Published in final edited form as:

Dev Med Child Neurol. 2020 June ; 62(6): 750–757. doi:10.1111/dmcn.14383.

Genetic variation in dopamine neurotransmission and motor development of infants born extremely-low-birthweight

GORDON WORLEY^{1,*}, STEPHEN W ERICKSON^{2,*}, KATHRYN E GUSTAFSON³, YULIYA S NIKOLOVA⁴, ALLISON E ASHLEY-KOCH⁵, DANIEL W BELSKY⁶, RICKI F GOLDSTEIN⁷, JOSHUA L LEVY², SCOTT A MCDONALD², GRIER P PAGE², C MICHAEL COTTEN³, EUNICE KENNEDY SHRIVER NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT NEONATAL RESEARCH NETWORK†

¹Division of Pediatric Neurology and Developmental Medicine, Department of Pediatrics, Duke University Medical Center, Durham, N.C. U.S.A.

²Social, Statistical and Environmental Sciences, RTI International, Research Triangle Park, N.C., U.S.A.

³Division of Neonatology, Department of Pediatrics, Duke University Medical Center, Durham N.C., U.S.A.

⁴Centre for Addiction and Mental Health, University of Toronto, Toronto, Ontario, Canada

⁵Duke Molecular Physiology Institute, Department of Medicine, Duke University Medical Center, Durham N.C., U.S.A.

⁶Department of Population Health Sciences, Duke University, Durham N.C., U.S.A.

⁷Division of Neonatology, Department of Pediatrics, Kentucky Children's Hospital, University of Kentucky Chandler Medical Center, Lexington, K.Y., U.S.A.

Abstract

¹Department of Pediatrics, Duke University, Durham, NC

²Social, Statistical and Environmental Sciences, RTI International, Research Triangle Park, NC

³Department of Pediatrics, University of Alabama at Birmingham, Birmingham, AL

⁴University of Iowa, Department of Pediatrics, Iowa City, IA

⁵Department of Pediatrics, University of Cincinnati, Cincinnati, OH

⁶Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD.

⁷Department of Pediatrics, Wayne State University, Detroit, MI

⁸Department of Pediatrics, Division of Neonatal and Developmental Medicine, Stanford University School of Medicine and Lucile Packard Children's Hospital, Palo Alto, CA

⁹Emory University School of Medicine, Department of Pediatrics, Children's Healthcare of Atlanta, Atlanta, GA

¹⁰Social, Statistical and Environmental Sciences, RTI International, Rockville, MD

Correspondence to Gordon Worley MD, Division of Pediatric Neurology, Department of Pediatrics, Duke University Medical Center, Durham, North Carolina 27710, USA, gordon.worley@duke.edu.

*These authors contributed equally to this manuscript.

The members of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network are as follows: C Michael Cotten¹; Grier Page²; Waldemar A Carlo³; Edward F Bell⁴; Ronald N Goldberg¹; Kurt Schibler⁵; Rosemary D Higgins⁶; Beena G Sood⁷; David K Stevenson⁸; Barbara J Stoll⁹; Krisa P Van Meurs⁷; Karen J Johnson⁴; Abhik Das¹⁰; Scott A McDonald²; Kristin M Zaterka-Baxter²; Jeffrey C Murray⁴.

AIM—To determine if genetic variation associated with decreased dopamine neurotransmission predicts a decrease in motor development in a convenience cohort study of infants born extremely-low-birthweight (ELBW).

METHOD—Four hundred and ninety-eight (498) infants born ELBW had genome-wide genotyping and a neurodevelopmental evaluation at 18 to 22 months of age, corrected for preterm birth. A polygenic risk score (PRS) was created to combine into one predictor variable the hypothesized influences on motor development of alleles at seven independent single nucleotide polymorphisms previously associated with relative decreases in both dopamine neurotransmission and motor learning, by summing the number of alleles present in each infant (range=0–14). The motor development outcome was the Psychomotor Development Index (PDI) of the Bayley Scales of Infant Development, Second Edition. The linear regression models were adjusted for seven clinical and four genetic ancestry covariates. The mean PRS of infants with cerebral palsy (CP) was compared to those without CP.

RESULTS—PRS was inversely related to PDI ($p=0.011$). Each 1-point increase in PRS resulted in an average decrease in PDI of 1.37 points. Patients with cerebral palsy (CP) did not have a greater mean PRS than those without ($p=0.67$), both with and without adjustment for covariates.

INTERPRETATION—Genetic variation that favors a decrease in dopamine neurotransmission predisposes to a decrease in motor development in infants born ELBW, but not to the diagnosis of CP.

Children born preterm at an extremely-low-birthweight (ELBW; <1000g) have a high prevalence of motor impairment. This is true both in children with cerebral palsy (CP) and in those without.¹ Motor learning is the acquisition, consolidation, and retention of new motor skills, resulting from ‘motor plasticity’, that is, changes that occur with motor learning in brain networks.² It is an important component of human motor development.

There is evidence that dopamine neurotransmission is integral to motor learning. In an animal model,³ exposure to a dopamine neurotransmission neurotoxin inhibited new motor learning. In humans, fetal exposure to a recreational drug that is a dopamine neurotransmission neurotoxin (3,4-methylenedioxymethamphetamine, commonly known as ecstasy) impedes motor development.⁴ In addition, augmentation of dopamine neurotransmission by levodopa administration can improve motor learning in some adults.⁵ Genetic variation that favors increased dopamine neurotransmission has been shown to be associated with relatively greater metabolic activity in a brain region known to have dopamine neurotransmission-regulated neural circuitry.⁶ It has also been associated with better motor learning in children with CP who received intensive therapy⁷ and in adults.⁵ Whether genetic variation of dopamine neurotransmission predicts motor development in infants born extremely preterm is not known. We reasoned that since genetic variation in dopamine neurotransmission has been related to motor learning and motor learning is important in human motor development, genetic variation in dopamine neurotransmission might be related to human motor development.

The Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network (NRN) is a research consortium of neonatal intensive care units and the National Institutes of Health designed to study factors influencing neonatal

outcomes. Comprehensive clinical data on infants born ELBW were collected, including developmental outcomes and, on a subset, genome-wide genotyping. At the time of patient enrollment for this study (1999–2002), the NRN comprised 16 sites.

In this study, we created a polygenic risk score (PRS) for relatively decreased dopamine neurotransmission composed of common alleles at seven independent single nucleotide polymorphism (SNPs) that had previously been associated with both relatively decreased dopamine neurotransmission and decreased motor learning. The total number of alleles in each infant was determined (range=0–14). In this PRS, a higher score reflected genetic variation associated with relatively decreased dopamine neurotransmission.

The Bayley Scales of Infant Development, Second Edition was used to assess the outcomes at 18 to 22 months corrected age. It has scales for both motor development (Psychomotor Development Index [PDI]) and cognitive development (Mental Development Index [MDI]).

The primary study aim was to analyse NRN data to determine if genetic variation that favors relatively decreased dopamine neurotransmission, reflected in a relatively increased PRS, was inversely related to our measure of motor development, the PDI, in a convenience cohort of 498 infants born ELBW who had genome-wide genotyping and a complete neurodevelopmental assessment at 18 to 22 months corrected age. Secondary aims were to determine: if there was an effect modification in the relationships of PRS to PDI according to sex or CP diagnosis; if a greater genetic load of risk alleles, reflected in a greater mean PRS, predisposed to the diagnosis of CP; and if the PRS was inversely related to our measure of cognitive development, the MDI.

METHOD

This was a cohort comparison study. Establishment of an anonymized DNA database, using blood spots collected on filter paper for clinical purposes, to study genetic associations with outcomes in infants born ELBW was approved by the institutional review board at each participating site. A waiver of institutional review board authorization for use of this anonymized data set was obtained; if required by a local institutional review board, informed, written permission was obtained from the parents.⁸ Additional approvals by institutional review boards at NRN sites allowed for genome-wide genotyping of the samples and for genome-wide analyses pertaining to conditions associated with extreme preterm birth, including our previously published work on bronchopulmonary dysplasia (BPD), which utilized this cohort.⁹

DNA was extracted from the earliest age blood spots. Whole-genome amplification was used for samples that did not provide adequate genomic DNA. The blood spot samples from 834 infants born ELBW were analysed for genetic variation using the HumanOmni1-Quad BeadChip v1.0_B (Illumina, San Diego, CA, USA), with 1.2 million SNPs genotyped. Imputation was run with Beagle v3.3.1 (Brian Browning; <https://faculty.washington.edu/browning/beagle/beagle.html>) using 769 757 SNPs, resulting in 7 500 443 SNPs being imputed.¹⁰ Patients who had a call rate less than 95%, duplicate samples as indicated by an identity by state greater than 90%, first-degree relatedness as indicated by an identity by

descent greater than 40%, sex discordance, or excessive homozygosity were excluded.¹¹ Also excluded were patients with SNPs with a call rate less than 95% and with deviation from the Hardy–Weinberg equilibrium at $p < 10^{-4}$.

Since only maternal self-reported ethnicity data were collected, the genetic ancestry of infants was defined using the first four principal components derived from genome-wide association data. GWASTools v1.3.1 (Bioconductor; <https://bioconductor.org/packages/release/bioc/html/GWASTools.html>)¹² was used to generate eigenvalues for the entire data set; these principal components were included as covariates in our analyses to adjust for population stratification. Figure S1 (online supporting information) shows a scatterplot matrix of the four genome-wide principal components in the study population.

The PRS consisted of common alleles at seven independent SNPs that had been previously reported to be associated with both relatively decreased dopamine neurotransmission and decreased motor learning. Furthermore, the alleles had to be either genotyped or imputed in our genome-wide genotyping. Included in our PRS were six SNPs from five genes that influence dopamine neurotransmission directly^{5,13,14} and one SNP from the brain derived neurotrophic factor (*BDNF*) gene that has been associated with both diminished dopamine neurotransmission and reduced neuroplasticity,^{15–18} The two SNPs from *DRD1* showed only moderate linkage disequilibrium in the ethnically diverse study population ($r^2=0.301$) and both were included in the PRS. The PRS was calculated for each infant by summing the total number of alleles of interest across all SNPs (range=0–14 for each infant; Table 1).

Neurodevelopmental assessments were done at 18 to 22 months corrected age in specialized neonatal follow-up clinics. They included the Bayley Scales of Infant Development, Second Edition and an examination for CP. The Bayley Scales of Infant Development, Second Edition is a reliable, validated, standardized norm-referenced assessment tool that yields standard scores with a mean of 100 and an SD of 15. The child's age corrected for preterm birth was used to derive the scores. It was administered by experienced examiners who had been trained and certified as examiners for NRN developmental follow-up studies.¹⁹ The diagnosis of CP was made by experienced, certified physician examiners who had been trained to reliability in annual two-day training and certification meetings and included CP of all severities.¹⁹

The PDI was the principal outcome variable. It included items that assessed both fine and gross motor skills. The PDI and MDI are reliable and valid measures of motor and cognitive development respectively in infants and toddlers. When samples and data were collected, the Bayley Scales of Infant Development, Second Edition was the most up-to-date version of the Bayley Scales of Infant Development and was used extensively in follow-up studies of infants born preterm. The PDI is also moderately associated with later motor development.²⁰

To identify patient characteristics associated with PDI, a univariate linear model for each relevant clinical characteristic was fitted where PDI at 18 to 22 months was the outcome variable and the clinical characteristic was the predictor variable. Using this model, the coefficient estimate (representing the change in mean PDI score associated with a unit

increase in the predictor variables), the r^2 , and the p -value for each predictor variable were derived.

The clinical characteristics with univariate associations to the PDI at $p < 0.20$ were considered as candidate covariates for a multivariate linear model where the PDI was the outcome and the PRS was the predictor of primary interest. The candidate covariates were then pruned via stepwise variable removal, subject to $p < 0.05$, in the multivariable model.

The clinical characteristics that remained significantly associated with PDI after pruning were included in the final multivariate linear model along with the four genome-wide principal components, since these quantify genetic ancestry with greater accuracy than self-reported ethnicity.

We also investigated whether the inverse relationship between the dopamine neurotransmission PRS and PDI differed according to sex, CP status, or BPD status. Specifically, we fitted three different models that included a sex by PRS, a CP status by PRS, or a BPD status by PRS interaction term, then performed likelihood-ratio tests to assess the evidence for effect modification. The changes in PDI predicted for each 1-point change in the PRS were calculated separately for the clinical characteristics of sex (male/female), CP status (yes/no), and BPD status (yes/no). These data, along with a histogram of the frequency of patients by PRS, were aligned with each other vertically so that the number of patients in the study population with any PRS could be related to PDI in the three covariates.

In addition, we tested the hypothesis that a greater genetic load of alleles for relatively decreased dopamine neurotransmission predisposes to CP, by comparing the mean PRS in infants with CP to those without, adjusting for covariates. A multivariate linear regression model similar to the PDI regression model as used with MDI as the outcome variable to determine if the PRS was associated with a decrease in cognitive development.

We performed a 'leave-one-out analysis' for the seven allele PRS where each allele was left out of the PRS and the PRS of the remaining six alleles was related to the PDI, using the same multivariable regression model as for the seven allele PRS, described earlier. Finally, we examined the relationship of each allele individually to the PDI, again using the same model.

RESULTS

The study population was a subset of the 1067 infants born ELBW who were enrolled from 1999 to 2002 in a study of cytokines and developmental outcomes.⁸ Of the 751 infants with successful genome-wide genotyping, a convenience cohort of 498 infants born ELBW who had no major congenital anomalies and who had neurodevelopmental assessments at 18 to 22 months corrected age was studied.

Table 2 presents the characteristics of all patients in the NRN ELBW cohort who had successful genome-wide genotyping in infancy ($n=751$), contrasted to the study population

of survivors to 18 to 22 months corrected age who also had a neurodevelopmental assessment ($n=498$).

To identify potential covariates, univariate associations between clinical characteristics and PDI at 18 to 22 months corrected age were determined (Table S1, online supporting information). Lower gestational age, male sex, CP diagnosis, Apgar score equal to or lower than 5, late-onset sepsis, grade 3 or 4 intraventricular hemorrhage, and BPD were all significantly associated with lower PDI ($p<0.05$) and were therefore included in the multivariable linear regression model. No additional covariates would have been added if the requirement for inclusion had been set at $p<0.20$ instead. After pruning by stepwise removal of covariates, subject to $p<0.05$, only male sex, CP diagnosis, and BPD remained as covariates significantly associated with PDI; these three covariates were included in the final multivariable linear regression model along with the four genome-wide PCs.

Table 3 presents the results from the multivariate linear regression model that was used to test the main hypothesis, that is, an inverse association between PRS and PDI. The parameter estimates are for a linear model where PDI at 18 to 22 months corrected age was the outcome, and PRS, sex, CP diagnosis, gestational age, and the four genome-wide principal components for genetic ancestry were the predictors. After pruning, the PRS and the remaining covariates of male sex, CP diagnosis, and BPD were all independently associated with decreased PDI (Table 3; $p<0.05$) or, in other words, with a relative decrease in motor development. A statistically significant inverse relationship of PRS with PDI was found after adjusting for these covariates ($p=0.011$; $\beta=-1.370$). Each 1-point increase in the PRS resulted in an average decrease in PDI of 1.37 points.

In likelihood-ratio tests using models of interactions of clinical characteristics by PRS, we observed no compelling evidence for effect modification due to any of the patient characteristics of sex ($p=0.61$), CP status ($p=0.10$), or BPD status ($p=0.14$). Figure 1 shows the relationship of PDI to PRS by sex, CP status, and BPD status along with a histogram of the distribution of the study population by PRS, as a guide to the clinical significance of change in PRS to PDI associated with these covariates.

Covariates for the diagnosis of CP were identified, analogously to the process used to identify covariates with motor development, as assessed by the PDI. We then ran a multivariable model that was fitted for small for gestational age, late-onset sepsis, and sex (all identified as candidate covariates at $p<0.20$) and the four genome-wide principal components. We observed a mean PRS of 6.350 in infants with CP and 6.377 in those without CP. The adjusted difference between infants with CP and infants without CP was 0.072 ($p=0.670$). Therefore, there is no evidence that the dopamine neurotransmission PRS is associated with the diagnosis of CP.

An analysis similar to the one used to test the relationship between PRS and PDI was done for the relationship of PRS to MDI. PRS was not related to MDI (Table S2, online supporting information).

The analysis of the relationships of individual leave-one-out analyses is presented in Table S3 (online supporting information). Only the *BDNF* Val66Met allele was independently

related to PDI ($p=0.046$). When this allele was subtracted from the PRS, the PRS of the remaining six alleles remained significantly associated with PDI ($p=0.037$).

DISCUSSION

We found a significant relationship between genetic variation associated with diminished dopamine neurotransmission and lower PDI, reflecting a relative decrease in motor development in infants born ELBW, after adjusting for clinical covariates and genome-wide genotyping association indicators of ethnicity. This represents a previously unknown factor that may predispose to a decrease in motor development. The average contribution of each individual allele to diminished dopamine neurotransmission was small, a decrease of 1.37 in the PDI, which is consistent with genetic variation in dopamine neurotransmission having a relatively minor influence on motor development, as is the case for most genetic associations with multifactorial, complex phenotypes. Genetic variation that favors decreased dopamine neurotransmission was not associated with a decrease in cognitive development, as assessed by the MDI, suggesting that the decrease in motor development we found was not just a consequence of decreased cognitive development. Because genetic variation in dopamine neurotransmission has been related to motor learning and because motor learning is integral to motor development, the finding that genetic variation favoring decreased dopamine neurotransmission was associated with delay in motor development was not surprising.

In a rat model, disruption of dopaminergic neurotransmission by the dopamine-specific neurotoxin 6-hydroxydopamine prevents motor learning but not the execution of previously learned motor skills.³ Exposure of the human fetus to 3,4-methylenedioxymethamphetamine (ecstasy), which affects dopamine neurotransmission, results in delayed motor development, but not in delayed cognitive development, at 24 months of age.⁴ These different effects of genetic variation that favors decreased dopamine neurotransmission on cognitive development compared to motor development are consistent with our results; our PRS was inversely related to PDI but not to MDI. A plausible explanation for these findings is that the neural circuitry involved in cognition (and presumably in cognitive development) may be different from that for motor learning and motor development, and that cognitive development may not be as closely linked to dopamine neurotransmission as is motor development.

Nikolova et al.⁶ created a polygenic score for dopamine neurotransmission that reflected the additive effects of alleles associated with relatively increased dopamine neurotransmission in five dopamine neurotransmission-related genes. A higher score reflected more alleles associated with greater dopamine neurotransmission. Their dopamine neurotransmission polygenic score was associated with greater reward-related ventral striatal reactivity, measured by blood-oxygen-level-dependent functional magnetic resonance imaging, providing evidence that genetic variation associated with dopamine neurotransmission can modulate activity in dopamine-regulated neural circuitry and, possibly, dopamine neurotransmission itself. Furthermore, this finding is relevant to our study since the striatal reward system has been shown to potentiate motor learning.²¹

Pearson-Fuhrhop et al.⁵ summed five dopamine neurotransmission alleles into a different polygenic score than the one used by Nikolova et al.,⁶ but with the overlap of alleles at two SNPs. Higher polygenic scores, which favored increased dopamine neurotransmission, were associated with relatively better skilled motor task learning and greater neuroplasticity, assessed by transcranial magnetic stimulation.

Using the same polygenic score as Pearson-Fuhrhop et al.,⁵ Diaz Heijtz et al.⁷ studied motor learning in 33 children with unilateral spastic CP who had participated in a study of an intensive therapy program for the involved upper extremity (constraint-induced movement therapy). Individuals with higher polygenic scores, reflecting genetic variation that favored greater dopamine neurotransmission, had more improvement in hand function after the intervention.

The Val66Met allele of *BDNF* was individually significantly associated with decreased PDI, which is a novel observation. In addition to its role in dopamine neurotransmission,¹³ it has other effects that may influence motor development. However, when this allele was subtracted from the PRS and a six-allele PRS composed only of alleles that directly affect dopamine neurotransmission was analysed, the six-allele PRS was still significantly inversely related to PDI.

In univariate analyses to identify covariates with PDI, we found that male sex was associated with lower PDI (Table S1). This is consistent with the findings of Hintz et al.,²² who also studied an NRN cohort of infants born ELBW and found that males had relatively decreased motor development. We did not find an effect modification of the inverse relationship of PRS to PDI by sex. Similarly, Hintz et al.²² could not find any differences by sex in either risk or protective factors that could explain the relatively decreased motor and cognitive development of ELBW males.

We did not find that a greater genetic load of alleles favoring decreased dopamine neurotransmission predisposed to the diagnosis of CP nor did we find that infants with CP had a greater effect per allele on motor development..

Pearson-Fuhrhop et al.⁵ studied the effect of levodopa administration on motor learning in adults in a randomized, double blind, placebo-controlled, crossover trial.⁷ In individuals with low polygenic scores, reflecting diminished dopamine neurotransmission, levodopa resulted in better motor learning compared to placebo; in contrast, in those individuals with high polygenic scores, reflecting increased dopamine neurotransmission, levodopa resulted in decreased motor learning. Levodopa administration has been reported to improve recovery after stroke in some adults.²³ A hypothesis for research supported by these studies is that pharmacological augmentation of diminished dopamine neurotransmission might improve motor learning in children with developmental motor impairment and a high PRS, if administered during periods when they receive intensive therapy.

This study has several limitations. The generalizability of our findings may be affected by the improved survival of infants born ELBW to 18 months corrected age since 2002, resulting in differences in prevalence of comorbidities. Also, the durability of our findings through childhood development is unknown.

Since using a PRS in analyses of genetic associations with phenotypes is a relatively new idea with which some readers may not be familiar, its advantages over sequential testing of associations of multiple individual SNPs are presented,²⁴ specifically: (1) it makes possible testing of hypothesis-based genetic mechanisms underlying associations of variants with phenotypes; (2) it aligns genetic analyses with theoretical models of the genetic architecture of complex phenotypes, which are thought to be polygenic, that is, influenced by many genes; (3) it combines multiple variants, each of which may have a small effect and a skewed distribution, into one predictor variable that measures a larger total effect and is normally distributed, thereby increasing statistical power; (4) it reduces the number of hypotheses tested to one, that is, the association of a PRS with a phenotype, thereby eliminating the need to correct statistically for analysing associations of multiple individual SNPs with the phenotype of interest, thus greatly reducing the size of the sample needed; (5) it can be updated by adding genetic variants that relate to the phenotype of interest as they are discovered; (6) it can be refined by quantifying the contributions of individual variants toward predicting a phenotype by including β coefficients for variants as they are determined (the ‘weights of variants’) to increase the power of the model to predict the phenotype; and (7) it can result in epistasis, a gain (or loss) in power toward predicting a phenotype that is greater (or less) than the summed contributions of the individual variants, as in Pearson-Fuhrhop et al.⁵

CONCLUSION

Genetic variation that favors a relative decrease in dopamine neurotransmission is a previously unrecognized factor associated with a decrease in motor development, but not in cognitive development, in infants born ELBW. It is not an explanation for the decreased motor development of ELBW males, nor does it predispose to the diagnosis of CP.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

Joshua L Levy and Scott A McDonald are additional authors of the paper.

[†] Members of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network can be found in the Acknowledgements.

Grant and other information can be found in Appendix S1 (online supporting information).

ABBREVIATIONS

BDNF	Brain derived neurotrophic factor
BPD	Bronchopulmonary dysplasia
CP	Cerebral palsy
ELBW	Extremely-low-birthweight

MDI	Mental Development Index
NRN	Neonatal Research Network
PDI	Psychomotor Development Index
PC	Principal Component
PRS	Polygenic risk score
SNP	Single nucleotide polymorphism

REFERENCES

1. Spittle AJ, Cameron K, Doyle LW, Cheong JL; Victorian Infant Collaborative Study Group. Motor impairment trends in extremely preterm children: 1991–2005. *Pediatrics* 2018; 141: e20173410.
2. Diaz Heijtz R, Forssberg H. Translational studies exploring neuroplasticity associated with motor skill learning and the regulatory role of the dopamine system. *Dev Med Child Neurol* 2015; 57(Suppl. 2): 10–4.
3. Hosp JA, Luft AR. Dopaminergic meso-cortical projections to m1: role in motor learning and motor cortex plasticity. *Front Neurol* 2013; 4: 145. [PubMed: 24109472]
4. Singer LT, Moore DG, Min MO, et al. Motor delays in MDMA (ecstasy) exposed infants persist to 2 years. *Neurotoxicol Teratol* 2016; 54: 22–8. [PubMed: 26806601]
5. Pearson-Fuhrhop KM, Minton B, Acevedo D, Shahbaba B, Cramer SC. Genetic variation in the human brain dopamine system influences motor learning and its modulation by L-dopa. *PLoS One* 2013; 8: e61197.
6. Nikolova YS, Ferrell RE, Manuck SB, Hariri AR. Multilocus genetic profile for dopamine signaling predicts ventral striatum reactivity. *Neuropsychopharmacology* 2011; 36: 1940–7. [PubMed: 21593733]
7. Diaz Heijtz R, Almeida R, Eliasson AC, Forssberg H. Genetic variation in the dopamine system influences intervention outcome in children with cerebral palsy. *EBioMedicine* 2018; 28: 162–7. [PubMed: 29339100]
8. Carlo WA, McDonald SA, Tyson JE, et al. Cytokines and neurodevelopmental outcomes in extremely low birth weight infants. *J Pediatr* 2011; 159: 919–25.e3. [PubMed: 21798559]
9. Ambalavanan N, Cotten CM, Page GP, et al. Integrated genomic analyses in bronchopulmonary dysplasia. *J Pediatr* 2015; 166: 531–7. [PubMed: 25449221]
10. Howie BN, Donnelly P, Marchini J. A flexible and accurate genotype imputation method for the next generation of genome-wide association studies. *PLoS Genet* 2009; 5: e1000529.
11. Delaneau O, Zagury JF, Marchini J. Improved whole-chromosome phasing for disease and population genetic studies. *Nat Methods* 2013; 10: 5–6. [PubMed: 23269371]
12. Gogarten SM, Bhangale T, Conomos MP, et al. GWASTools: an R/Bioconductor package for quality control and analysis of genome-wide association studies. *Bioinformatics* 2012; 28: 3329–31. [PubMed: 23052040]
13. Noohi F, Boyden NB, Kwak Y, et al. Interactive effects of age and multi-gene profile on motor learning and sensorimotor adaptation. *Neuropsychologia* 2016; 84: 222–34. [PubMed: 26926580]
14. Baetu I, Burns NR, Urry K, Barbante GG, Pitcher JB. Commonly-occurring polymorphisms in the COMT, DRD1 and DRD2 genes influence different aspects of motor sequence learning in humans. *Neurobiol Learn Mem* 2015; 125: 176–88. [PubMed: 26419600]
15. Hyman C, Hofer M, Barde YA, et al. BDNF is a neurotrophic factor for dopaminergic neurons of the substantia nigra. *Nature* 1991; 350: 230–2. [PubMed: 2005978]
16. Guillin O, Diaz J, Carroll P, Griffon N, Schwartz JC, Sokoloff P. BDNF controls dopamine D3 receptor expression and triggers behavioral sensitization. *Nature* 2001; 411: 86–9. [PubMed: 11333982]

17. Egan MF, Kojima M, Callicott JH, et al. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell* 2003; 112: 257–69. [PubMed: 12553913]
18. Hünnerkopf R, Strobel A, Gutknecht L, Brocke B, Lesch KP. Interaction between BDNF Val66Met and dopamine transporter gene variation influences anxiety-related traits. *Neuropsychopharmacology* 2007; 32: 2552–60. [PubMed: 17392738]
19. Vohr BR, Wright LL, Dusick AM, et al. Neurodevelopmental and functional outcomes of extremely low birth weight infants in the National Institute of Child Health and Human Development Neonatal Research Network, 1993–1994. *Pediatrics* 2000; 105: 1216–26. [PubMed: 10835060]
20. Luttikhuisen dos Santos ES, de Kieviet JF, Königs M, van Elburg RM, Oosterlaan J. Predictive value of the Bayley scales of infant development on development of very preterm/very low birth weight children: a meta-analysis. *Early Hum Dev* 2013; 89: 487–96. [PubMed: 23597678]
21. Widmer M, Ziegler N, Held J, Luft A, Lutz K. Rewarding feedback promotes motor skill consolidation via striatal activity. *Prog Brain Res* 2016; 229: 303–23. [PubMed: 27926445]
22. Hintz SR, Kendrick DE, Vohr BR, Kenneth Poole W, Higgins RD; NICHD Neonatal Research Network. Gender differences in neurodevelopmental outcomes among extremely preterm, extremely-low-birthweight infants. *Acta Paediatr* 2006; 95: 1239–48. [PubMed: 16982497]
23. Scheidtmann K, Fries W, Müller F, Koenig E. Effect of levodopa in combination with physiotherapy on functional motor recovery after stroke: a prospective, randomised, double-blind study. *Lancet* 2001; 358: 787–90. [PubMed: 11564483]
24. Belsky DW, Israel S. Integrating genetics and social science: genetic risk scores. *Biodemography Soc Biol* 2014; 60: 137–55. [PubMed: 25343363]

What this paper adds

- Genetic variation associated with a decrease in dopamine neurotransmission, as assessed by a polygenic risk score (PRS), was associated with a decrease in motor development at 18 to 22 months of age corrected for preterm birth in infants born at an extremely-low-birthweight.
- It does not predispose to the diagnosis of cerebral palsy.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Figure 1:

Predicted Mean Bayley PDI at 18 Months as a Function of the Dopamine Neurotransmission PRS and Other Patient Characteristics

Panel A shows the predicted Average Bayley PDI at 18 Months as a Function of the DNT PRS, sex, CP status, and BDP status, based on results of the multivariable linear model (Table 3). Panel B shows a histogram of the DNT PRS among enrolled infants.

PRS=polygenic risk score

Table 1:

Components of the dopamine neurotransmission polygenic risk score

Gene	SNP	Alternate name	Risk allele	Protective allele	Risk allele frequency	Study
<i>BDNF</i> ^a	rs6265	Val66Met	A	G	0.078	Noohi et al. ¹³
<i>COMT</i>	rs4680	Val158Met	G (Val)	A (Met)	0.632	Pearson-Fuhrhop et al. ⁵
<i>DRD1</i>	rs686		G	A	0.445	Baetu et al. ¹⁴
<i>DRD1</i>	rs4532		A	G	0.807	Pearson-Fuhrhop et al. ⁵
<i>DRD2</i>	rs1076560	DRD2 G>T	A	C	0.184	Noohi et al. ¹³
<i>DRD2/ANKK1</i>	rs7118900 (proxy for rs1800497 [Taq1A])		G	A	0.681	Noohi et al. ¹³
<i>DRD3</i>	rs6280	Ser9Gly	Ser	Gly	0.413	Pearson-Fuhrhop et al. ⁵

^a *BDNF* interacts with dopamine neurotransmission.^{15–18} SNP, single nucleotide polymorphism.

Table 2:

Characteristics of enrolled infants

Variable	Entire population	Patients with 18-month PDI
Sample size	751	498
Bayley PDI, 18mo, mean (SD, IQR)	84.5 (18.9, 74.0–98.0)	84.5 (18.9, 74.0–98.0)
Bayley MDI, 18mo, mean (SD, IQR)	78.4 (17.9, 64.0–91.0)	78.4 (17.9, 64.0–91.0)
Dopamine neurotransmission genetic risk score, mean (SD, IQR)	6.4 (1.3, 5.0–7.0)	6.4 (1.3, 6.0–7.0)
Gestational age, wks, mean (SD, IQR)	25.8 (2.0, 24.0–27.0)	26.1 (1.9, 25.0–27.0)
Small for gestational age, <i>n</i> (%)	105 (14.0)	79 (15.9)
Cerebral palsy, <i>n</i> (%)	77 (14.2)	65 (13.2)
Ethnicity, <i>n</i> (%)		
Black	404 (53.8)	269 (54.0)
White	339 (45.1)	225 (45.2)
Other	8 (1.1)	4 (0.8)
Hispanic ethnicity, <i>n</i> (%)	156 (20.8)	107 (21.5)
Male sex, <i>n</i> (%)	354 (47.1)	223 (44.8)
Apgar at 5min <5, <i>n</i> (%)	103 (13.9)	63 (12.8)
Necrotizing enterocolitis, <i>n</i> (%)	81 (10.8)	41 (8.2)
Late-onset sepsis, <i>n</i> (%)	320 (43.5)	201 (40.4)
Grade III or IV intraventricular hemorrhage, <i>n</i> (%)	123 (16.7)	59 (11.9)
Periventricular leukomalacia, <i>n</i> (%)	36 (4.9)	22 (4.4)
Bronchopulmonary dysplasia, <i>n</i> (%)	310 (48.8)	230 (46.2)

Percentages computed in patients with populated data for a given variable. Bayley, Bayley Scales of Infant Development; PDI, Psychomotor Development Index; SD, standard deviation; IQR, Interquartile range; MDI, Mental Development Index.

Table 3:

Multivariate linear regression model of Bayley Scales of Infant Development, Second Edition Psychomotor Development Index at 18 to 22 months corrected age as a function of the dopaminergic neurotransmission polygenic risk score (PRS) and other patient characteristics

	Coefficient estimate	Standard error	<i>t</i>	<i>p</i>	95% confidence interval	Standardized coefficient
Variable of interest						
Dopamine neurotransmission PRS	-1.370	0.540	-2.539	0.011	-2.431 to -0.310	-0.097
Covariates						
Cerebral palsy	-23.197	2.184	-10.621	<0.001	-27.488 to -18.906	-0.414
Male sex	-3.242	1.478	-2.194	0.029	-6.145 to -0.338	-0.085
BPD	-9.012	1.487	-6.063	<0.001	-11.933 to -6.091	-0.237
PC1	-12.531	20.316	-0.617	0.538	-52.450 to 27.387	-0.024
PC2	11.843	20.845	0.568	0.570	-29.116 to 52.801	0.022
PC3	3.518	21.244	0.166	0.869	-38.224 to 45.260	0.006
PC4	-24.580	31.538	-0.779	0.436	-86.548 to 37.387	-0.030

PC1–PC4 are the genome-wide principal components used to categorize and quantify genetic ancestry with greater accuracy than self-reported ethnic group; they are included as covariates to adjust for population stratification. Other patient characteristics included as covariates in the multivariate model were selected based on stepwise variable selection requiring $p < 0.05$. BPD, bronchopulmonary dysplasia.