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published in
JAMA Psychiatry
2018

DOI (link to publisher)
10.1001/jamapsychiatry.2017.3459

document version
Publisher's PDF, also known as Version of record

RESEARCH LETTER

Association of Genetic Risk for Schizophrenia and Bipolar Disorder With Infant Neuromotor Development

Schizophrenia and bipolar disorder (BD) are heritable disorders with similarities in clinical symptoms and typical onset after puberty.[1] While research shows that impaired motor coordination can have an association with schizophrenia,[2] there are limited data on childhood development preceding BD. Murray et al[1] proposed a developmental model for similarities and dissimilarities between schizophrenia and BD, but it remains unknown if dissimilarities exist in early infancy and if they covary with genetic liability for these disorders. Using polygenic risk scores (PRSs), we explored whether genetic risk for schizophrenia and genetic risk for BD are associated with neuromotor development in infancy.

Methods | The present study was embedded in the Generation R Study (n = 7893), a population-based study from fetal life forward in Rotterdam, the Netherlands. From this cohort, we identified a pediatric sample of European ancestry (defined by genetic principal components [based on population-specific variations in allele distribution]) by genotype data (n = 2830).[3] Of these, 1174 infants (41.5%) underwent neuromotor examination at 2.9 months (range, 2-5 months). Polygenic risk scores were calculated using an R script (PRSice version 1.25) for schizophrenia and BD using genome-wide association study

Table 1. Items for Assessing Neuromotor Development[a]

Subscale and Position	Item Description	Answering Categories		
		Nonoptimal	Optimal	Nonoptimal
Tone				
Supine	Resting posture	Legs flat on the surface	Semiflexed legs; slight abduction at the hips	Legs stretched
	Adductor angle	>140°	>80° to <140°	<80°
	Popliteal angle	130° to 180°	90° to 130°	<90°
	Ankle angle	<20°	>20° to <90°	>90°
	Head preference	Yes	No	
	Opening and closing hands	Sometimes closed	Yes	Always closed
	Alternating leg movements	Decreased	Yes	Absent
	Grasps with one hand	Decreased	Yes	Absent
	Hyperextension	Sometimes	No	Yes
	Dyskinesia	Sometimes	No	Yes
Supine to sit	Traction response	Arms fully extended, no resistance	Arms moderately flexed	Strong resistance, flexion elbows, legs extended
	Traction response, head control	Head lag	Active lift of head	Exaggerated
Horizontal	Ventral tone	Low tone	Normal tone	Back and limbs stretched
Vertical	Head	Low tone	Normal tone	High tone
	Shoulders	Low tone	Normal tone	High tone
	Trunk	Low tone	Normal tone	High tone
	Legs	Low tone	Normal tone	High tone
Prone	Pulls arms up	No	Yes	
	Turns head	No	Yes	
	Lifts head	No	Yes	Overstretched
Sitting	Needs support	No	Yes	
	Head control	No	Yes	
	Shoulder retraction	Yes	No	
	Shape of the back	Straight	Round	Scoliosis

(continued)

Table 1. Items for Assessing Neuromotor Development[a] (continued)

Subscale and Position	Item Description	Answering Categories		
		Nonoptimal	Optimal	Nonoptimal
Physical Responses				
Supine	Asymmetrical tonic neck reflex	Yes	Weak	Exaggerated
	Babinski reflex	Exaggerated	Yes	Spontaneous
Prone	Bauer reflex	Exaggerated	Yes / weak	
Vertical	Stepping movements	Yes	No	Exaggerated
	Moro intensity	Exaggerated	Yes / weak	
	Moro opening hands	No	Yes	
Other				
Supine	Strabismus	Sometimes	No	Yes
	Fixation eyes	Decreased	Yes	No
	Following movements eyes	Decreased	Smooth	No
	Hearing	Moderate	Yes	No
	Sweating	Yes	No	
	Startles	Sometimes	No	Yes

[a]This table has been adapted from information in van Batenburg-Eddes, et al.[5]

Table 2. Nonoptimal Neuromotor Development in 1174 Infants Aged 2 to 5 Months, Corrected for Age[a]

Threshold	OR (95% CI)	*P* Value	SNP,[b] No.
Schizophrenia			
P < .0005	1.14 (1.00-1.29)	.05	2965
P < .001	1.14 (1.00-1.29)	.04	4148
P < .005	1.14 (1.01-1.30)	.04	9547
P < .01	1.14 (1.01-1.30)	.03	13 916
P < .05	1.15 (1.01-1.30)	.03	34 947
P < .10	1.12 (0.99-1.27)	.08	52 256
P < .50	1.12 (0.99-1.26)	.08	126 674
Bipolar Disorder			
P < .0005	0.87 (0.77-0.98)	.02	525
P < .001	0.92 (0.82-1.04)	.20	915
P < .005	0.99 (0.88-1.11)	.85	2946
P < .01	0.95 (0.84-1.07)	.40	4992
P < .05	0.95 (0.84-1.08)	.44	16 461
P < .10	0.91 (0.81-1.03)	.14	27 366
P < .50	0.92 (0.81-1.03)	.15	79 569

Abbreviations: OR, odds ratio; SNP, single-nucleotide polymorphism.

[a] The models are adjusted for sex and the first 4 genetic principal components based on population-specific variations in allele distribution.

[b] SNPs were clumped prior to calculation of score.

(GWAS) summary statistics and were standardized to a mean (SD) of 0 (1) for interpretability. Additive PRS were calculated for each individual by multiplying the allele count by the allele log of the odds ratio (OR). Single-nucleotide polymorphisms were clumped prior to calculation of the score.[4] Full details have been described elsewhere.[4] The Erasmus Medical Center Medical Ethics Committee approved the study. Written informed consent was obtained from parents of infants.

Research nurses assessed neuromotor development during a home visit using an adapted version of the Touwen Neurodevelopmental Examination (**Table 1**).[5] The lowest and middle tertiles were classified as optimal. Nonoptimal neuromotor development was defined as an age-corrected score in the highest tertile. We performed logistic regression adjusted for sex and population structure by including the first 4 genetic principal components. Two-sided *P* < .05 was the threshold of statistical significance.

Results | Among the 1174 infants examined, 596 (50.8%) were male and 578 (49.2%) were female. In this cohort, a higher PRS for schizophrenia was associated with nonoptimal overall infant neuromotor development at age 2 to 5 months (GWAS *P* value threshold <.05) (OR, 1.15; 95% CI, 1.01-1.30; *P* = .03). The results remained essentially unchanged across the range from *P* < .05 to *P* < .0005). A PRS for BD was not consistently associated with nonoptimal overall infant neuromotor development (OR, 0.95; 95% CI, 0.84-1.08; *P* = .44) (**Table 2**).

Discussion | This report indicates that the PRSs for schizophrenia are associated with nonoptimal overall infant neuromotor development, whereas no consistent associations were observed for BD PRSs. Similarly, Burton et al[6] found an association between motor development at 7 years with familial risk for schizophrenia, but not with familial risk for BD. To date, the earliest age for manifestation of genetic predisposition for schizophrenia was

reported by Jansen et al[4] in 3-year-old children. Research suggests that impaired neuromotor development precedes schizophrenia onset, although most children with impaired neuromotor functioning do not develop schizophrenia.[2] In contrast, children who later met criteria for BD exhibited a higher level of motor performance during childhood than controls.[1] Our results highlight that the genetic predisposition for schizophrenia covaries with motor deficits observable during infancy in a community-based sample. Given that the prevalence of schizophrenia is low, these early features represent indices of liability rather than precursors of the disorder.

This study has certain limitations. Genetic pleiotropy or early environmental factors could also explain the association.[1] Selective nonresponse to neuromotor assessment could bias the analysis. The power of the BD GWAS might have been insufficient to detect associations between BD PRS and neuromotor development. Despite limitations, this study has several strengths, including an objective and prospectively assessed measure of neuromotor development in a large homogenous sample of infants.

To our knowledge, this is the first evidence that genetic liability for schizophrenia may covary with altered neuromotor development in infancy. Future research will show whether early neuromotor development can support early screening of susceptible groups possibly defined by genetic risk.

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Accepted for Publication: September 20, 2017.

Published Online: November 8, 2017. doi:10.1001/jamapsychiatry.2017.3459

Author Contributions: Drs Serdarevic and Tiemeier had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Serdarevic, Jansen, Jaddoe, Tiemeier.
Acquisition, analysis, or interpretation of data: Serdarevic, Jansen, Ghassabian, White, Posthuma, Tiemeier.
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Obtained funding: White, Posthuma, Tiemeier.
Administrative, technical, or material support: White.
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Conflict of Interest Disclosures: None reported.

Funding/Support: Dr Tiemeier was supported by NWO 024.001.003 from the Dutch Ministry of Education, Culture and NWO 016.VICI.170.200 from the Science and the Netherlands Organization for Scientific Research Consortium on Individual Development. Dr Serdarevic was supported by grant 2013-2548/001-001-EMA2 from Erasmus Mundus Western Balkans postdoctoral scholarship financed by the European Commission. Dr Jansen was supported by grant SSWO S14-27 from the Sophia Foundation for Scientific Research. The Generation R Study is supported by the Erasmus Medical Center-Rotterdam, the Erasmus University Rotterdam, the Netherlands Organization for Scientific Research, and the Ministry of Health, Welfare, and Sport.

Role of the Funder/Sponsor: The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: We gratefully acknowledge the contribution of participating mothers, general practitioners, hospitals, midwives, and pharmacies in Rotterdam. Frank C. Verhulst, MD, PhD (Department of Child and Adolescent Psychiatry and/ Psychology, Erasmus Medical Center), and Tamara van Batenburg, PhD (Department of Child and Adolescent Psychiatry and Psychology, Erasmus Medical Center), provided neuromotor data. They did not receive compensation for their contribution to this study.

Additional Information: Drs Serdarevic, Jansen, and White are members of the Generation R Study Group, Erasmus Medical Center Rotterdam, the Netherlands.

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Assessment of Symptom Network Density as a Prognostic Marker of Treatment Response in Adolescent Depression

One in 4 adolescents with depression does not respond favorably to treatment.[1] Prognostic markers to identify this nonresponder group are lacking and urgently needed.[2] It has been suggested that the network structure of depressive symptoms (ie, group-level covariance or connectivity between symptoms) may be informative in this regard.[3] Intuitively, one may expect that more densely connected networks would be more inclined to result in negative spirals (eg, sleeplessness causes an individual to be too tired to go out, which leads to a lack of friends, resulting in sadness) and therefore more liable to nonresponse. An influential naturalistic study by van Borkulo et al published in *JAMA Psychiatry*[3] reported that adult patients with depression who continue to experience problems in sub-