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LEAD ARTICLE

Developmental Differences Between Schizophrenia and Bipolar Disorder

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Ample evidence supports a neurodevelopmental origin in some cases of schizophrenia (SZ). More inconsistent information is available for bipolar disorder (BD). We herein review studies with a focus on premorbid (adjustment and functionality) and early developmental milestones that include both SZ and BD patients. A search was performed in the PubMed electronic database, retrieving 619 abstracts; 30 were ultimately included in this systematic review. Eight prospective cohorts, 15 retrospective studies, and 7 studies based on national registries. Psychomotor developmental deviations and general adjustment problems characterize the childhood of subjects later diagnosed with SZ or BD; they are more marked in those later diagnosed with SZ vs BD, earlier onset vs later onset, and psychotic vs nonpsychotic disorders. Cognitive impairment follows a linear risk trend for SZ and a U-shaped trend for BD. Social isolation and visuoperceptual/reading anomalies more frequently antecede SZ. Pervasive developmental disorders increase the risk for both SZ and BD, more so in cases with normal intelligence. The predictive risk of each isolated developmental marker is low, but a significant percentage of subjects with SZ and a minority of adults with BD showed signs of premorbid abnormalities in childhood. The great limitation is still the lack of studies comparing SZ and BD that include psychotic and nonpsychotic bipolar cases separately. There are many cases, even in childhood/adolescent SZ, where no premorbid anomalies are found, and immunological disorders or other etiologies should be searched for. At least in cases with clear neurodevelopmental markers, rare genetic variants should be investigated.

Key words: neurodevelopment/premorbid/cognition/psychosis/prediction

Introduction

The idea that schizophrenia (SZ), or at least a subgroup of patients with SZ, should be understood in the light of developmental psychopathology has been around forever[1] and has achieved particular prominence in the last 50 years.[2–4] A large amount of evidence has been gathered in recent decades supporting a neurodevelopmental origin in some cases of SZ[5,6] (see ref.[7,8] for current updates, this issue).[7,8] Premorbid clinical manifestations (before a specific psychiatric diagnosis) may indicate deviant development or rather be early morbid manifestations of the disorder to be later identified. Cognitive and (adjustment to the environment) impairments in SZ are present in coincidence with the first time psychotic symptoms appear, but also in high-risk subjects and even in early infancy, before the clinical high-risk state is apparent.[9–11] Indeed, in the latest version of the DSM,[12] SZ has been placed in proximity to neurodevelopmental disorders in the metastructure of the classification of mental disorders.[13]

Developmental pathology in bipolar disorder (BD) is associated with early onset and is generally milder than observed in SZ. The 2 disorders may share some risk factors while others may lead to the greater severity in SZ.[1,11] However, very few studies have looked at premorbid abnormalities in both disorders in the same study in order to assess the specificity of the predictive value of distinct developmental deviations. In addition, among the available studies, very few have made premorbid adjustment or functioning their main objective.

In order to have a better and more generalizable idea of comparative premorbid abnormalities in SZ and BD, and of their magnitude, we aimed at reviewing studies that (1) looked at childhood and adolescent adjustment to the environment, functionality, and early developmental milestones in SZ and BD, as a principal objective and that (2) had addressed the issue by focusing on both disorders at the same time.

The heterotypic continuity of child to adult psychopathology and the unspecificity of child psychological/psychiatric difficulties with respect to adult psychiatric disorders has been the subject of very frequent comment,

and largely theorized[14–16] but only occasionally studied in a systematic way. We will therefore include in this review studies that look at the predictive risk of premorbid anomalies toward symptoms relevant to SZ or BD.

Methodology

We conducted a comprehensive review summarizing studies that met the following *inclusion criteria*: (1) included subjects with SZ and with BD in the study population and (2) included among objectives a structured or semi-structured assessment of any of the following: psychomotor developmental milestones, premorbid general or social adjustment, educational attainment, premorbid cognitive abilities, or premorbid learning difficulties. We used PubMed MeSH terms to determine a final search strategy including both disorders of interest and developmental data. We set no limits with regard to year published, and articles written in English, German, French, or Spanish were included.

Search Strategy

We performed the following search in PubMed on June 17, 2017: ((((((schizophrenia[Title/Abstract]) OR psychotic disorders[Title/Abstract])) AND ((((((((((learning[Title/Abstract]) OR language[Title/Abstract]) OR childhood [Title/Abstract]) OR early childhood) OR premorbid development[Title/Abstract]) OR psychomotor development[Title/Abstract]) OR early development[Title/Abstract]) OR child development[Title/Abstract])) AND bipolar))) AND ((((((((((learning[Title/Abstract]) OR language[Title/Abstract]) OR childhood[Title/Abstract]) OR early childhood) OR premorbid development[Title/Abstract]) OR psychomotor development[Title/Abstract]) OR early development[Title/Abstract]) OR child development[Title/Abstract])) AND manic-depressive[Title/Abstract])) OR ((((((((((learning[Title/Abstract]) OR language[Title/Abstract]) OR childhood[Title/Abstract]) OR early childhood) OR premorbid development[Title/Abstract]) OR psychomotor development[Title/Abstract]) OR early development[Title/Abstract]) OR child development[Title/Abstract])) AND bipolar))). The search was filtered for articles published since 1975.

Data Collection

A PubMed search and abstract review was performed by two of the authors (M.P. and M.B.). Two authors (M.P. and S.G.V.) independently reviewed the full-text articles selected. A priori selected characteristics of the articles were established, and a summary of findings table was built to extract the information systematically. The extracted data were authors, year, and journal of publication; study design (including retrospective study, prospective study, national registry, and others); sample specificities (sample size, recruitment area, site, or scope); type of premorbid assessment; outcome measure; main findings (table 1).

Results

Our PubMed review retrieved 619 articles. We excluded studies that targeted only bipolar or SZ samples, except where different publications presented data on SZ and BD derived from the same source study and methodology (as in MacCabe[17] and McCabe[18]). Of these, 41 were selected for full review (figure 1) and 23 were selected from the reference lists of the former. Of the 64 finally fully reviewed studies, 30 studies were finally selected for inclusion in this study.

Prospective Cohorts and National Registries

Delayed milestones have been reported as antecedents in both SZ patients and those with other psychoses (including, but not restricted to, BDs). In the 1966 North Finland Birth Cohort study,[19] 155 subjects (1.4% of the sample) were diagnosed with a psychotic disorder by their 31st birthday. Not walking and/or not speaking at year 1 in males and not being potty trained at that same age in females was associated with a psychotic outcome in the sample of 81 patients with both assessments. No finding was specific to SZ compared with other psychoses, and in fact, speech delay only appeared when SZ and other psychosis groups were combined.

In New Zealand, all children born during a 1-year period in 1972–1973 in Dunedin (n = 1037) were followed up,[20] and developmental assessments were performed at different ages. IQ was assessed several times before 11 years. Expressive and language disorders, motor development, social adjustment, and internalizing/externalizing problems were also assessed in childhood. Neuromotor developmental abnormalities as early as 3 years of age and over the course of development predicted schizophreniform outcome at 26 years of age. Receptive language and cognitive impairments throughout infancy also predicted schizophreniform disorders, but not mania (as compared with the control outcome group). Emotional and interpersonal difficulties were associated with any psychiatric outcome. A new analysis was performed on this cohort, with diagnosis by age 32.[21] Again, lower childhood IQ predicted more risk of a SZ spectrum disorder (as well as other disorders); for each standard deviation increase in childhood IQ, the participants had a 42% reduction in the odds of a lifetime SZ spectrum diagnosis; higher IQ was associated with risk for mania (albeit very small sample). A different prospective cohort, also in Australia, showed that developmental delays predict early-onset mania.[22]

The British Birth Cohort study was established in 1946 and included a random sample of 5362 subjects born in a specific week. They were followed up until adulthood.

Table 1. Details of Included Studies

First Author	Type of Study	Recruitment Source	Sample Size	Premorbid Assessment	Outcome Assessment	Main Findings
Velthorst[42]	R and P	Psychiatric units in Suffolk County, NY, US	SZ:139, MD:40, BD:83	PAS, relative information, school records	SCID; trajectories of social functioning	SZ worse social trajectory, 53% premorbid decline, 75% show severe and persistent social impairment since childhood; BD 18% severe; 42% preserved (similar to control)
Selten[31]	NR	SYC, Sweden	480 623 (AS:9062, NAPD:248, BD:179)	ASD DSM-IV or ICD-10	ICD-10	ASD higher risk of NAPD and BD than controls and siblings. Non-ID ASD has higher risk for psychoses.
Del Rey-Mejías[43]	R and P	6 Spanish university hospitals	SZ:51, BD:34	PAS	C-GAS	Deterioration in 28.2%, stability in 57.6%. No SD in functional deterioration between SSD and AFP group. Nonstatistically significant poorer PMA or deterioration in SZ.
Betts[22]	P	Brisbane Misericordiae Hospital, Brisbane, Australia	2566 (BD:1.7%; any PD:1.4%)	CBCL at 5 years; PPVT-R; DDST	CIDI-auto interview-lay trained interviewers	Premorbid cognitive ability predicted psychotic spectrum; DD predicted mania spectrum; behavioral problems predicted psychotic spectrum
Cuesta[35]	R	16 centers across Spain	FEP:266, C:225	PAS	GAF, neurocognitive assessments	Worse PAS in NAPD
Dalteg	R	General Psychiatric Clinic in Gotland, Forensic and nonforensic patients from Canada, Finland, Germany and Sweden	GOTLAND SZ:119, BD:73, other psychosis:39; AFTERCARE SZ:239, SA:56	Clinically derived DSM-IV; WURS-25. SCID-II-screen	Clinically derived DSM-IV	ADHD and CD more common in patients, regardless of diagnosis
Cederlöf[44]	P	Twins born in Sweden	5812	A-TAC	CMRS-PV, MDQ	Problems with communication, reading or maths in childhood have an increased risk of developing PLE and juvenile mania symptoms in adolescence
Payá[40]	R	6 psychiatric units in Spain	SZ: 46, BD:23, C:91	PAS	Diagnosis of SZ and BD	SZ shows earlier and more severe social impairment than psychotic BD and higher rates of development abnormalities. Low intelligence and adaptive scholastic difficulties do not differentiate between BD and SZ.
Andersen[27]	NR and R	DPCRR, DCR, Denmark	SZ:1,277, BD:543	Diagnosis preceding BD or SZ: ICD-8, ICD-9 and ICD-10	ICD-8, ICD-9, ICD-10	SZ > BD: psychoses other than SZ (41%), SUD (27%, specially cannabis), AD (11%) and PD (21.4%). BD > SZ: AfD (46.6%), ADHD (4.2%). CD very low in both. RS equal. Preceding diagnoses were diagnosed earlier in SZ than BD.

Table 1. *Continued*

First Author	Type of Study	Recruitment Source	Sample Size	Premorbid Assessment	Outcome Assessment	Main Findings
Seidman[25]	P	NEFS, New England, US	SZ: 45, BD:5 C:101	PCA derived neuropsychological data	Records linkages or direct interviews (SCID)	SZ associated with lower IQ, academic achievement, verbal ability, and attention/ working memory in childhood. BD, with minor premorbid neuropsychological impairment.
MacCabe[17]	R	NSR and SHDR, Sweden	715401; BD:280 (linked to MacCabe[18])	GPA	BD, ICD-9, and ICD-10	Grades: U-shape (quadratic) risk for BD; low grades x2, high grades x4. Stronger signal in males.
Koenen[21]	P	Dunedin cohort, New Zealand	1037 (SZ:3.6 %; BD: 0.8 %)	IQ: WISC-R at ages 7, 9, and 11; IQs averaged	At 32 years, DIS interview (DSM-IV)	Lower childhood IQ predicted SZ spectrum disorder; higher IQ predicted risk for mania
MacCabe[18]	NR	NSR and SHDR, Sweden	907011 (SZ:493; SA:95; OP:937)	GPA	SAD, OP, ICD-9 and ICD-10	Repeating a year was significant predictor of SZ Low grades: x4 risk for SZ and SAD and x3 risk of NAPD. 4. Moderately poor grades: x2 risk for all psychoses. 5. Above average grades: decreased risk for SZ and schizoaffective disorder.
Hutton	P	Outpatients at Maudsley Hospital; London, UK	ASD:135	ASD (clinical diagnosis plus ADI, ADOS) and IQ > 30	ICD-10 based on CAPA	1 BD, none SZ
Osler[26]	NR	Project Metropolit, DPCR, Copenhagen, Denmark	6923 (SZ + SSD: 133)	At age of 12: Härnquist test (spatial, arithmetic and verbal subtests). At age 18: letter matrices, verbal analogies, number series, and geometric figures	ICD-8, ICD-10	Cognitive function at 12 and 18 inversely related with a diagnosis of SZ/SSD; cognitive decline 12–18 associated with risk for SSD
Uzelac[37]	R	2 convenience hospitalized patients studies	SZ:53, BD:39	PAS	DSM-IV after SCID	Adaptation to school and social sexual adjustment better in adolescence of BD
Zammit[29]	P	Swedish men conscripted for military service	50053 (SZ:362; BD:108)	IQ at 18–20 years old	ICD-9	No association between IQ and BD. Association between low IQ and SZ and SAD, as well as more risk for SZ in subjects with average IQ compared to those with high IQ.
McClellan[41]	R	Inpatients and outpatients in Washington hospital and at the University of Washington, US	Early onset SZ: 27, BD: 22, psychoses NOS: 20	PAS	DSM-IV after SCID	Children with SZ had higher rates of premorbid social withdrawal and global impairment

Table 1. *Continued*

First Author	Type of Study	Recruitment Source	Sample Size	Premorbid Assessment	Outcome Assessment	Main Findings
Hollis[39]	R	Maudsley Hospital in South London, UK	110 children and adolescents with psychosis	GDS, CBS, PAS	ICD-8	SZ: More childhood social impairments, language, reading delays and urinary incontinence. Baseline IQ was lower in SZ, mean around 70 vs mean around 90 in others. Negative dimension associated with impaired premorbid functioning and urinary incontinence.
Reichenberg[30]	NR	Israeli draft board for military service; NPHCR	SZ:536, SAD:3, NPBD:68	Battery of cognitive tests including language ability	SZ, schizoaffective and nonpsychotic bipolar ICD-9, ICD-10	SZ < C; NPBD = C; SZ < NPBD (in adolescence intellectual functioning and reading measures). SAD performed as SZ.
Guerra[47]	R	Maudsley Bethlem Royal and Dulwich North Hospitals, UK	SZ:101, SAD:32, BD:45, Unspecified psychoses:11.	PSA, interview with mother; developmental milestones achievement—PSST	PSA, NART, PSST	RDC criteria
Cannon[20]	P	Dunedin cohort, New Zealand	1037 children, at 26 years old, SZ:36; mania:20	RDS 3 and 5 years; subtests of the ITPA (7 and 9); PPVT (at 3), Stanford-Binet Intelligence Scales for Children- R (at 5); Weschler Tests (at 7, 9 and 11); Rutter Child Scales at 5,7,8,11; interpersonal adjustment: self-devised Likert scale (3 point scale) (at 5,7,9,11)	DSM-IV	Emotional and interpersonal problems associated with all psychiatric outcomes. Deviances in motor development predicted SZ and negatively predicted mania. Neuromotor, receptive language and cognitive impairments only in SZ.
Isohanni[19]	NR	North Finland birth cohort; FHDR	11 017	12-months of age developmental milestones	DSM-III-R	Speech and walk milestones predicted psychosis (in general); in girls, not being potty trained
McClellan	R	Inpatients and outpatients in Washington hospital and at the University of Washington, US	SZ:18, BD:15, SA:6, Psychosis NOS:15	Medical records and parents reports	DSM-IV from SCID	Poor premorbid functioning and negative symptoms: best predictors of follow-up functioning. BD less premorbid impairment than SZ.
Malmberg[28]	P	Swedish conscripts	50 024 (SZ:195; NSZP, including BD:195)	Self-devised questionnaire of personality traits	ICD-9	Early problems with interpersonal relationships strongly associated with later SZ, less with NSZP, even after early-onset cases were excluded

Table 1. *Continued*

First Author	Type of Study	Recruitment Source	Sample Size	Premorbid Assessment	Outcome Assessment	Main Findings
Cannon[36]	R	3 hospitals in South London, UK	SZ: 100, BD: 49, C: 100.	PAS, parts of the Cannon-Spoor	DSM-III	SZ: scored worse than control and BP on childhood, adolescence and overall adjustment. BP: scored worse than C on adolescence and overall adjustment. BP. better performance in school than SZ.
van Os[24]	NR	NSHD, UK	3262	Neurodevelopmental data (speech abnormalities, motor milestones) from medical examinations and teachers' observations. Cognitive test at age 8, 11, and 15	PSE, DSM-III-R	Low childhood cognitive function predicted adult AfD. Abnormal speech and motor development was associated with early onset.
Vocisano[38]	R	Pilgrim Psychiatric Center in Long Island, NY, US	SZ: 29, BD: 27	PAS	DSM-III_R after SCID-P	Poor childhood and adolescent PAS associated with functional decline
Foerster	R	Psychiatric inpatients in Bethlem Royal and Maudsley Hospitals	SZ: 45, AfP: 28)	PSA-modified from PAS	DSM-III	Obstetric complications and family history were predictors of PAS and of an earlier onset

Note: AD, anxiety disorder; ADI, autism diagnostic interview; ADOS, autism diagnostic observation; AfD, affective disorders; ASD, autism spectrum disorders; A-TAC-Autism-Tics, AD/HD and other comorbidities inventory; BD, bipolar disorder; C, control subjects; CMRS-PV, Child Mania Rating Scale-Parent Version; CAPA, Child and Adolescent Psychiatric Assessment; CBS, Childhood Behavior Scale; CD, conduct disorder; DPCR, Danish Psychiatric Central Register; DPCRR, Danish Psychiatric Central Research Register; DCR, Danish Central Civil Registration Register; FEP, first-episode psychosis; FHDR, Finish Hospital Discharge Register; GDS, General Developmental Scale; GPA, grade point average; IQ, intellectual quotient; ITPA, Illinois test of psycholinguistic abilities; MDQ, Mood Disorder Questionnaire; NAPD, nonaffective psychotic disorders; NEFS, New England Family Study; NOS, not otherwise specified; NART, National Adult Redding Test; NPBD, nonpsychotic bipolar disorder; NPHCR, national psychiatric hospitalization case registry; NR, national registry; NSHD, Medical Research Council National Survey of Health and Development; NSR, national school register; NSZP, nonschizophrenia psychosis; OP, other psychosis; P, prospective; PAS, Premorbid Adjustment Scale; PD, personality disorder; PLE, psychotic-like experiences; PMA, premorbid abnormalities; PPVT, Peabody Picture Vocabulary Test; PSA, Scale for developmental problems, interview with mother; PSE, present state examination; PSST, premorbid schizoid and schizoaffective traits; R, retrospective; RDS, Reynell Developmental Scales; RS, reaction to stress; SAD, schizoaffective disorder; SCID, Structured Clinical Interview for DSM-IV; SUD, substance use disorder; SYC, Stockholm Youth Cohort; SHDR, Swedish hospital discharge register; SSD, schizophrenia spectrum disorder; SZ, schizophrenia; WURS-25, Wender–Utah Rating Scale; = , no-different than.

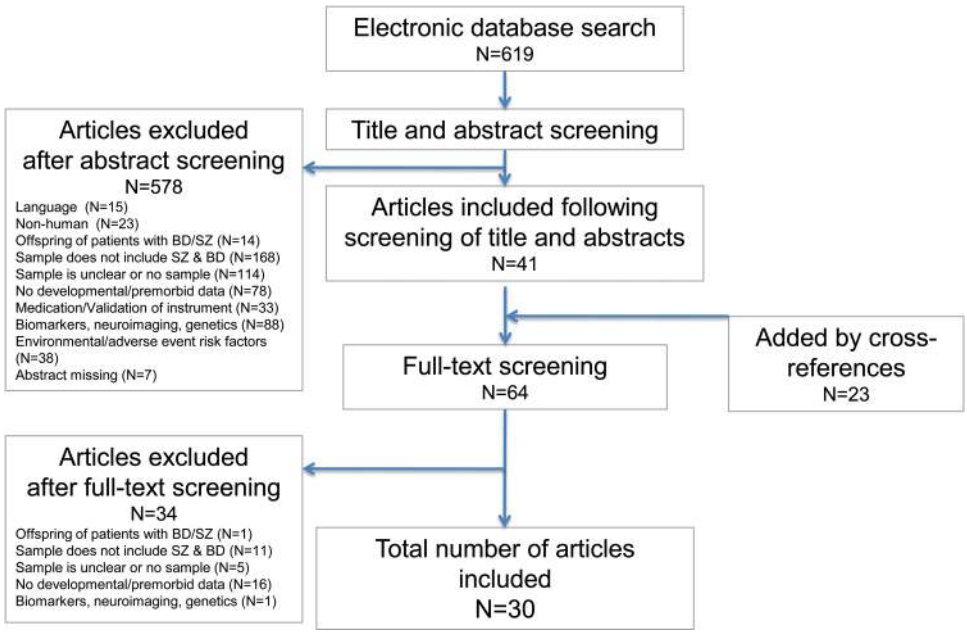

Fig. 1. Flow diagram of systematic search and study selection.

Adult psychiatric outcomes have been reported separately for affective disorders and for SZ but no analysis was performed with regard to BD within the category of affective disorders.[23,24] Developmental precursors of SZ included childhood delayed motor and language milestones, schizoid social functioning, and poor educational achievement; different patterns of maladjustment were present in boys and girls at the 7 and 11 year evaluations, with an un-reactive and an over-reactive type, respectively. Affective psychotic disorder was also associated with neuromotor signs in infancy.

Seidman et al[25] recruited 99 subjects in Massachusetts and Rhode Island with a diagnosis of psychosis (0.18% of the sample) who had been evaluated for neuropsychological performance in the context of the New England Family Study (NEFS). The objective was to differentiate premorbid abnormalities in SZ, other nonaffective psychosis, and affective psychosis. A trend for a dimensional effect was present when compared with control subjects; children later diagnosed with SZ had more diffuse difficulties in neurocognitive functioning, followed by affective psychosis patients. In terms of specificity, it seemed that both groups with psychotic symptoms (SZ and affective psychosis) had the same difficulties in verbal and perceptual/motor abilities and that bipolar patients (even if psychotic) had fewer academic performance problems than SZ patients.

Two topically relevant studies with adult psychiatric data derived from the Danish Psychiatric Central Register were reviewed. This registry contains information on all hospital admissions due to mental health problems in Denmark since 1969. The first study[26] includes data on all men between 19 and 49 years of age for whom there were specific premorbid data: (1) from a school-based survey at age 12 that included a questionnaire administered by their class teachers (spatial, arithmetic, and verbal subtests), (2) from cognitive tests given at 18 years of age as part of an assessment for military eligibility. The final sample included 6923 patients, 133 of whom had a discharge diagnosis of SZ and 16 of whom had a diagnosis of BD. Cognitive function at ages 12 and 18 was inversely associated with SZ (stronger for the 18-year assessment) and BD. Decline in cognitive function between ages 12 and 18 was positively associated with SZ but not with BD (the sample was very small). The second study[27] looked at lifetime contacts with mental health services in subjects diagnosed with SZ or BD at age 21–34. Only 1.1% and 0.7% of patients with SZ and BD, respectively, had a diagnosis of ADHD before age 18, and only 1.1% and 2% had a diagnosis of conduct disorder before age 18. There was a birth cohort effect, and patients born after 1980 were more likely to have any psychiatric diagnosis.

The Swedish Conscript Study, with a larger sample of 195 subjects with SZ and 193 with other psychosis, reported below average IQ in adolescents in both groups of patients, more marked again in SZ.[28] In a later analysis of this same register, now with $n = 50053$, including 362 who had developed SZ and 108 BD, IQ seemed to have a linear relationship with risk of SZ.[29] No association was found with BD. Two Swedish registries were also used to assess the predictive value of school performance with regard to hospital admissions for psychosis. Subjects with a lower level of performance had increased risk for SZ (2- to 4-fold) and a moderately increased risk (2-fold) for BD. The relationship with SZ seemed to be a linear one. A quadratic relationship was observed for BD, with

pupils at the higher end of performance (over 2 SD of the mean) having a 4-fold increased risk. The registry of Swedish conscripts was used to assess personality traits (evaluation performed at 18 years of age, with contemporary and retrospective assessment, in nonpsychotic subjects) at the time of military eligibility assessment prior to a psychosis diagnosis, in a 15-year follow-up study. Early problems in interpersonal relationships were strongly associated with later SZ and, to a lesser extent, with non-SZ psychosis.[28] Prodromal symptomatology could not be excluded and may have confounded the results.

Intellectual, language, and behavioral abnormalities in healthy subjects who subsequently developed SZ, schizoaffective or nonpsychotic BD were studied using Israeli national registers.[30] Here, 536 subjects (up to the age of 27) were identified in the National Psychiatric Hospitalization Case Registry as having any of the abovementioned diagnoses. Data were also compiled for these same subjects from the Israeli Draft Board Registry (IDBR) used to assess eligibility for military service in subjects 15 or 16 years of age. Subjects later diagnosed with SZ differed from healthy control subjects and from nonpsychotic bipolar subjects in having worse premorbid intellectual abilities and reading difficulties and more behavioral disturbances. Adolescents that were later diagnosed with nonpsychotic BDs did not differ from control subjects. In adolescence, future schizoaffective disorder subjects did perform very similarly to SZ patients.

A different approach was taken by Selten et al[31] who examined the rate of nonaffective psychotic disorders and BDs in the outcomes of subjects with a diagnosis of autism spectrum disorder (ASD). All individuals up to 17 years of age who had ever resided in Stockholm County in Sweden were included in a cohort. Here, 9062 individuals ever diagnosed with ASD, their unaffected full siblings, and control individuals were followed for 10 years. The age range of the cohort was therefore 17–27. The risk of a diagnosis of nonaffective psychosis (NAP) or BD in the ASD group was, respectively, 5.6 and 5.8 times greater than in healthy controls, with an even greater risk for those diagnosed with ASD without intellectual disability (ID). No distinction was made in the outcomes for psychotic (9.8% of the BD sample) and nonpsychotic BD or for SZ or unspecified nonaffective psychosis (45.6% of the NAP sample).

Retrospective Studies

In an early study of 1000 hospitalized patients with psychosis,[32] both those with SZ and with BDs (cycloid psychosis and affective psychosis) had histories of poor school performance. Subsequent studies with a wide range of sample sizes (73–266) have shown quite consistently that, in hospitalized patients, premorbid abnormalities (most frequently assessed with the Cannon-Spoor Premorbid Adjustment Scale, PAS[33]) or cognitive performance are more marked in SZ than in affective psychosis.[17,34–44] Those with worse premorbid adjustment had worse cognitive performance after psychosis onset.[38] In a sample of 70 patients with SZ and 28 patients with psychotic BD with a mean age around 23, recruited at the time of admission to hospitals in South London, Cannon et al[37] reported that SZ patients scored significantly worse than normal controls and psychotic bipolar patients, and the latter scored worse than controls. Both patient groups showed a deteriorating course in adolescence, greater in SZ patients. School adjustment was better in bipolar than SZ patients. A self-administered PAS was also used in a study of 93 patients with either SZ (n = 54) or BD (n = 39) recruited after hospitalization.[42] These authors found that premorbid adjustment was not different in the childhood or early adolescence of patients in either group, but bipolar patients reported better social, sexual, and school functioning in late adolescence. There were correlations between higher scores on the Hamilton Depression Scale and a poorer premorbid adjustment during childhood in bipolar patients and premorbid adjustment in childhood and negative symptoms in SZ. Even in patients with deteriorating BD such as those recruited among residents of a large state hospital in Long Island,[43] who had worse premorbid adjustment than nondeteriorating BD, the premorbid adjustment was worse in patients with SZ.

Hollis[40] compared premorbid difficulties between SZ and affective psychosis in a large and unselected sample of children and adolescents with early-onset psychosis (n = 110) seen at Maudsley hospital over a period of almost 20 years. The authors retrospectively reviewed the clinical records of the patients using a structured methodology. SZ patients more frequently had delayed urinary competence and had more impairment in premorbid social functioning than other psychosis patients; no difference was found between SZ patients and other-psychosis patients in any motor, language, or reading indicators (although there was not a separate analysis for affective psychosis within the other-psychosis group). Reading difficulties were found in 28% of patients with SZ and 22% in non-SZ psychotic patients. Continuity was found between urinary incompetence, poor premorbid functioning, and a negative dimension. In another early-onset psychosis study, Payá et al[41] reported on a sample of 46 patients with SZ and 23 with BD. Patients with either diagnosis performed worse than controls in all dimensions of the infancy-PAS. SZ patients' infancies were characterized by more withdrawal and social problems than those of bipolar patients or controls. A study-specific interview was devised to record developmental abnormalities (including language and motor delays or deviances). This global measure identified significant differences between groups, with 27.3% of abnormalities in SZ patients, 4.3% in bipolar patients, and 11.1% in controls. With regard to early adolescent adjustment (up to 15 years of age), both

groups performed worse than controls in all areas and both showed a decline from childhood.

Another study with a very similar sample of 49 early-onset psychosis patients[44] also reported that children with SZ had higher rates of premorbid social withdrawal and global impairment than children/adolescents with BD.

Premorbid to Postonset Studies

Velthorst et al[45] recruited 262 psychosis patients from 12 psychiatric units in Suffolk and 262 controls, and followed them up for 20 years. PAS and school records for premorbid assessment were gathered. A modified version of the Heinrichs-Carpenter Quality of Life Scale (HCQOL) was also used. PAS and HCQOL scores were transformed in order to build a social index that was comparable from premorbid (retrospective) to postonset (up to 20 years) information. Social functioning scores according to social trajectories yielded from latent class growth analysis showed 4 distinct trajectories: profoundly impaired (very few in the bipolar group and more than 20% of the SZ group), severely and persistent impaired (SZ 75%; BD 18%), moderately impaired (40% in the bipolar group and just over 20% in the SZ group), and preserved (BD 42%, similar to controls and very few patients with SZ, only 1.5%). All these differences were already evident in childhood. Premorbid social adjustment (for the most part impaired social functioning was already present in childhood) was a strong predictor of social functioning in both SZ and BD and was a good (but not exclusive) predictor of a SZ diagnosis. Overall, there were worse social outcomes in SZ spectrum disorders and remarkably stable long-term impairments in social functioning after illness onset across all diagnoses. Del Rey-Mejías et al[46] examined the course of functional adjustment in adolescents with SZ and affective psychosis, taking premorbid adjustment as the starting point. With a sample of 85 patients (51 with SZ or schizoaffective disorder and 34 with affective psychosis, 29 bipolar), mean infancy-premorbid adjustment and categorical infancy-premorbid adjustment (good, moderate, and poor) were not different between SZ and affective psychosis groups. Only bipolar patients with psychotic symptoms were included in these studies.

In the latter two studies, there was low average premorbid functioning that remained stable in a significant number of patients across diagnoses; more patients with SZ disorders had impaired trajectories and more with mood disorders had better functioning trajectories.[45,46]

Psychopathological Dimensions As Outcomes

In the prospective follow-up of a pre-birth cohort of 7,223 pregnant women in Brisbane, Australia,[22] psychopathological domains were assessed in 2,566 subjects at the age of 21. Their cognitive abilities and developmental stage had been assessed when they were 5. Premorbid cognitive ability was associated only with psychotic spectrum symptoms; developmental delay correlated only with mania spectrum symptoms, and behavioral problems predicted depressive and psychotic spectrums (all associations low to moderate).

Late adolescent symptoms of psychosis or mania were ascertained at age 15 or 18 in 5,812 children who formed part of the Child and Adolescent Twin Study in Sweden[47] for whom developmental information was available through parent interviews when they were 9–12. Children with parent-reported problems with communication, reading, or mathematics assessed with the Autism-Tics, AD/HD and other Comorbidities Inventory (A-TAC)[48] were at increased risk of developing auditory hallucinations and mania symptoms in late adolescence.

Factor scores derived from OPCRIT items[49] were associated with premorbid abnormalities in Hollis.[40] Higher PAS scores (worse premorbid functioning) were associated with a negative syndrome dimension while better premorbid functioning was associated with higher scores in the mania and depressive dimensions. Incontinence was associated only with the negative dimension.

A sample of 189 hospitalized patients were assessed for delusions, hallucinations, mania, and thought disorder.[34] A developmental interview was administered to the mother and factor analytic techniques (principal component analysis [PCA] in this case) used to establish premorbid risk dimensions, leading to the identification of one social and one cognitive dimension. In the absence of manifest cognitive impairments, which was an exclusion criteria for the study, poor school functioning in adolescence was associated with delusions/hallucinations. Normal cognitive performance was associated with symptoms of mania. No association was found between deviant neurodevelopmental milestones and affective dimensions.

Discussion

Prospective and national registry studies clearly show that SZ patients as a group, when compared with control subjects, do show an increased mean in premorbid deviances, particularly in neurocognitive performance and in psychomotor development milestones in general. However, it is much less clear if patients with bipolar (psychotic and nonpsychotic) disorders do share the same risk markers. In general, it seems that patients with BDs may have childhood and adolescent maladjustment but not cognitive impairment or bad academic performance. When directly compared, neurodevelopmental deviations (including neuromotor and cognitive impairment) are shown in both SZ and BD, but more strongly and extensively in the former.[17,18,20,22,25,28] In fact, it is likely that childhood motor and speech abnormalities in the antecedents of BD are confined to those with an earlier onset.[20,22,40,41] The information, however, is far from robust. First, the literature does not make it clear enough whether a larger

proportion of SZ patients than bipolar patients do have premorbid abnormalities or if premorbid abnormalities are more severe in SZ. Second, only occasionally have nonpsychotic bipolar patients been compared with SZ; Reichenberg et al[30] included only nonpsychotic affective disorders in their comparison study with SZ and found that the latter performed worse in all cognitive measures and bipolar patients did not differ from control subjects. In addition, because of the low prevalence of psychosis, the number of patients who end with a diagnosis of SZ or BD in the follow-up time of these cohorts is usually not large. One of the cohorts with a more detailed developmental assessment over the course of infancy reported clear differences between patients later diagnosed with SZ compared with control subjects and no differences between the future bipolar group and controls, but no direct comparison between patient groups was presented and the sample size of the mania group was quite limited ($n = 20$).[20]

In addition, several studies have correlated above average cognitive performance with manic symptoms.[17,20,21] While cognitive limitations seem to have a linear effect in generating risk for SZ[17,18,26,29] a U-shaped effect better explains the relationship between IQ and BDs; above-average cognitive performance increases the risk even more than low IQ.[17] In the one study involving *nonpsychotic* BD only,[30] no relationship was shown between premorbid low cognitive ability and later BD.

Two aspects have been more clearly associated with SZ, ie, social isolation (while other types of social maladjustment are also present in children diagnosed with psychotic BD later in life) and cognitive performance decline before illness onset.[26,30,45] The findings with regard to nonpsychotic BD are more difficult to sum up as few studies separate those from other BDs.

However, even though it seems that having developmental delays is a clear risk factor for SZ, the predictive validity of any individual risk indicator is very low. For example, the North Finland Birth Cohort study[19] showed that, of all children not speaking words at 1 year of age, only 0.88% would develop SZ (a statistically significant difference, but a low risk); below average IQ in Swedish subjects assessed at 18 conferred a 3% risk of SZ.[28]

Although similar to those of prospective studies, findings from retrospective studies tend to report a greater magnitude of the prevalence of premorbid abnormalities in SZ. Most retrospective studies include hospitalized psychotic patients and generally show that patients with SZ have poor premorbid adjustment and that BDs have either no premorbid maladjustment or an adjustment that is intermediate between SZ and healthy controls.[20,38,42,43] Worse adjustment has been shown to be associated with cognition[38] after a first episode and also with deterioration[43] and with negative symptoms,[37] signaling a bad outcome subgroup of SZ. Social impairment seems to mark a persistent course.[34]

When early-onset cases are studied,[40,41,44] SZ patients report more social premorbid adjustment than bipolar subjects; when patients are compared with control subjects,[41] SZ patients do show more social withdrawal than the former, and bipolar patients also show a trend for general social premorbid difficulties. Interestingly, even in cases with the highest developmental load as child/adolescent-onset cases of SZ, fewer than half of the patients show premorbid abnormalities. For example, broadly impaired social development was present in 34% of children in the Hollis[40] sample of children/adolescents with SZ recruited in general child and adolescent services or 27% of any delayed milestone was reported in severely ill hospitalized adolescents with SZ.[41] Motor, language, or reading difficulties are numerically but not statistically greater in early onset SZ than in early onset psychotic BD.[40,41] As most subjects with developmental anomalies will not end up having SZ, it is also the case that some persons with no developmental problems will end up being psychotic or fulfilling diagnostic criteria for SZ. These data highlight the idea that SZ and BD are better thought of as clinical syndromes rather than disorders. A good developmental history is of great relevance in any case of psychosis/SZ. As an example, in cases of no evidence of neurodevelopmental problems, autoimmune encephalitis (with auto antibodies such as NMDA, AMPA, or K channel among many others) should be ruled out.[50,51] A recent review and meta-analysis has reported a prevalence of 8% of anti-NMDA receptor antibody positive in patients with psychosis.[52]

Premorbid to postonset studies question the idea that biological deterioration is a hallmark of SZ. However, the question of degenerative pathology sometimes seems to be supported by an apparent deterioration after psychosis onset, which may just reflect differences present before psychosis.[46] Once patients get older and need to operate in a more independent and therefore challenging type of life, separated from family protection, the gap with peer functioning may get larger, leading to the downward shift detected in many studies.

The mechanisms underlying the relationship between premorbid impairments and SZ/BD are likely a mixture of the following: (1) common etiologies (genetic and/or environmental), (2) cognitive mechanisms whereby cognitive difficulties drive social difficulties in adjustment to the environment and reality testing[53] (conversely, good cognitive abilities could protect from developing psychosis in genetically/environmental high-risk individuals), (3) premorbid abnormalities and cognitive impairment may be independent risk factors for psychosis,[34] (4) reverse causality (premorbid abnormalities being early symptoms of the pathology) and/or residual confounding (parental education, family social class being the common underlying features for both premorbid conditions and diagnoses).[26] Both premorbid abnormalities and premorbid cognitive decline in SZ clearly suggest a latent

disease process present for many years before the onset of psychotic symptoms.

Within mechanisms of association between poor premorbid adjustment and psychosis, the difficulty in interpreting others peoples' mental states together with isolation in ASD patients, could limit opportunities for reality testing[28] increasing the risk for psychosis. A prior diagnosis of ASD has been associated with both SZ and BD in sufficiently large samples.[31,54] Indeed, the association of pervasive developmental disorders (PDD) and psychosis is in consonance with the finding, from the NIMH very early-onset SZ sample, of a history of PDD (as per DSM-III) in roughly a third of the patients with SZ.[55] Nonintellectually disabled children with ASD have been shown to have greater risk of a SZ outcome.[31] This result contrasts with the well-documented fact that low intelligence is associated with increased risk of SZ and other psychoses. It has been interpreted as greater awareness of their impairments on the part of non-ID ASD patients increasing the risk for psychosis.[31] We put forward the alternative explanation that autistic traits in the context of ID may exert a protective effect for psychotic symptoms (via their diminished social contact and expectations toward social relationships).

In addition to general intellectual functioning difficulties, reading abilities seem to characterize the childhood of subjects who are later diagnosed with SZ. This has been shown in register studies[30] and retrospective studies.[40] That some type of language disorder may be part of the same phenomenon that is later expressed in the form of reality distortion is a long-held idea.[56,57] Deterioration of visual information acquisition and processing has been postulated to contribute to higher-order cognitive dysfunctions and ultimately to SZ symptoms,[58] signaling another possible pathway to psychotic symptoms.

One effect that cannot be discarded in this area of research is the information bias or Pygmalion effect. In the last few decades, as authors started to identify neurodevelopmental problems in the infancies of patients with SZ and preeminent experts have considered this a neurodevelopmental disorder, at least in some cases, clinicians may be inclined toward a diagnosis of SZ in the presence of abnormal premorbid adjustment. More so in the case of deterioration before "illness onset," which may immediately incline the diagnosis toward SZ. In addition, when the same rater assesses psychopathology and premorbid issues, the current diagnosis can bias the assessment and interpretation of previous problems.[40]

As a more general comment, the studies reviewed try to find distinct developmental trajectories between disorders that are now known to have a great symptomatic and etiological overlap. These disorders are no longer considered distinct entities in the way they were by authors in the 70s,[59] who increasingly tried to refine the distinction between diagnoses. Only a few authors[20,22,34] have tried to study the antecedents of specific symptomatic domains (mania, psychotic symptoms, etc.). The findings of these studies clearly support the absence of a categorically distinct diagnosis, but somehow the existence of different (developmental marker-symptomatic domain) dimensions.

The developmental psychopathology perspective taken in the studies herein reviewed shows the changing picture of the clinical manifestations. The route may start in a very unspecific picture of early developmental deviances and follow an increasing more specific social and/or cognitive adjustment difficulties path that can elapse in some cases in SZ and in others in other types of psychosis. This complicates the study of the true morbid phenomenon. The search for common underlying biological processes, that interact with maturational/developmental processes at different ages, may help clarifying the physiopathological process. The various developmental abnormalities associated with psychotic illnesses need to be understood at the mechanism level and further understood in the context of causal pathways to psychoses. Current clinical and preclinical paradigms are addressed in commentaries.[60,61]

In the same vein as single risk genes have pleiotropic effects leading to diverse outcomes and similar outcomes can be associated with different risk genes, individual developmental markers can have pluripotencial outcomes and same outcome can have different pathways that lead to it.[62,63] How the identification of early manifestations of risk markers may be translated into preventive interventions to avoid worst outcomes is still a matter of debate. Great efforts are been made in some exceptional settings to identify and treat markers of deviant development or early symptoms with the hope that this will prevent major disorders to appear or reduce associated disability.[63] Some data is being gathered with respect to treating high-risk prodromic states to prevent transition to psychosis[52] still with limited results. Early intervention studies to treat social and behavioral symptoms have proven to change the symptomatic picture, but no study has yet been so big to prove that these interventions reduce the rate of SZ or BD.[64]

Limitations

In theory, the ideal methodology for assessing premorbid abnormalities in patients with psychiatric disorders should be prospective follow-ups of unselected cohorts. However, low prevalence of psychotic disorders, changes in psychiatric nosology, availability of appropriate assessment instruments, and new empirical data being accumulated that would inform and change the original design and selected indicators, make it imperative that studies with less ideal methodologies be taken into account. The duration of longitudinal studies, not long enough to include the whole age range for appearance of psychotic disorders and the attrition rate (which is not independent of diagnosis) are other limitations. Albeit they permit

the recruitment of bigger samples of disorders with a low prevalence, retrospective studies endorse important limitations such as recall bias (informants selectively report developmental difficulties in problem-subjects), selection bias (most patients included in these studies are hospitalized and therefore represent a more severe end of the spectrum), and the fact that most bipolar patients included have psychotic BDs.

The variability in premorbid adjustment and cognition assessment is a general limitation. The most widely used instrument for premorbid adjustment, the PAS, was designed for SZ and may not capture different premorbid abnormalities present in BD. Occasionally,[42] self-report PAS has been used at the time of a psychotic decompensation. The account of past adjustment can clearly be biased by present symptomatology. With regard to cognitive performance, very few studies have used direct and contemporary assessments of cognitive functioning[17,18,20]; many others have used scholastic attainment as a proxy of cognitive impairment; school grades may partially reflect political and social laws and practices in addition to pupils' abilities. In fact, school performance has been shown to correlate only moderately with intelligence[65]; some studies have used cognitive measurements too close to the age of onset of psychotic disorders (the studies with conscripts) and a number of other studies have used *premorbid intelligence* at the time of recruitment (the latter were not included in this review).

Conclusions

Early evidence of developmental pathologies commonly precedes the onset of psychotic symptoms associated with SZ and BD. These pathologies vary within SZ and BDs and tend to be more severe and/or common in SZ. They provide a critical roadmap for the study of causal pathways and provide clinicians with important prognostic information.

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