | | Nonaffective Psychoses[a] | | Nonaffective Psychoses[b] | | Affective Psychoses[c] | |
		Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
Object-oriented EII	Beta	**.031**	**.039**	**.025**	**.032**	.017	.023	.003	.006
	SE	**0.014**	**0.014**	**0.011**	**0.012**	0.016	0.012	0.011	0.011
	P value	**.02**	**.006**	**.03**	**.008**	.29	.16	.81	.57
People-oriented EII	Beta	.038	**.044**	.021	.032	−.003	.011	**.032**	**.033**
	SE	0.020	**0.020**	0.017	0.017	0.023	0.023	**0.016**	**0.016**
	P value	.06	**.03**	.20	.06	.90	.62	**.04**	**.04**
Body-oriented EII	OR	**2.9**	**3.0**	2.4	2.4	1.5	1.8	1.2	1.3
	95% CI	**1.0–8.0**	**1.1–8.6**	0.9–5.9	1.0–6.2	0.4–5.6	0.5–6.5	0.5–3.2	0.5–3.3
	P value	**.04**	**.04**	.07	.06	.51	.36	.65	.61

Note: Analyses were adjusted for the child's age and gender, for the ill parent's gender for the variables mother's age birth year and race. Values in bold are statistically significant.
[a]Includes offspring of parents with schizophrenia, schizoaffective disorder depressed type, psychosis not otherwise specified, and delusional disorder.
[b]Includes offspring of parents with schizoaffective disorder depressed type, psychosis not otherwise specified, and delusional disorder.
[c]Includes offspring of parents with bipolar disorder with psychosis, major depressive disorder with psychosis, and schizoaffective disorder bipolar type.

analysis combining all items of the 3 EII categories were more highly significant but similar to the results of the analysis for the different categories of EII abnormalities.

To summarize, body-related and object-related EII abnormalities were significantly increased in offspring of parents with schizophrenia compared with control offspring, whereas there was no evidence of a significant association between offspring of parents with affective psychoses and control offspring. Moreover, in the analysis of nonaffective psychoses (including schizophrenia,
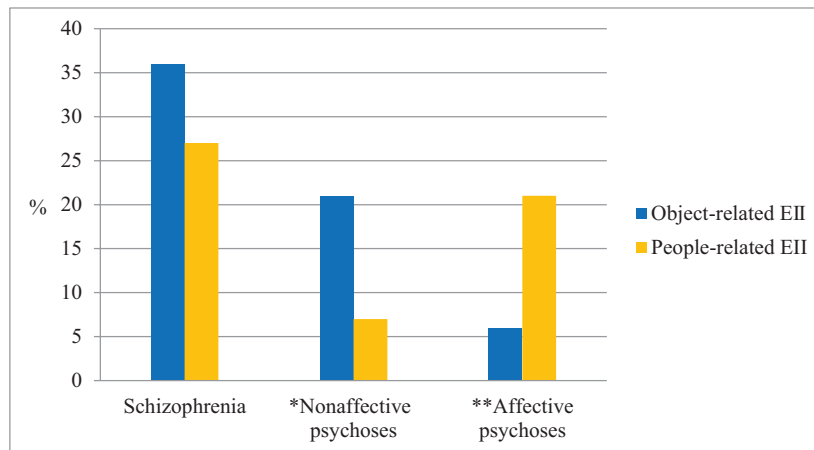
Fig. 1. Percentage increase of the object- and people-related early intermodal integration (EII) mean score in different high-risk groups compared with the control group. All analyses were adjusted for the child's age and gender, birth year, and race and for the ill parent's gender and the mother's age. *Includes offspring of parents with schizoaffective disorder depressed type, psychosis not otherwise specified, and delusional disorder. **Includes offspring of parents with bipolar disorder with psychosis, major depressive disorder with psychosis, and schizoaffective disorder bipolar type.
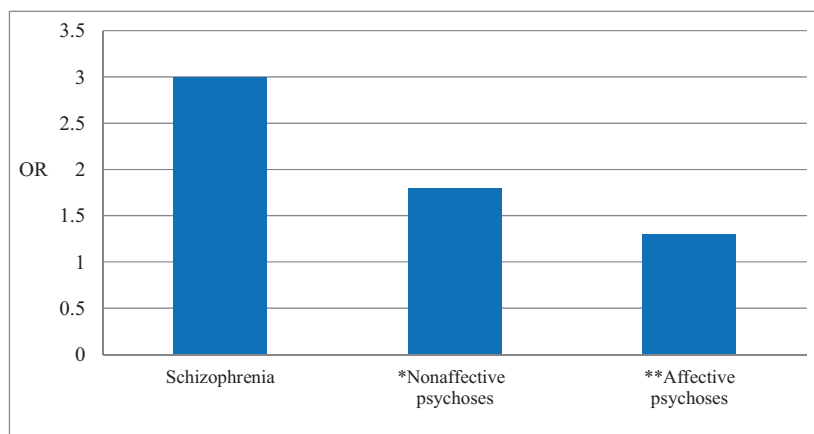
Fig. 2. Main effects of different high-risk groups on body-oriented early intermodal integration (EII). Analyses were adjusted for age and gender. In addition to these covariates, the analysis for affective psychoses and for nonaffective psychoses excluding schizophrenia was adjusted for the ill parent's gender. *Includes offspring of parents with schizoaffective disorder depressed type, psychosis not otherwise specified, and delusional disorder. **Includes offspring of parents with bipolar disorder with psychosis, major depressive disorder with psychosis, and schizoaffective disorder bipolar type.

schizoaffective disorder depressed type, psychosis not otherwise specified, and delusional disorder), the association with object- and body-related EII abnormalities was attenuated and mainly due to the infants of parents with schizophrenia (see table 3). EII abnormalities in relation to social interactions were significantly increased in offspring of parents with schizophrenia and offspring of parents with affective psychoses compared with control offspring (see table 3 and figure 1).

Discussion

The results of our study supported the hypothesis that 8-month-old infants of parents with schizophrenia have more EII abnormalities than infants of healthy parents. There was a significant increase in EII abnormalities in relation to the self (or one's own body), objects, and social interactions. EII abnormalities in relation to social interactions were significantly increased in infants of parents with schizophrenia and infants of parents with affective psychoses. It is also of note that within "nonaffective psychoses," results were strongest in the HR schizophrenia group. Thus, findings suggest that EII abnormalities in relation to self and objects are indicators of vulnerability to schizophrenia, whereas EII abnormalities in relation to social interactions are associated with being at risk for psychoses.

In general, the results suggest a continuum of impairments in infants with HR for schizophrenia on

the more severe end compared with those at risk for other nonaffective psychoses and for affective psychoses. These results are largely consistent with the literature that consists of other vulnerability indicators, such as behavioral problems,[33] neurocognitive functioning,[18,19,34] and neurological abnormalities,[22] among others. It is not yet clear what etiological precursors may cause the greater frequency or severity in those at HR for schizophrenia, especially at such an early age. However, leading causes implicate disruption of brain development during gestation,[35] eg, as demonstrated in our recent NEFS case-control study of psychoses.[36] However, while there is evidence of distinctive neurobiological features of schizophrenia and affective psychoses,[37] there is also evidence of shared genetic liability.[38,39] Our findings with regard to the specificity for increased body- and object-related EII abnormalities in infants of parents with schizophrenia must be replicated. However, our results do suggest there may be both shared and distinct early expressions of gestational complications and genetic underpinnings of different forms of psychoses.

It is also possible that the EII abnormalities in infants of parents with psychosis are associated with psychosocial risks, such as rearing environment, or their interactions with biological risk factors.[40] Parents with schizophrenia have been shown to have more interactional behavior deficits, including less sensitivity and responsiveness to their infants and, in some cases, more intrusiveness, than parents with affective disorder.[40,41] Further, their infants were found more avoidant than infants of parents with affective disorders.[40,41] Children of parents with schizophrenia may be more often exposed to maladaptive parental behavior, such as lack of stimulation, affection, structure, and socialization. They might have more difficulties in the development of intersubjectivity, the sense of shared experience emerging from reciprocity, given that their parents are more prone to misinterpretation of the intent and meaning of the child's action and have more difficulties in understanding the context.[42–44] Impaired communicative reciprocity with the parent during the preverbal period of an infants' development might lead to diminished social competence and increased vulnerability. In the Finnish Adoptive Family Study of Schizophrenia, adoptees at familial HR for schizophrenia who had rearing parents with high communication deviance showed an increased risk of social maladjustment compared with the corresponding low-risk adoptees.[45,46] Future work must address the relationship between biological and psychosocial processes and measures from conception onward in order to clarify the causes of EII difficulties.

Finally, the relationship between developmental EII difficulties and later self-disturbances hypothesized to be associated with schizophrenia is speculative at this point and must be demonstrated empirically across premorbid and postmorbid development. Empirical studies confirm that self-disorders are an indicator of clinical vulnerability to schizophrenia and a discriminant psychopathological feature of the schizophrenia spectrum.[47] "Basic symptoms," similar to anomalous self-experiences, have been shown to precede the development of psychotic symptoms often for many years.[48] Conceptually, the self-experience construct in adult patients can be linked to EII. That is, self-experience is affected in all 3 dimensions of subjectivity in relation to oneself (self-awareness), the world (intentionality), and others (intersubjectivity). These dimensions of subjectivity are comparable to the domains considered by developmental psychologists when defining an infant's psychological world. Future work will be needed to test the associations between EII abnormalities and adult anomalies of self.

There are 3 potential limitations to the study presented here: (1) the validity of the measures for EII, (2) potential information bias, and (3) issues of generalizability. First, the validity of our measures for EII is limited by the use of secondary data, which leads to a less detailed assessment of EII than, eg, current empirical tests from developmental psychology. In addition, our data do not allow for validation of the EII measures with a gold standard. To our knowledge, a specific scale for the investigation of EII abnormalities has not yet been developed. Therefore, the validity of the measures relies on the a priori selection and classification of the EII items with an expert in developmental psychology, ie, on face validity and a measure of Cronbach's alpha. Future validation studies assessing the concurrent validity (eg, with empirical tests in developmental psychology) and predictive validity (eg, prediction of schizophrenia in adulthood or abnormalities in complex mental functions assessed by neuropsychological tests) are required.

Another potential limitation is that, although psychologists had no information on the child's HR status, they might have perceived the mother's illness when she accompanied her child to the examination. Nevertheless, the data were not collected in the context of a study of schizophrenia but in the context of a population-based study of the relationship of perinatal events to mental and motor development. Thus, information bias is less likely. Finally, limited generalizability of the results is a problem to the degree that screened controls are not representative of the general population of the CPP. Future studies with unscreened controls can address this.

The strengths of this study include the novel approach, a larger sample size than that of most prior HR studies, good diagnostic reliability and validity, prospectively collected data on EII, and the adjustment for a substantial number of potential confounders. Further studies are needed to confirm and extend the results of this study. Finally, if EII abnormalities reflect the premorbid state of schizophrenia, they may be part of noninvasive prevention efforts that treat developmental dysfunctions and improve the functioning of these youngsters.

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