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Liability indicators aggregate many years before transition to illness in offspring descending from kindreds affected by schizophrenia or bipolar disorder

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ABSTRACT

Objectives: Offspring born to patients with affective and non-affective psychoses display indicators of brain dysfunctions that affected parents carry. Such indicators may help understand the risk trajectory.
Methods: We followed up the clinical/developmental trajectories of 84 young offspring born to affected parents descending from the Quebec kindreds affected by schizophrenia or bipolar disorder. We longitudinally characterized childhood trajectories using 5 established risk indicators: cognitive impairments, psychotic-like experiences, non-psychotic DSM diagnosis and episodes of poor functioning, trauma and drug use.
Results: Overall, offspring individually presented a high rate of risk indicators with 39% having 3 or more indicators. Thirty-three offspring progressed to an axis 1 DSM-IV disorder, 15 of whom transitioned to a major affective or non-affective disorder. The relative risks for each risk indicator were low in these vulnerable offspring (RR = 1.92 to 2.99). Remarkably, transitioners accumulated more risk indicators in childhood-adolescence than non-transitioners (Wilcoxon rank test; $Z = 2.64$, $p = 0.008$). Heterogeneity in the risk trajectories was observed. Outcome was not specific to parent's diagnosis.
Conclusion: Young offspring descending from kindreds affected by major psychoses would accumulate risk indicators many years before transition. A clustering of risk factors has also been observed in children at risk of metabolic-cardiovascular disorders and influences practice guidelines in this field. Our findings may be significant for the primary care surveillance of millions of children born to affected parents in the G7 nations. Future longitudinal risk research of children at genetic risk should explore concurrently several intrinsic and environmental risk modalities to increase predictivity.

1. Introduction

Major psychoses, as other complex disorders, have determinants in childhood (Maziade and Paccalet, 2013; Shonkoff et al., 2009). Research on major psychoses is shifting from psychotic symptoms to dimensional components and neurodevelopmental trajectories (Insel, 2010, 2014). Congruently, the "*Just the Facts*" series published in this *Journal* proposed to convert our reasoning about schizophrenia by rethinking the disease modeling (Keshavan et al., 2011b). In a new era where knowledge is acquired in developmental vulnerabilities and in new interventions in clinical high-risk (CHR) youths (Seidman and Nordentoft, 2015), longitudinal risk studies beginning in childhood can transform our views of the early phases of the trajectories preceding major affective or non-affective disorders.

Many documented risk indicators may characterize the risk trajectories. For instance cognitive impairments are present before the prodromal phase of major psychoses although their relative predictivity is still being debated (Bora et al., 2014; McGorry, 2013). Other childhood-adolescence risk factors, such as psychotic-like experiences (Dominguez et al., 2011; van Os et al., 2009), non-psychotic DSM diagnosis (Axelson et al., 2015; Hans et al., 2004; Maziade et al., 2008), drug use (Gage et al., 2015; Kraan et al., 2015) and trauma (Berthelot et al., 2015; Varese et al., 2012) may also provide meaningful information. Few longitudinal studies have investigated the relative predictive value of cognitive impairments in the context of these four other childhood-adolescence risk indicators in offspring at genetic risk.

Previous long-term longitudinal studies of offspring of parents affected by schizophrenia (SZ) that reached the age of disease incidence

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(reviewed in Erlenmeyer-Kimling, 2000) found delays in developmental milestones and cognitive impairments in 50% of these offspring (Agnew-Blais and Seidman, 2013; Maziade et al., 2008). Longitudinal studies of offspring of bipolar (BP) patients overall showed that early psychopathologies (Duffy et al., 2014) or sub-threshold manic symptoms (Axelson et al., 2015) tended to predict the later incidence of mood disorders.

Our 25-year longitudinal research in children and adults from a quasi-total sample of multi-affected kindreds in the Eastern Quebec population has bridged family-genetics and developmental psychopathology. The program produced many complementary bodies of familial and developmental findings recently revisited in this *Journal* (Maziade and Paccalet, 2013). This re-examination led to four empirical observations that needed to be reconciled. Inspired by research in cancer mechanisms, we posited a protective-compensatory model in which a 'defective protective gene' running in families would impact the developmental trajectory of the child at risk inheriting it.

We found that many risk endophenotypes would be shared by offspring of parents with SZ or BP, which is congruent with the genetic and phenotypic commonalities otherwise observed in adult SZ and BP patients (Maziade et al., 2011; Van Snellenberg and de Candia, 2009), which does not exclude a degree of specificity. These findings appeared in continuity with new populational data suggesting that the earliest expression of psychosis or mood disorder would be a non-specific mix of symptoms across multiple diagnostic categories (Fusar-Poli et al., 2014; McGorry and van Os, 2013; van Os, 2013). In the young offspring descending from these families, we also found that trauma may negatively impact in childhood/adolescence the cognitive domains (Berthelot et al., 2015) that are impaired in adult patients.

We have never before presented a complete clinical and developmental portrait of the high-risk offspring descending from these kindreds. The *present objective* is thus to provide this portrait composed of many behavioral and environmental risk indicators such as cognitive dysfunctions, psychotic-like experiences, non-psychotic DSM diagnosis in childhood, drug use and childhood trauma, and to use these risk indicators to characterize trajectories. Also, since many offspring have now reached the age of incidence and some have progressed to a major affective or non-affective DSM-IV disorder (schizophrenia spectrum disorders, bipolar disorder or major depressive disorder) or other axis I disorders, *our second objective* was to describe their adult outcome in relation to their earlier trajectories.

2. Methods

2.1. Sample

2.1.1. Kindred sample

We targeted all the multigenerational families densely affected by schizophrenia (SZ) or bipolar disorder (BP) in the Eastern Quebec (Canada) catchment area as described in Supplemental Methods and in Maziade et al. (2005). Over 1800 adult family members in 48 kindreds have been enrolled and >400 hundred patients were diagnosed DSM-IV schizophrenia or mood disorders (Fig. S1). This regional screening setting facilitated the follow-up of the offspring as defined below and the tracking of all health records.

2.1.2. Sampling of offspring

A signed consent was obtained from all subjects and their parents when children were under 18, as reviewed by our University Ethics Committee. The offspring (n = 84) were born to affected parents descending from the kindreds [32 had DSM-IV SZ parent, 40 had BP and 12 had recurrent major depression (RMD)]. The RMD parents had on average 3.5 lifetime episodes. We regrouped the BP and the RMD parents.

The *inclusion criterion* was having a parent with a definite DSM-IV schizophrenia or bipolar disorder. The *exclusion criterion* was the presence of brain injury or metabolic disorders. Controls were recruited through ads in the same population as described in Supplemental methods. The sample characteristics are in Table 1.

2.2. Measures and prospective methods

2.2.1. Offspring follow-up procedure

Time 1 assessments consisted of two separate assessments in a close time sequence: the clinical status evaluation and the cognitive battery. Time 1 also permitted to evaluate the 5 risk indicators: Presence of a cognitive deficit, presence of a childhood non-psychotic diagnosis and/or poor episode of social functioning, psychotic-like experiences, trauma, and drug use (Table 2). Following Time 1 assessments, we installed a year by year follow-up inspired by the lifechart used in Post et al. (1988) relying on all available clinical information, contact with families and medical records, with yearly updates. This continuous survey completed the information from Time 1 assessments, and was permitted by our relationship with the catchment area clinical network established over the last 25 years. Each year during the Xmas holiday period, a letter of greetings and general news about the study was sent to families to maintain the relationship.

Time 2 assessments comprised a clinical status and the cognitive battery. The duration of follow-up from Time 1 and the last clinical update (Time 2) was 11.5 years (SD: 4.0). The retention rate was 95%: 4 children-adolescents out of 88 withdrew consent.

2.2.2. Cognitive battery

The choice of the cognitive measures was based on two criteria: impairments in domains consistently reported in patients with the largest effect sizes (ES of 0.8 to 1.2) (Fioravanti et al., 2012; Mesholam-Gately et al., 2009); impairments in domains also reported in children at

Table 1
Characteristics of the offspring.

Variable	HR (n = 84)		n	HR SZ (n = 32)		n	HR BP (n = 52)		*p*-Value[a]
	Mean or freq	SD or %		Mean or freq	SD or %		Mean or freq	SD or %	
Current age	27.65	6.08	32	29.62	4.77	52	26.43	6.52	0.019[c]
Age at Time 1 evaluation	16.02	4.88							
Age at transition[b]			9	20.11	5.86	6	19.0	4.47	0.70[c]
Gender (% of males)	38	45.2	32	11	34.4	52	27	51.9	0.12[d]
Socioeconomic status[e]	39.80	16.1	31	34.86	15.11	51	42.32	16.15	0.04[c]
IQ	97.24	12.94	32	94	10.84	52	99.23	13.80	0.07[c]

[a] Comparison between high-risk offspring of schizophrenia parents (HR-SZ) and high-risk offspring of bipolar parents (HR-BP).
[b] Transition to an axis 1 DSM IV affective or non-affective disorder (schizophrenia spectrum disorder, bipolar disorder or major depressive disorder).
[c] *t*-Tests comparing offspring of a SZ parent to offspring of a BP parent, with significance levels set at 0.05, using SAS/STAT software, Version 9.4 of the SAS System for Windows. Copyright © 2013 SAS Institute Inc.
[d] Chi-square (χ^2) test comparing offspring of a SZ parent to offspring of a BP parent.
[e] We used the Blishen index (Blishen et al., 1987) according to the highest socioeconomic status of the two parents. This index is based on education and income and on a Canadian census of 514 occupational categories according to the Canadian Classification and Dictionary of Occupations.

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