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Brain Development and Cognitive Functioning in Preschoolers Born Very Preterm

Author
Hasler, Holly Marie Girard

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Brain Development and Cognitive Functioning in Preschoolers Born Very Preterm

A dissertation submitted in partial satisfaction of the
requirements for the degree Doctor of Philosophy

in

Clinical Psychology

by

Holly Marie Girard Hasler

Committee in charge:

University of California San Diego

Professor Natacha Akshoomoff, Chair
Professor Timothy T. Brown
Professor Carrie R. McDonald

San Diego State University

Professor Sarah N. Mattson
Professor Scott C. Roesch

2019

The Dissertation of Holly Marie Girard Hasler is approved and it is acceptable in quality and form for publication on microfilm and electronically:

Chair

University of California San Diego

San Diego State University

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I would also like to thank the other members of my dissertation committee for their contributions to this work as well as my professional development more broadly. In addition, I would like to thank the other coauthors who contributed to the manuscripts associated with this dissertation. In particular, Dr. Martha Fuller and Dr. Yvonne Vaucher for sharing their incredible knowledge of the field and providing feedback that has undoubtedly improved this and my future work. In addition, to Dr. Joan Stiles and Dr. Terry Jernigan for providing such extraordinary examples of women role models and for their consultation on each and every project I have undertaken.

I would like to express my sincere gratitude to every family who participated in this research. Importantly, I would like to thank everyone at the BEE Lab who made this work possible by supporting scheduling, data collection, double-entry, and the myriad of other tasks that made my life so much easier.

Certainly not least, I would like to acknowledge the village that has supported me to this point. In particular, Matt and my parents for never doubting what I was capable of even when I did. Also, to my graduate cohort for keeping me on track, and to Ben and Mary for reviewing my projects and providing endless encouragement.

Please note that Chapter 2, in full, is a reprint of the material as it appears in *Child Neuropsychology*, 2019, Taylor & Francis Group. The dissertation author was the primary investigator and author of this material. Chapter 3, in full, has been submitted for publication of the material as it may appear in Early Human Development, Elsevier US. The dissertation author was the primary investigator and author of this material. Additionally, Chapter 4, in full, has been submitted for publication of the material as it may appear in Brain Imaging and Behavior, Springer US. The dissertation author was the primary investigator and author of this material.

VITA

Education

September 2019 **Doctor of Philosophy in Clinical Psychology**
San Diego State University/University of California San Diego
Joint Doctoral Program in Clinical Psychology
Concentration: Neuropsychology
Dissertation Title: Brain development and cognitive functioning in preschoolers born very preterm
Dissertation Chair: Natacha Akshoomoff, Ph.D.

August 2015 **Masters of Science in Clinical Psychology**
San Diego State University
Thesis Title: Relationship among calculation abilities and general cognitive factors in children and adolescents

June 2009 **Bachelors of Arts in Cognitive Science**
University of California, San Diego

Awards and Honors

2015 – 2016 **Frontiers of Innovation Scholars Fellowship**
University of California, San Diego
Mentors: Natacha Akshoomoff, Ph.D. and Joan Stiles, Ph.D.
1-year, $25,000 fellowship to support a mentored, interdisciplinary research project.

2015 – 2016 **Dorathe L. Frick Memorial Award**
San Diego State University/University of California, San Diego
Awarded to third year doctoral student voted by faculty to have made a significant contribution to the doctoral program and training facility.

May 2014 **Sponsored Presenter**
Development of Mathematical Cognition: Neural Substrates and Genetic Influences Conference, May 19-20th 2014 Washington D.C.
Selected as one of 8 posters to be presented and sponsored attendance.

Research Experience

2013 – Present **Graduate Student Researcher**
Center for Human Development
Brain and Early Experiences Laboratory
University of California, San Diego
Neural Basis of Emergent Math Difficulties in Healthy Preterm Children
Principal Investigator: Natacha Akshoomoff, Ph.D.

- Longitudinal investigation of neurocognitive development in children preschool age to second grade who were born preterm utilizing structural magnetic resonance imaging, diffusion tensor imaging, and neuropsychological measures.
- Certified scanner operator in charge of mock scan training sessions and brain imaging collection (170 scan sessions collected)
- Management, processing, and analysis of neuroimaging data
- Collection of neuropsychological and behavioral data
- Preparation of yearly reports of performance on neuropsychological measures for participants' caregivers
- Training and supervision of staff to collect and score behavioral data

Pediatric Longitudinal Imaging, Neurocognition, and Genetics Project & Pediatric Imaging, Neurocognition, and Genetics Project

- Investigation of neurocognitive development of typically developing children ages three to thirteen.
- Training and supervision of staff to perform neuropsychological assessments
- Ad-hoc scanner operator
- Coordination and analysis of neuroimaging and neuropsychological data

2008 – 2013 **Research Associate**
Multimodal Imaging Laboratory
University of California, San Diego

Multimodal Imaging of Language in the Preoperative Evaluation of Epilepsy
Neuropsychological and Neuroanatomical Profiles of Children with Temporal Lobe Epilepsy
Principal Investigator: Carrie McDonald, Ph.D., ABPP-CN

- Multi-site magnetic resonance imaging (MRI, fMRI, DTI, fcMRI) collection, processing, and analysis
- Magnetoencephalogram and neuropsychological assessment collection, processing and analysis

Structural and Functional Imaging of Changes in Cognition in Healthy Aging and in Age-Related Disorders
Principal Investigator: Linda McEvoy, Ph.D.

- Multi-site magnetic resonance imaging (MRI and DTI) collection, processing, and analysis
- Magnetoencephalogram and neuropsychological data collection, processing, and analysis

2007 – 2008 **Undergraduate Research Assistant**
Project in Cognitive and Neural Development
University of California, San Diego

Auditory and Visual Sensory Processing Project
Principal Investigator: Rita Ceponiene, MD., Ph.D.

- Electroencephalogram data collection and analysis in children with

Cystinosis and Autism
- Presentation of ERP concepts and journal articles in weekly laboratory meetings

Graduate Clinical Experience

2018 - Current **Pre-Doctoral Intern**

Pediatric Neuropsychology - Epilepsy Specialty Clinic
Dell Children's Medical Center of Central Texas
Supervisor: *Nancy Nussbaum, Ph.D., ABPP-CN*
- Co-conducted intake interviews with children's guardian, administered measures, and led feedback sessions
- Assessments conducted on the Epilepsy Monitoring Unit during prolonged video-EEG to characterize seizures, outpatient pre-surgical assessments, and post-surgical follow-up assessments

Comprehensive Care Center
Dell Children's Medical Center of Central Texas
Supervisor: *Amanda Winter-Greenberg, Ph.D.*
- Primary care clinic for children with complex medical needs, requiring regular visits with two or more specialists (e.g., Cerebral Palsy, Spinabifida, Down Syndrome, Costello Syndrome, CHARGE Syndrome)
- Co-conducted parent intake interviews, administered measures, and assisted with providing assessment feedback

Children's Blood and Cancer Center
Dell Children's Medical Center of Central Texas
Supervisor: *Emily Greenspahn, Ph.D.*
- Pre- and post-treatment assessment of children and adolescents with a variety of blood disorders and cancers including primary brain tumors.

Concussion/Traumatic Brain Injury Clinic
Dell Children's Medical Center of Central Texas
Supervisor: *Kelly Jones, Ph.D.*
- Brief initial assessments during acute injury phase as well as re-assessment during recovery and return to baseline.
- Bedside assessments and consultation on the Rehabilitation Unit with children who are in the acute stage of a variety of injuries

Texas Child Study Center
Supervisor: *Sasha Jaquez, Ph.D.*
- Community clinic providing outpatient therapy
- Provided evidence-based treatment for children and adolescents with a variety of presenting concerns including depression, behavioral problems, adjusting to new medical diagnosis, and anxiety

2017 – 2018 **Practicum Trainee**

Child and Adolescent Psychiatry Service
Rady Children's Hospital San Diego

__Supervisor:__ Sandra J. Brown, Ph.D.

- Inpatient unit for children and teens placed on psychiatric holds with psychiatric disorders including anxiety, depression, psychosis, post-traumatic stress disorder, borderline personality disorder, intellectual disability, and autism spectrum disorder (ASD)
- Brief emotional, cognitive, and psychological assessments
- Leader of group and individual therapy sessions using Dialectical Behavior Therapy and Cognitive-Behavioral Therapy techniques
- Conducted family meetings and safety planning prior to discharge

2016 – 2017 **Practicum Trainee**

Neuropsychological Assessment Unit

Veterans Administration San Diego Healthcare System

__Supervisors:__ Mark Bondi, Ph.D., J. Vincent Filoteo, Ph.D., and Gregory Brown, Ph.D.

- Assessment administration, interpretation, and integrated report writing
- Cognitive and psychological evaluation and report writing for Veterans of all ages referred for a variety of causes included suspected neurodegenerative processes, functioning after brain injury, and long-standing learning issues.

2016 – 2017 **Practicum Trainee**

Heaton Neuropsychology Laboratory

University of California, San Diego

__Supervisor:__ Robert Heaton, Ph.D.

- Test interpretation and integrated report writing
- Completed integrated reports for patients from individuals who had experienced injury, accidents, or medical conditions who were referred for evaluation primarily through litigation.

2015 – 2016 **Practicum Trainee**

Outpatient Psychiatry Service

Rady Children's Hospital San Diego

__Supervisors:__ Katherine Williams, Ph.D. and Lauren Brookman-Frazee, Ph.D.

- Outpatient clinic serving children, adolescents, and families providing therapy and neuropsychological assessment
- Experience treating ADHD, Oppositional Defiant Disorder, OCD, anxiety, and depression
- Individual and family therapy including Parent Management Training, Exposure and Response Prevention, and Organizational Skills Training
- Member of Anxiety and Obsessive-Compulsive Disorder consultation group, within-clinic group designed for advanced treatment of these disorders.

2014 – 2015 **Practicum Trainee**

Joint Doctoral Program Psychology Clinic
San Diego State University

***Supervisors**: Vanessa Malcarne, Ph.D. and Monica Ullibari, Ph.D.*

- Outpatient, sliding fee scale community clinic serving adults and children
- Treatment of anxiety, depression, and OCD
- Training and experience with Cognitive-Behavioral Therapy, Couple's Therapy, Exposure and Response Prevention, and Acceptance and Commitment Therapy

Specialized Clinical Training

September 2018 Motivational Interviewing (MI): An Introductory Workshop
- Two-day course covering the basics of
- Conducted by Lloyd Berg, Ph.D. and Jane Gray, Ph.D. of the Department of Psychiatry, Dell Medical School at the University of Texas at Austin

August 2018 Modular Approach to Therapy for Children with Anxiety, Depression, Trauma, or Conduct Problems (MATCH – ADTC)
- Five-day training covering the fundamentals of each module for the four presenting problems addressed in the MATCH – ADTC treatment program
- Conducted by Sarah Kate Bearman, Ph.D. and Jane Gray, Ph.D. of the University of Texas at Austin Department of Educational Psychology

September 2017 Dialectical Behavior Therapy (DBT) & Eating Disorders
- Two-day, intensive training designed to cover the basics of DBT treatment and its application
- Conducted by Leslie Anderson, Ph.D. and Julie Trim, Ph.D. of the University of California, San Diego Eating Disorders Center for Treatment and Research.

September 2016 Autism Diagnostic Observation Schedule – Second Edition (ADOS-2)
- Certified reliable in administration and scoring
- Conducted by Natacha Akshoomoff, Ph.D. of Rady Children's Hospital Autism Discovery Institute

January 2016 Tic and Tourette Syndrome Symposium
- Full-day training covering current research on the causes, assessment, evidence-based treatment, and comorbidities of tics and Tourette Syndrome
- Conducted by Rady Children's Hospital Tic/Tourette Center and University of California, San Diego School of Medicine

September 2016 Seminar: Child Development and Neuropsychology
- Elective quarter-length course on clinical and research practice from a developmental perspective
- Discussion of relevant literature, a variety of assessment and intervention

approaches, and recent research findings

Other Clinical Experience

2009 – 2013 **Epilepsy Surgical Evaluation Team Member**
Epilepsy Center, Department of Neurosciences
University of California, San Diego
- Observation of intracarotid amobarbitol (Wada) procedures
- Discussion of research and medical results at monthly case conferences

2010 – 2012 **Certified Psychometrist**
UCSD Health Stroke Center
University of California, San Diego
Principal Investigator: Brett C. Meyer, MD.
Secondary Prevention of Small Subcortical Strokes
- Clinical trial evaluating adults with primary cortical strokes
- Administration and scoring of neuropsychological batteries

Teaching Experience

04/03/2019 **Dell Children's Medical Center Pediatric Neuropsychology Seminar**
Lecture title: The Effects of Prematurity on Brain Development and Cognition
Dell Children's Medical Center of Central Texas
- Scheduled invited talk on the current state of performance validity in neuropsychological assessment of children
- Intended audience of neuropsychologists and trainees including postdoctoral fellows, interns, and graduate practicum students

01/26/2016 **Rady Children's Outpatient Psychology Seminar Series**
Lecture title: Neuropsychological Evaluation & Its Role in Child Mental Health Care
Rady Children's Hospital San Diego
- Lecture on overview of clinical psychological and neuropsychological assessment for non-neuropsychologists
- Audience of clinicians, social work and marriage and family therapy trainees, and researchers affiliated with Rady Children's Hospital mental health services

2011 – 2013 **FreeSurfer Processing Instructor**
San Diego State University; Center for Behavioral Teratology
University of California, San Diego; Aging and Cognition Laboratory
Trainer of graduate students and research assistants in FreeSurfer MRI processing

2009 – 2013 **Laboratory Staff Trainer**

Multimodal Imaging Laboratory
University of California, San Diego

Training of incoming post-doctoral students, graduate students, and research assistants in data collection and analysis techniques for MRI and MEG including:

- FreeSurfer processing
- MEG Independent Component Analysis
- MEG dynamic statistical parametric mapping
- Administration and scoring of neuropsychological measures

Service

August 2017 **Graduate Student Consultant**
Summer Training Academy for Research Success
University of California, San Diego

- Intensive research program for undergraduate students from underrepresented groups who are interested in graduate school
- Met with students interested in applying to clinical psychology programs to advise on how to choose a program and the application process

2016 **Ad-hoc Reviewer -** Neuropsychologia

2014 – 2016 **Student Selection Application Review and Interviewer**
SDSU/University of California, San Diego Joint Doctoral Program in Clinical Psychology

- Reviewed applications for prospective graduate students
- Conducted interviews with potential candidates
- Organized housing and transportation with current students for applicants invited for interviews
- Coordinated events for current students and applicants including welcome and three track-specific social events.

04/10/2016 **Invited Panel Speaker**
Cognitive Science Alumni Career Panel
University of California, San Diego

- Meeting for current undergraduates and community members to discuss career paths and experiences with cognitive science alumni

11/6/2014 **Psychology Pathways to Ph.D. Panel Member**
University of California, San Diego

- Representative for clinical psychology Ph.D.
- Discussed experience in graduate school and preparation for applications at a meeting of Psychology undergraduate students.

2011 – 2013 **Lead Volunteer**
Expressive Arts Program

Epilepsy Foundation of San Diego

- Children, Teen, and Young Adult programs
- Assisted the Expressive Arts Therapist in planning and implementation of sessions
- Coordination of volunteers and implementation of projects during sessions

Publications

Peer Reviewed

Hasler, H. M., Brown, T. T., & Akshoomoff, N. (Submitted). Variations in brain morphometry among healthy preschoolers born very preterm. *Early Human Development*

Hasler, H. M., Fuller, M. G., Vaucher, Y. E., Brown, T. T., Stiles, J., Dale, A. M., Jernigan, T. L., & Akshoomoff N. (Under Review). Movement abilities and brain development in preschoolers born very preterm. *Brain Imaging and Behavior*

Hasler, H. M. and Akshoomoff, A. (2019). Mathematics ability and related skills in preschoolers born very preterm. *Child Neuropsychology.* 1-17. doi: 10.1080/09297049.2017.141241

Kucukboyaci, N. E., Kemmostu, N., Leyden, K. M., **Girard, H. M.**, Tecoma, E. S., Iragui V. J., & McDonald, C.R. (2014). Integration of multimodal MRI data via PCA to explain language performance. *NeuroImage: Clinical, 5,* 197-207. doi:10.1016/j.nicl.2014.05.006

Kemmostu, N., Kucukboyaci, N.E., Cheng, C. E., **Girard, H. M.**, Tecoma, E. S., Iragui, V. J. & McDonald, C. R. (2013). Alterations in functional connectivity between the hippocampus and prefrontal cortex as a correlate of depressive symptoms in temporal lobe epilepsy. *Epilepsy and Behavior, 29(3),* 552-559. doi:10.1016/j.yebeh.2013.09.039

Kucukboyaci, N.E., Kemmostu, N., Cheng, C. E., **Girard**, **H. M.**, Tecoma, E. S., Iragui, V.J., & McDonald, C. R. (2013). Functional connectivity of the hippocampus in temporal lobe epilepsy: Feasibility of a task-regressed seed-based approach. *Brain Connectivity, 3(5),* 464-474. doi:10.1089/brain.2013.0150

Kothari, P. D., White, N. S., Farid, N., Chung, R., Kuperman, J. M., **Girard, H. M.**, Shankaranarayanan, A., Kesari, S., & *McDonald, C. R. *Dale, A. M. (2013). Longitudinal restriction spectrum imaging is resistant to pseudoresponse in patients with high-grade gliomas treated with Bevacizumab. *American Journal of Neuroradiology, 34,* 1752-1757. doi:10.3174/ajnr.A3506

Kemmotsu, N., **Girard, H. M.**, Kucukboyaci, N. E., McEvoy, L. K., Hagler Jr., D. J., Dale, A. M., Halgren, E., & McDonald, C. R. (2012). Age-related changes in the neurophysiology of language in adults: Relationship to regional cortical thinning and white matter microstructure. *Journal of Neuroscience, 35,* 12204-12213. doi: 10.1523/jneurosci.0136-12.2012

Farid, N., **Girard, H. M.**, Kemmotsu, N., Smith, M. E., Magda, S. W., Lim, W. Y., Lee, R. R., & McDonald, C. R. (2012). Temporal lobe epilepsy: Quantitative MR volumetry in detection of hippocampal atrophy. *Radiology, 264,* 242-550. doi: 10.1148/radiol.12112638

Thesen, T., McDonald, C. R., Carlson, C., Doyle, W., Cash, S., Sherfey, J., Felsovalyi, O., **Girard, H. M.**, Barr, W., Devinsky, O., Kuzniecky, R., & Halgren E. (2012). Sequential then interactive processing of letters and words. *Nature Communications, 3,* 1284. doi:10.1038/ncomms2220

Kucukboyaci, N. E., **Girard, H. M.**, Hagler Jr., D. J., Kuperman, J., Tecoma, E. S., Iragui, V.J., Halgren, E., & McDonald, C. R. (2012). Role of frontotemporal fiber tract integrity in task-switching performance of healthy controls and patients with temporal lobe epilepsy. *Journal of the International Neuropsychological Society, 18,* 57-67. doi: 10.1017/S1355617711001391

Kemmotsu, N., **Girard, H. M.**, Bernhardt, B. C., Bonilha, L., Lin, J. J., Tecoma, E. S., Iragui, V. J., Hagler Jr., D. J., Halgren, E., & McDonald C. R. (2011). MRI analysis in temporal lobe epilepsy: Cortical thinning and white matter disruptions are related to side of seizure onset. *Epilepsia, 52*, 2257-2266. doi: 10.1111/j.1528-1167.2011.03278.x

McDonald, C. R., Hagler Jr, D. J., **Girard, H. M.**, Pung, C., Ahmadi, M. E., Holland, D., Patel, R. H., Barba, D., Tecoma, E. S., Iragui, V. J., Halgren, E., & Dale, A. M. (2010). Changes in fiber tract integrity and after anterior temporal lobectomy. *Neurology, 7* 1631-1638. doi: 10.1212/WNL.0b013e3181fb44db

McDonald, C. R., Thesen, T., Carlson, C., Blumberg, M., **Girard, H. M.**, Trongnetrpunya, A., Sherfey, J. S., Devinsky, O., Kuzniecky, R., Doyle, W., Cash, S. S., Leonard, M. K., Hagler Jr., D. J., Dale, A. M., & Halgren, E. (2010). Multimodal imaging of repetition priming: Using fMRI, MEG, and intracranial EEG to reveal spatiotemporal profiles of word processing. *Neuroimage, 53*, 707-717. doi: 10.1016/j.neuroimage.2010.06.06

Abstracts (Paper and Poster Presentations)

Hasler, H. M., Haist, F., Jernigan, T. L., Stiles, J., & Akshoomoff, N. (2019, February) Growth of Formal and Informal Mathematics Skills in Children Born Very Preterm. Accepted as a poster presentation for the annual meeting of the International Neuropsychological Society, New York, NY.

Fuller, M. G., **Hasler H. M.**, Vaucher, Y.E., & Stiles, J. Akshoomoff, N., (2018, May). White Matter Abnormalities and Motor Skill Deficits in Preschoolers Born Very Preterm. Poster presentation at the annual meeting of the Pediatric Academic Societies, Toronto, Canada.

Akshoomoff, N., **Hasler, H. M.**, Fuller, M. G., Torres, S., Vaucher, Y. E., & Stiles, J. (2016, May). Motor skill differences and MRI brain measures in healthy preschoolers born very

preterm. Platform presentation at the annual meeting of the Pediatric Academic Societies, Baltimore, MD.

Hasler, H. M., Torres, S., Fuller, M. G., Stiles, J., Vaucher, Y. E., & Akshoomoff, N. (2016, February). Moved to learn: Movement abilities correlate with cognition in preschoolers born very preterm. *Journal of the International Neuropsychological Society.* Poster presented at the annual meeting of the International Neuropsychological Society, Boston, MA.

Torres, S., **Hasler, H. M.**, Han, J., Stiles, J., & Akshoomoff, N. (2016, February). "When touch your head means touch your toes?": Executive function deficits in preterm children. *Journal of the International Neuropsychological Society.* Poster presented at the annual meeting of the International Neuropsychological Society, Boston, MA.

Atkinson, J., Braddick, O., Wattam-Bell, J., Akshoomoff, N., Newman, E., **Girard, H. M.**, Dale, A. M., Jernigan, T. (2014, May). Global motion, mathematics and movement: Dorsal stream sensitivity relates to children's individual differences in cognitive abilities and regional brain development. *Journal of Vision*, *14*, 1324-1324. Presented at the annual meeting of the Vision Science Society. St. Pete Beach, FL.

Girard, H. M. (2014, May). Math on the mind: Investigating the relationship of white matter development to mathematics achievement in five to twelve-year-olds. Poster presented at the Development of Mathematical Cognition: Neural Substrates and Genetic Influences Conference, Washington, D.C.

Girard H. M., Kemmotsu, N., Kucukboyaci, N. E., Kuperman, J. M., Dale, A.M., & McDonald, C. R. (2013, February). Beginning to see clearly: Application of prospective motion correction (PROMO) MRI to pediatric epilepsy. *Journal of the International Neuropsychological Society.* Poster presented at the International Neuropsychological Society Annual Meeting, Waikoloa, HI.

Girard, H. M., Kemmotsu, N., Kucukboyaci, N. E., Hagler Jr., D. J., Tecoma, E. S., Iragui, V. J., & McDonald C. R. (2012, November). Quantifying the contribution of thalamic volume and white matter microstructure to regional cortical thinning in mesial temporal lobe epilepsy (MTLE). Poster presented at the annual meeting of the American Epilepsy Society, San Diego, CA.

Girard, H. M., Kemmotsu, N., Kucukboyaci, N. E., Tecoma, E. S., Iragui, V. J., & McDonald, C. R. (2011, December). Diffusion of subcortical structures enhances the prediction of verbal memory performance and seizure lateralization in mesial temporal lobe epilepsy. *Epilepsia. Abstract No 1.241*. Poster presented at the annual meeting of the American Epilepsy Society, Baltimore, MD.

Girard, H. M., Kemmotsu, N., Hagler Jr., D. J., Iragui, V. J., Tecoma, E. S., & McDonald C. R. (2010, December). Effects of age of seizure onset and disease duration on cortical thinning and white matter compromise in mesial temporal lobe epilepsy. *Journal of the*

International Neuropsychological Society. Poster presented at the annual meeting of the International Neuropsychological Society, Boston, MA.

McDonald, C. R., Hagler Jr., D. J., **Girard, H. M.,** Pung, C., Ahmadi, M. E., Holland, D., Patel, R. H., Barba, D., Tecoma, E. S., Iragui, V. J., Halgren, E., & Dale, A. M. (2010, December) Changes in fiber tract integrity and visual fields after anterior temporal lobectomy. *Epilepsia*. *Abstract No. 2.116*. Poster presented at the annual meeting of the American Epilepsy Society, San Antonio, TX.

McDonald, C. R., **Girard, H. M.**, Gharapetian, L., Hagler Jr., D. J., Kuperman, J., Iragui, V. J., Tecoma, E. S., Dale, A. M., & Halgren, E. (2009**,** December). Relationships between fiber tract compromise and regional cortical thinning in patients with mesial temporal lobe epilepsy (MTLE). *Epilepsia. 50(s11),* 76. Poster presented at the annual meeting of the American Epilepsy Society, Boston, MA.

ABSTRACT OF THE DISSERTATION

Brain Development and Cognitive Functioning in Preschoolers Born Very Preterm

by

Holly Marie Girard Hasler

Doctor of Philosophy in Clinical Psychology

University of California, San Diego, 2019
San Diego State University, 2019

Professor Natacha Akshoomoff, Chair

Rationale. Very preterm (VPT) birth, birth before 33 weeks gestational age, puts children at increased risk for a variety of neurodevelopmental, cognitive, and behavioral difficulties as they grow. Severe complications of VPT birth (e.g., Grade 3-4 intraventricular hemorrhage, cystic periventricular leukomalacia, bronchopulmonary dysplasia) are associated with more serious functional deficits and often prompt extensive follow-up. However, milder

brain injury may result in subtle deficits that may only become apparent when children begin to struggle in elementary school, particularly with regard to neuromotor functioning, mathematics, and related skills. A better understanding of the neuropsychological and neuroanatomical variations related to VPT birth as these children are entering kindergarten is therefore needed to develop screening procedures and guide appropriate interventions in the future.

Design. 60 children born VPT without severe birth-related complications and 40 children born full term (FT) were enrolled in this study within six months of beginning kindergarten. Each child underwent structural magnetic resonance imaging (MRI), diffusion-tensor imaging (DTI), and a battery of neuropsychological measures. The aims of this study were to (1) evaluate mathematics abilities and determine the set of skills across a set of a priori measures from related cognitive domains that mediate the group differences between performance on a mathematics measure using a multiple mediation model, (2) utilize structural MRI to conduct an exploratory analysis to compare cortical morphometry measures of gray matter thickness, surface area, and sulcal depth between groups using a voxel-wise, surface-based method, and (3) examine overall group differences in motor task performance, and compare an a priori set of regional white matter integrity measures and brain structural volumes in VPT children with and without motor deficits.

Results. Groups did not differ significantly on age, sex distribution, or socioeconomic status (a combination of maternal education and household income). Study 1 found that children born VPT scored significantly lower on the mathematics measure. The difference between VPT and FT groups was mediated by scores on tests of visual-motor integration, verbal comprehension, and phonological awareness but not but by motor skills, parent-reported executive functioning, spatial working memory, or phonological working memory. In Study 2, VPT-born children showed a widespread pattern of reduced cortical thickness in the temporal and lateral parietal lobes and increased cortical thickness in the medial occipital lobe. Cortical surface area was larger in the medial cingulate in the VPT-born group but smaller in the fusiform area. In Study 3, the VPT-born children performed significantly worse on the motor measure, with 50% demonstrating clinically significant deficits. The VPT-born children with motor deficits demonstrated lower fractional anisotropy (FA) and higher mean diffusivity (MD) in the forceps major compared to the VPT group without motor deficits. The VPT group with motor deficits also showed higher MD in the corpus callosum and lower FA compared to the FT group in the forceps major, anterior thalamic radiations (ATR), and cingulum. Both VPT groups had significantly reduced volumes of the thalamus, brainstem, and cerebellar white matter compared to the FT group. Additional regions that were initially hypothesized to be related but were not significant between-group predictors were volume of the corpus callosum, forceps minor, ATR, and cortical-spinal tract (CST), as well as volumes of the ventral diencephalon and basal ganglia. White matter diffusion measures (FA and MD) of the inferior frontal-occipital fasciculus, thalamus, basal ganglia, superior cortical striatal fibers, and CST were not significant predictors of group.

Conclusion. Advances in medical care have resulted in decreased mortality and reduced rates of more severe neurological complications in children born preterm. However as shown here, even children born very preterm with a relatively benign early health history often demonstrate difficulties in mathematics and motor skills. These difficulties are related to subtle differences in neuroanatomical areas often affected by very preterm birth. Pre-kindergarten screening of motor functioning, mathematics, and related cognitive skills may assist in early detection of difficulties, leading to increased opportunities for appropriate support and interventions, and potentially improvement of long-term outcomes.

Chapter 1:

Integrated Introduction

In the United States about 1 in 10 babies are born preterm and the rate of early birth continues to increase (Martin, Hamilton, Osterman, Driscoll, & Mathews, 2017). Very preterm (VPT) birth, gestational age of less than 33 weeks, has been correlated with an increased risk of serious health issues. Due to advances in neonatal care, an increasing number of infants survive preterm birth and more severe forms of birth defects (e.g., cerebral palsy or periventricular leukomalacia grade IV) are becoming less common (Martin, Hamilton, & Osterman, 2016). However, 25-50% VPT born children experience some form of subtle brain injury, cognitive, and/or behavioral difficulties (Volpe, 2001). Even in the absence of known neurological insults, children who were born preterm are more likely than term-born children to have developmental, behavioral, and/or learning problems as they grow (Anderson, 2014). Prominent lags in emotional and cognitive school readiness have been found as early as preschool (Chen, Claessens, & Msall, 2014). This same study found that preschool attendance alone does not fully remediate this lack of readiness. Further understanding of the constellation of factors that predicts if a child will have difficulties is needed and preschool age is an ideal time for early identification and beginning targeted intervention. The current study aims to characterize the behavioral, neuropsychological, and neuroanatomical profiles of preschoolers who were born very preterm. This study is part of a larger, ongoing project that will follow-up on all the children at two additional timepoints, before first grade and before second grade. Therefore, the current study will characterize only the first of three timepoints and will be used for future studies to determine if and how academic and behavioral outcomes can be predicted in VPT born children.

Preterm birth is associated with adverse neuropsychological outcomes

Academic difficulties and behavioral problems are more prevalent among children born very preterm (Pritchard et al., 2009b). Lower scores on measures of processing speed, attention, memory, and language have been demonstrated in various studies and have been previously reviewed by Anderson (2014). One meta-analysis included studies of children in early adolescence into early adulthood found significantly lower scores in VPT children compared to full-term born controls in mathematics, reading, spelling, executive functioning as well as informant reported attention, internalizing, and externalizing problem behaviors (Aarnoudse-Moens, Weisglas-Kuperus, van Goudoever, & Oosterlaan, 2009). Mathematics has been shown to be a particular weakness in children born preterm (Akshoomoff et al., 2017; Taylor, Espy, & Anderson, 2009; Taylor, Klein, Drotar, Schluchter, & Hack, 2006). Yet, there are few studies that have focused on preschool age children and examine the precursor skills that are necessary for academic success in mathematics. There have been studies that examine the relationship between teacher's grades and school-based measures of mathematics that demonstrate lower performance in preterm born individuals in kindergarten (Taylor, Klein, et al., 2011) and at six years of age (Pritchard et al., 2009a). A large, prospective longitudinal study of children's health risk-factors at birth found a correlation between neonatal risk factors (i.e., preterm birth and/or low birth weight) and school readiness including pre-reading, picture vocabulary, and mathematics on the TEMA-3 at 4.75-6.25 years of age (Kull & Coley, 2015).

Many skills have been shown to be related to mathematics (Geary & Moore, 2016) and examining these skills in preschoolers born very preterm would allow for a better understanding of the mechanisms of mathematics difficulties. Previous studies of typically developing children and adolescents have shown mathematics to be related to an extended set of cognitive abilities including IQ, working memory, processing speed, visual-motor integration, visual memory, and phonological awareness (De Smedt, Taylor, Archibald, & Ansari, 2010; Geary, 2011; Mayes, Calhoun, Bixler, & Zimmerman, 2009; Szucs, Devine, Soltesz, Nobes, & Gabriel, 2014). Motor skills have also been shown to be related to mathematics in children born VPT, even in the absence of cerebral palsy, at six and eight years of age (Marlow, Hennessy, Bracewell, Wolke, & Group, 2007; Wocadlo & Rieger, 2008). Executive functions have been shown to be related to children's success in school (Cameron et al., 2012) and executive function deficits in VPT born children compared to full-term born individuals is a common finding among studies. Deficits have been found in VPT children at age 6-12 years (Bayless & Stevenson, 2007). In a follow-up of young adults, executive function and attention were shown to be significantly lower in individuals born at a very low birth weight (Ostgard et al., 2016).

Preterm birth is associated with an increased risk of brain injury

Very preterm birth has been associated with an increased rate of brain injury and abnormal development of both white and gray matter of the brain (Duerden, Taylor, & Miller, 2013). These injuries are caused by a cascade of in utero and neonatal factors. In utero and at birth, infection, immature vasculature, and inflammation can cause damage to oligodendroglia precursors and can lead to gray matter maturational change (Hagberg et al., 2015). In addition, a neonate's immature lungs at birth can cause chronic hypoxic and ischemic changes in the brain (Behrman & Butler, 2007). Severe brain damage and significant adverse outcomes (e.g., cerebral palsy) are becoming relatively uncommon in children born preterm (Kidokoro et al., 2014; Mathur, Neil, & Inder, 2010; Moore et al., 2012). Yet, the constellation of more subtle brain injury and cognitive difficulties described as "encencephalopathy of prematurity" are more common, and are seen even in the absence of known hypoxic events (Gilles, Gressens, Dammann, & Leviton, 2017). The children in the proposed study were selected based on their relatively uncomplicated neonatal course and often do not have a history of known hypoxic events, therefore they are likely to exhibit the subtle pattern known as encencephalopathy of prematurity. Understanding this milder brain injury is paramount in understanding development and outcomes for the majority of children born very preterm.

Structural brain injury, defined as by lower surface area, increased gyrification, differences in gray matter thickness, and lower volumes of brain structures have been detected in children born very preterm with conventional MRI (Lax et al., 2013; Ment, Hirtz, & Hüppi, 2009; Ostgard et al., 2014). Gray matter lesions are infrequent in VPT born children, but reduced volumes and delayed maturation, measured by cortical gyrification are frequently reported (Anderson, Cheong, & Thompson, 2015). Surface area hemispheric asymmetry at two years of age has been shown to be a predictor of outcomes for VPT born children (Kersbergen et al., 2016). In addition, lower cortical surface area and lower gyrification, indicating more "shallow" sulci were also noted in a group of 7-year-old children born VPT (Zhang et al., 2015). Cortical thickness, as measured by the distance between the white matter and outer gray matter boundary, has been shown to exhibit delays in the developmental trajectories compared to term born peers. Children born very preterm have been shown to have higher cortical thickness values compared to their term born peers, indicating that the typical process of pruning is delayed in these children (Mürner-Lavanchy et al., 2014). As early as term-equivalent age, total gray matter volume, frontal and temporal lobar gray matter, and thalamic volume have shown significant, positive association with gestational age at birth (Ball et al., 2012). Studies have demonstrated global reductions in whole brain volume, cortical gray matter volume, and gray matter thickness as well as subcortical gray matter volume (Solsnes et al., 2016; Taylor, Filipek, et al., 2011). Lower volumes of the thalamus and connected structures has been found as early as term-equivalent age (Ball et al., 2012) and persists into middle childhood (Lax et al., 2013) and adolescence (Nagy et al., 2009). One study of 18- to 22- and 36- to 47-month-old toddlers born VPT found lower white matter and parietal lobe volume and larger lateral and third ventricles in toddlers born very preterm (Lowe et al., 2011). Lax et al. (2013) demonstrated lower total brain volume and higher proportion of gray matter compared to white matter in a group of seven- to ten-year-old children born VPT. Most brain imaging studies of VPT born individuals have included infants at term-equivalent age or older children to adults, leaving a gap in our knowledge of gray matter processes that happen between infancy period and first years of formal schooling.

Diffusion-weighted imaging allows for imaging of water molecules through the brain, and is often considered an index of tissue maturation and white matter integrity (Johansen-Berg, 2010). White matter tracts are particularly vulnerable to damage caused by the effects of preterm birth and changes in diffusion have been demonstrated across white matter tracts (Volpe, 2009). At term-equivalent age, infants born VPT have been shown to have alterations in diffusivity of the corpus callosum, internal capsule, and periventricular white matter when compared with term-born infants (Ball et al., 2012). An additional study demonstrated lower integrity in the optic radiations when neonates were imaged within two weeks of birth (Pavaine et al., 2016). Diffuse white matter abnormalities have been shown to persist into adulthood, yet the precise pathology underlying white matter changes has not yet been determined by previous studies (Salmaso, Jablonska, Scafidi, Vaccarino, & Gallo, 2014).

Subtle neuropsychological weaknesses are correlated with neuroanatomical measures

Detection of subtle damage to the brain alone is an important finding for children born VPT, but the power of detection lies when the brain findings can be related to cognitive or behavioral outcomes. If sensitive and specific brain markers for particular deficits in VPT children can be found, identification of children at risk for problems can occur as early as the neonatal period.

Gray Matter. Differences in regional gray matter properties have been shown to be correlated with behavior in children born very preterm. Surface area at term equivalent age has been shown to be predictive of fine motor skills and overall cognition subscales from the Bayley Scales of Infant and Toddler Development at two years of age (Kersbergen et al., 2016). Deep gray matter and cerebellar structural abnormalities at term equivalent age have been shown to predict attention and processing speed at seven years of age in VPT children (Murray et al., 2014). A study of young adults (18-22 years of age) born VPT found that widespread measures of cortical surface area explained variance in visual-motor integration as measured by the Beery-Buktenica Developmental Test of Visual-Motor Integration (Sripada et al., 2015). Executive function was shown to be correlated with surface area of the anterior medial and superior frontal as well as the lateral temporal lobes in individuals 19- to 20-years-old born VLBW (Ostgard et al., 2016). In regard to mathematics, one study found that neonatal gray matter surface area was correlated with mathematics at both five and seven years of age in a large group of children born VPT (Ullman et al., 2015). Most available studies follow this same method and use neonatal or infant imaging to predict later cognitive scores, or use a model of neuropsychological test scores and brain images collected about the same time in adolescents and adults. The proposed study is unique in that we measured mathematics and brain images in preschoolers at the same visit.

White Matter. Cerebral white matter volume has been shown to be correlated with IQ, language, memory, visual-motor, and executive functioning VPT adolescents (Taylor, Filipek, et al., 2011). A study of 18- to 22-month-old children born preterm found that lower scores on the

Cognitive Composite scores on the Bayley-Scales-of-Infant-Toddler-Development, 3rd-Edition was predicted by higher mean diffusivity of the posterior limb of the internal capsule and genu of the corpus callosum from near-term MRI scans (Rose et al., 2015). Additionally, early development has been shown to correlate with fractional anisotropy of the corpus callosum and cingulum (Counsell et al., 2008). In a study of young adults born VPT, there was a significant, positive association between visual-motor integration fractional anisotropy of the corpus callosum, optic radiations, inferior longitudinal fasciculi, inferior fronto-occipital fasciculi, uncinate fasciculi, and anterior thalamic radiations (Sripada et al., 2015). With respect to mathematics skills, one study demonstrated a correlation between fractional anisotropy of the corpus callosum in imaging collected during the neonatal period and mathematics at seven years of age (Thompson et al., 2015). White matter abnormalities, as measured by FA of fiber tracts have also been shown to be associated with cognitive deficits in adolescents born very low birthweight (Skranes et al., 2007). Very low birthweight has often been considered an estimate of prematurity, particularly in studies of adults when calculation of gestational age was not as precise as in more recent births.

Chapter 2:

Study 1

The content within this section, titled "Chapter 2: Study 1," reflects material from a paper that has been published in the journal *Child Neuropsychology*. The full citation is as follows:

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Abstract

Children born very preterm (VPT) are at risk for academic, behavioral, and/or emotional problems. Mathematics is a particular weakness and better understanding of the relationship between preterm birth and early mathematics ability is needed, particularly as early as possible to aid in early intervention. Preschoolers born VPT (*n* = 58) and those born full term (FT; *n* = 29) were administered a large battery of measures within six months of beginning kindergarten. A multiple-mediation model was utilized to characterize the difference in skills underlying mathematics ability between groups. Children born VPT performed significantly worse than FT born children on a measure of mathematics ability as well as full scale IQ, verbal skills, visual-motor integration, phonological awareness, phonological working memory, motor skills, and executive functioning. Mathematics was significantly correlated with verbal skills, visual-motor integration, phonological processing, and motor skills across both groups. When entered into the mediation model, verbal skills, visual-motor integration, and phonological awareness were significant mediators of the group differences**.** This analysis provides insights into the pre-academic skills that are weak in preschoolers born very preterm and their relationship to mathematics. It is important to identify children who will have difficulties as early as possible, particularly for VPT children who are at higher risk for academic difficulties. Therefore, this model may be used in evaluating VPT children for emerging difficulties as well as an indicator that if other weaknesses are found, an assessment of mathematics should be conducted.

Keywords: very preterm birth, mathematics, preschool, Test of Early Mathematics Ability, academic skills, child neuropsychology

Mathematics ability and related skills in preschoolers born very preterm

In the United States about 1 in 10 babies are born preterm and rates continue to increase each year. Preterm birth, gestational age (GA) of less than 37 weeks, has been correlated with an increased risk of serious health issues. Due to advances in medical care, neonatal survival rates continue to improve (Martin, Hamilton, & Osterman, 2016) and more severe forms of birth defects (e.g., cerebral palsy or periventricular leukomalacia grade IV) occur less frequently. Yet, even children without severe brain damage are more likely to have developmental, behavioral, and/or learning problems as they grow (Anderson, 2014).

Children born very preterm (VPT; GA less than 33 weeks) are at increased risk for academic difficulties, and even children without low IQs are more likely than their full-term born peers to have specific learning disabilities or underachievement in reading, spelling, and/or mathematics (Aarnoudse-Moens, Weisglas-Kuperus, van Goudoever, & Oosterlaan, 2009; Litt, Taylor, Klein, & Hack, 2005). Previous studies with independent samples have shown mathematics to be a particular weakness (Akshoomoff et al., 2017; Taylor, Espy, & Anderson, 2009; Taylor, Klein, Drotar, Schluchter, & Hack, 2006). Preschool is an important period in a child's development and early identification of academic weaknesses and targeted intervention are essential to improving outcomes. This is particularly relevant for children born VPT who are at increased risk of having difficulties.

A few studies have examined mathematics skills in preschoolers and young school-age children born VPT. One study found that VPT born children as early as preschool age performed significantly worse than their term-born peers on school-based measures of mathematics (Aarnoudse-Moens, Oosterlaan, Duivenvoorden, van Goudoever, & Weisglas-Kuperus, 2011) and another study found prominent lags across multiple measures of mathematics at age six

(Pritchard et al., 2009). Academic weaknesses, particularly in mathematics, were found in kindergarten among children born extremely preterm (Taylor et al., 2011). Scores on the Test of Early Mathematics Ability – Third Edition (TEMA-3) (Ginsburg & Baroody, 2003) were highly correlated with neonatal risk factors (i.e., preterm birth and/or low birth weight) in a large, longitudinal cohort that was tested as they were entering kindergarten as part of a prospective study of the effects of early health indicators on development (Kull & Coley, 2015).

In order to better understand the nature of mathematics difficulties in children who were born VPT, it is imperative to examine the large set of skills that have been shown are related to success in mathematics in typical development (Geary & Moore, 2016). In FT-born, typically developing children, mathematics has been shown to depend on a variety of skills including verbal and visual working memory, visual-spatial skills, fine motor skills, attention, inhibitory control, processing speed, visual-motor integration, visual memory, and phonological awareness (Barnes & Raghubar, 2014; De Smedt, Taylor, Archibald, & Ansari, 2010; Geary, 2004, 2011; Mayes, Calhoun, Bixler, & Zimmerman, 2009; Szucs, Devine, Soltesz, Nobes, & Gabriel, 2014). Mathematics and reading have shown to be strongly correlated in school-age children (Ashkenazi, Rubinsten, & De Smedt, 2017). This relationship may in part reflect the involvement of common skills such as phonological processing, verbal comprehension, and working memory (Jordan, Wylie, & Mulhern, 2010; Szucs et al., 2014; Willcutt et al., 2013). The relationship between verbal skills (i.e., phonological awareness and verbal comprehension) and mathematics specifically is likely due to the language system being used for representing and manipulating information, such as articulating number words (Geary, 2004). In addition, fine motor skills and attention in kindergarten have been shown to predict later achievement in mathematics (Grissmer, Grimm, Aiyer, Murrah, & Steele, 2010).

The relationship between many of the same cognitive skills and mathematics has been examined across several studies in school-age children born VPT. In early elementary school-age children born extremely preterm, general intelligence, reading skills, and visuospatial skills were shown to predict scores on the Wechsler Individual Achievement Test in mathematics (Simms et al., 2013). Studies have shown that VPT born children are often weaker than their FT born peers in vocabulary and language functioning (van Noort-van der Spek, Franken, & Weisglas-Kuperus, 2012). Johnson, Wolke, Hennessy, and Marlow (2011) found that letter knowledge and performance on a phoneme deletion task at 6 years of age predicted mathematics scores for extremely preterm born 11-year-old children. Motor and visual-motor integration skills are also weaknesses in children born VPT (Mayes et al., 2009; Zhang, Mahoney, & Pinto-Martin, 2013). Motor skills were found to be related to mathematics achievement in a group of 6-year-old children born extremely preterm (Marlow, Hennessy, Bracewell, Wolke, & Group, 2007) and in a group of 8-year-old children born VPT (Wocadlo & Rieger, 2008), even in the absence of cerebral palsy. Mathematics underperformance in VPT born children has been related to visuospatial processing and working memory (Simms et al., 2015). Executive functions have been shown to be affected in VPT born school-aged children (Bayless & Stevenson, 2007) and are also related to children's success in school (Cameron et al., 2012).

Specifically, in preschoolers born FT, many of these same skills are related to mathematics. Preschool mathematics performance has been shown to be related to visuospatial abilities (Verdine, Golinkoff, Hirsh-Pasek, & Newcombe, 2017), visual working memory (Toll, Kroesbergen, & Van Luit, 2016), phonological awareness (Krajewski & Schneider, 2009), and reading comprehension (Grimm, 2008). Executive function also plays a prominent role in preschoolers' mathematics ability and predicts their mathematics achievement (Clark et al., 2014;

Purpura, Schmitt, & Ganley, 2017). Working memory and behavioral self-regulation have been shown to be related to visual-motor integration in early school-aged children, which in turn also predicts later performance on measures of mathematics, word reading, and receptive vocabulary (Becker, Miao, Duncan, & McClelland, 2014; Mayes et al., 2009). One study demonstrated that teacher-rated executive function, using the Behavior Rating of Executive Functioning – Preschool version (BRIEF-P), predicted mathematics achievement above and beyond reading and general intelligence (Clark, Pritchard, & Woodward, 2010). Though previous studies have examined the relationship between mathematics and other skills in preschoolers, there are few studies that investigate these same relationships in preschoolers who were born VPT.

The purpose of this study was to examine mathematics skills in preschoolers born VPT and a cohort of term-born peers. We were also interested in assessing the skills that are known to contribute to development of mathematics skills, and to explore if and how these skills predict weakness in early mathematics in children born VPT. To accomplish this goal, we utilized a multiple mediation model, a method that has previously been shown to be useful when investigating the relationship between mathematics and other skills in children with a disorder that affects mathematics (Raghubar et al., 2015). This model included measures previously shown to be related to mathematics in preschoolers and school-age children, as well as those shown to be weaker in children who were born VPT. The multiple mediation technique allows for evaluation of the skills measured by each instrument as a model of the differences in mathematics performance between VPT and FT born children. A multiple mediation model also allows for the establishment of a profile of skill weaknesses related to mathematics in children born VPT. This profile allows for higher sensitivity in detecting children who may have difficulties. As evidenced by the wide range of measures and skills that have been included in previous studies, it is clear that there are multiple domains that contribute to mathematics. By including multiple related domains in one model, we are able to form a more complete picture of the skills that contribute to weaknesses in mathematics ability seen in children born VPT. In addition, we are in the unique position to help create criteria that might identify VPT born children who will not perform as well as their peers in school.

Method

Participants

The data in this study were collected as part on an ongoing, longitudinal investigation of neurocognitive development of children born VPT as they begin formal schooling. Children born VPT (n = 58) as well as FT born (n = 29) participants were recruited into the study within six months of starting kindergarten, which typically requires the child to be five years of age by September of the year they will begin school. The full longitudinal study will include a large battery of measures as well as neuroimaging to be completed at two additional timepoints between school years (i.e., after kindergarten and after first grade). It is expected that data collection will be complete in the fall of 2018. Children born FT were recruited via the University of California, San Diego (UCSD) Center for Human Development (CHD) database of parents who consented, through an internet contact form or flyers and representatives at community events, to be contacted regarding studies conducted by the CHD. Children in the VPT group (born 24-32 weeks GA) were recruited primarily from the UCSD High-Risk Infant Follow-up Clinic. Children with a history of severe brain injury (e.g., Grade 3-4 intraventricular hemorrhage, cystic periventricular leukomalacia, moderate-severe ventricular dilation), evidence of significant disability (e.g., moderate-severe cerebral palsy, bilateral blindness, bilateral deafness), chromosomal or genetic abnormalities likely to affect development, or any neurological disorder not related to preterm birth (e.g., closed head injury) were excluded from the study. FT children were included if they were born at 38 or more weeks GA and had no history of neurological, psychiatric, or developmental disorders. All participants in the study were required to be primarily English speaking and without a known history of in utero maternal substance abuse. All children were screened for significant hearing and vision difficulties. Children with a known history of significant anxiety that might interfere with study tasks, or metallic implants that are contraindicated for magnetic resonance imaging (MRI) were also excluded from the study. Additionally, all children were screened using the Wechsler Preschool and Primary Scale of Intelligence – Fourth Edition (WPPSI-IV), and children with a Verbal Comprehension Index (VCI) below 80 were excluded from the current study. The larger study aims to predict educational outcomes in children who are "healthy preterm," those with a relatively benign neonatal course who are more commonly deemed as performing within the expected range at infant/toddler follow-up. The VCI cutoff criterion was also intended as an additional way to exclude children who would have difficulty understanding and completing the entire battery of test measures.

The sample includes 12 children who were born "extremely preterm" (24-27 weeks GA). Previous studies have shown mixed results, with some showing a relationship between GA at birth and academic, cognitive, or behavioral outcomes while others do not show such a relationship (Aarnoudse-Moens et al., 2009; Bhutta, Cleves, Casey, Cradock, & Anand, 2002). In addition, some studies distinguish between children born VPT (28-32 weeks gestation) and children born extremely preterm (24-27 weeks gestation). In the current study, there is no significant correlation between GA and TEMA-3 ($r = -.133$; $p = .321$), Full-Scale IQ ($r = -.073$; $p = .585$), VCI ($r = -.106$; $p = .427$), VMI ($r = -.066$; $p = .622$), CTOPP-Elision ($r = .054$; $p =$

.688), CTOPP-NWR (r = .110; p = .409), or BRIEF GEC (r = -.154; p = .249). Therefore the 12 children born extremely preterm were included in the VPT Group.

The Human Research Protections Programs and Institutional Review Board at the UCSD approved all procedures, and each participant's legal guardian gave informed consent. The ongoing study will track these children each year for a total of three years. Data continue to be collected, as this is a longitudinal study in progress, the current data represent only children who completed the first year of study visits and had valid data for all of the measures of interest.

Cognitive and Behavioral Measures

All children were administered a large, standardized battery of measures intended to characterize their cognitive, behavioral, and academic skills. Children were assessed in a series of four testing sessions, about two hours each, to minimize possible fatigue. All measures and sessions were completed in a standardized order with exceptions only in rare cases, related to equipment or staff availability. Sessions were scheduled at the family's convenience, with a target of completion of all sessions within six weeks. During the assessment, the parent or guardian completed a set of standardized questionnaires regarding the child's current skills and behavior, the child's health history, and demographic information. In the current analysis, a subset of these measures was selected based on previous studies of mathematics.

Test of Early Mathematics Ability – Third Edition (TEMA-3)

The TEMA-3 is an individually administered, single measure with items capturing formal and informal mathematics. It is designed to measure mathematics ability in children 3-8:11 years of age (Ginsburg & Baroody, 2003). The measure produces a score, the Math Ability Score, which is a standard score calculated as the sum of all items correctly answered corrected for age.

Wechsler Preschool and Primary Scale of Intelligence - Fourth Edition (WPPSI - IV)

The WPPSI-IV is a broad measure of cognitive abilities used in children and includes indices of verbal comprehension, visual spatial abilities, fluid reasoning, working memory, and processing speed (Wechsler, 2012). The primary measure of interest for the current study was the Verbal Comprehension Index (VCI). This Index was selected to account for verbal skills typically learned from a child's environment and school, measured by verbal concept formation and verbal reasoning. Children who are born preterm may have weaknesses in verbal abilities (van Noort-van der Spek et al., 2012), though weaknesses in mathematics have been shown to persist even when controlling for verbal abilities (Taylor et al., 2009). This specific index was chosen to capture children's verbal reasoning skills.

Beery-Buktenica Developmental Test of Visual-Motor Integration (VMI)

The VMI is a pencil and paper task that requires participants to copy line drawings of geometric figures of increasing complexity. This task measures visual-motor integration which requires visual-spatial perception, visual and motor coordination, and fine motor skills (Beery, Buktenica, & Beery, 2004).

Behavior Rating Inventory of Executive Function - Preschool Version (BRIEF-P)

The BRIEF-P is a questionnaire designed to measures executive function behaviors in children 2-5 years of age (Gioia, Isquith, & Guy, 2002). This measure was given to the child's primary guardian, who was most often the mother. The overall composite, the Global Executive Composite (GEC), was used in this analysis. The score reflects the number of problem behaviors endorsed and therefore, a higher score indicates more concerns.

Cambridge Neuropsychological Test Automated Battery (CANTAB) – Spatial Working Memory (SWM)

The CANTAB is a computerized battery of tasks designed to measure a variety of cognitive functions. The SWM task requires the participant to search and find a series of blue “tokens” hidden in boxes by pressing the boxes on the screen. There is only one token hidden at a time and tokens are never hidden in the same box twice. Therefore, the child must remember where they previously found a token and not return to the same box, as there will never be a token there. The number of boxes increases with each trial to a total of eight boxes. The measure of interest, the "between-errors" score, represents the total number of times a child returned to a box where they had already found a token within a trial. This task is intended to measure spatial working memory, an aspect of executive function.

Comprehensive Test of Phonological Processing - Second Edition (CTOPP-2).

The CTOPP-2 measures reading-related phonological processing abilities and includes nine subtests designed to measure phonological awareness, phonological working memory, and rapid naming (Wagner, Torgesen, Rashotte, & Pearson, 2013). For this study, two subtests, Elision and Nonword Repetition, were included in the analysis. These two measures were selected because they have been used previously to account for specific, basic verbal skills when investigating mathematics (De Smedt et al., 2010).

Elision. This subtest measures the phonological skills of the individual by asking them to say a word and then say the same word, dropping a designated sound from the word. The dropped sound is either a syllable or single word. This task is designed to measure phonological awareness.

Nonword Repetition. This subtest requires listening to recorded pronounceable non-words and repeat them back to the examiner. The purpose of this test is to measure phonological working memory.

Movement Assessment Battery for Children – Second Edition (MABC-2)

The MABC-2 is a measure of children's movement skills and measures manual dexterity, balance, and visual-motor coordination through a series of motor tasks (Henderson, Sugden, & Barnett, 2007). This measure includes a total score that summarizes the child's scores across the domains of motor functioning, which was the primary measure used in this analysis.

Statistical Analyses

Statistical analyses were completed in SPSS 23 (SPSS, 2014). Standard scores on the TEMA-3 were inspected for outliers using boxplots. No child's scores were considered outliers, and therefore all 87 children were included in the final analysis. Alpha for all analyses was set at $p \leq .05$. Demographic information was analyzed using chi-square (sex, race) and analysis of variance (ANOVA; age, socioeconomic status [SES]). SES was calculated as a combination of parent-reported household income and years of maternal education (or primary caregiver in cases where the biological mother was not the primary caregiver) stratified into levels, each level re-coded as an ordinal value, and then summed to make a single score. Maternal education was coded as: 1 = high school graduate or less, 2 = 1 to 3 years of college, 3 = college graduate, 4 = professional degree. Income was coded as 1 = $0 - 49,999, 2 = $50,000 – 99,999, 3 = $100,000 - 199,999, and 4 = $200,000 and above. This resulted in a value from 1 to 8 for each child (see Table 1 for means and percentage of sample in each bin). Group comparisons were made between groups on each of the measures using analysis of variance (ANOVA). In order to investigate the relationship among variables, whole-sample Pearson correlations were conducted.

The final approach used in this study was data-driven multiple mediation model using the process extension for SPSS (Hayes, 2013). We applied this model to investigate the cognitive factors that contribute to group differences in mathematics ability and provide additional information above and beyond traditional regression models by simultaneously modeling the direct and indirect factors explaining variance in mathematics between groups. A non-parametric bootstrapping procedure, designed to balance statistical power and Type-I error, was applied for assessing indirect effects (Preacher & Hayes, 2008). For the current analysis, boot-strapped samples were set to 5,000. The traditional four-step requirements initially laid out in Baron and Kenny (1986) were used to determine if mediation had occurred. These requirements are (1) the independent variable (X) must be a significant predictor of the dependent variable (Y), this is termed the total effect, or *c* path. (2) The independent variable must be significantly correlated to the mediator variables (M), this is the *a* path. (3) Mediator variables are significant predictors of the dependent variable while the independent variable is in the model, the *b* path 4) When the mediators are included, the independent variable no longer significantly predicts the dependent variable, the direct effect or *c'* path. The indirect effect is the reduction between *c* and *c'* caused by inclusion of the mediators. Given these steps, any variables not significantly correlated with TEMA-3 scores will not be included in the mediation model.

Results

Group Characteristics

Participant characteristics are listed in Table 1. There were no significant differences between groups for sex (χ^2 [df = 1] = .052; p = .819), race (χ^2 [df = 4] = 4.840; p = .304), age (F [1, 85] = .658, p = .420), or SES (F (1,85) = .455; p = .502). As expected, the groups were significantly different for GA at birth (*F* [1,85] = 543.02; $p < .001$) and weight at birth (*F* [1,85] = 389.21; $p < .001$).

Correlational Analysis

Correlational analyses are presented in Table 2. Significant correlations were found between the TEMA-3 and WPPSI-IV VCI ($r = .508$, $p < .001$), VMI ($r = .482$, $p < .001$), CTOPP-2 Elision ($r = .549$, $p < .001$), CTOPP-2 Nonword Repetition ($r = .302$, $p = .006$), and MABC-2 ($r = .296$, $p = .007$).

Between-Group Differences

Group means are presented in Table 3. Group differences were found among many measures entered into the initial analysis. Children born VPT performed significantly worse on TEMA-3 (*F* [1,85] = 8.00; $p = .006$)), WPPSI-IV Full Scale IQ (*F* (1,85) = 9.88; $p = .002$)), Fluid Reasoning Index (*F* [1,85] = 17.18; $p < .001$), and Verbal Comprehension Index (*F* [1,85] = 5.46; $p = .022$)). In addition, cognitive and behavioral scores were significantly different, with VPT born children performing more poorly on VMI (*F* [1,85] = 7.87; $p = .006$)), BRIEF GEC (*F* [1,85] = 4.49; $p = .037$)), MABC-2 (*F* [1,85] = 24.93; $p < .001$)), CTOPP-2 Elision (*F* [1,85] = 5.05; $p = .027$)), and CTOPP-2 Nonword Repetition (*F* [1,85] = 8.45; $p < .005$)). The scores were not significantly different between groups on the CANTAB spatial working memory task.

It is important to emphasize that both Groups' mean scores for all measures were in the Average normative range, with the exception of the total MABC-2 score. The mean score for the children born VPT was in the Low Average/Borderline range. Yet, the VPT born children, on average perform more poorly on every measure of interest with the exception of the spatial working memory task.

Multiple Mediation Analysis

As previously mentioned, only variables that were significantly correlated with TEMA-3 scores were entered in the multiple mediation analysis. The final model included VMI, MABC-2 Total Score, VCI, CTOPP-Elision, and CTOPP-Nonword Repetition. In the analysis before entering the mediators, Group was shown to be a significant predictor of TEMA-3 scores (R^2 = .0889, F [1,85] = 8.00, p = .006). This relationship is show in part a of Figure 1. The total effect is 9.732, and this represents the *c* path, and the significant relationship satisfies Step 1 of mediation.

The total overall effect was significant, indicating that Group and the full set of mediators were a significant predictor of TEMA-3 scores (R^2 = .420, F [6,81] = 9.273, $p < .001$). While all variables were significantly related to Group, only a subset of the variables significantly mediated the relationship between Group and mathematics. WPPSI-IV VCI, VMI, and CTOPP-Elision, were all significant mediators in the model (see Figure 1 for unstandardized path coefficients). Significant mediators were VCI (unstandardized β = .270; t [80] = 2.156; p = .034), VMI (unstandardized β = .347; t [80] = 2.117.; p = .038), and CTOPP Elision (unstandardized β = 1.409; t [80] = 2.353; p = .021). Two of the mediators then predicting TEMA-3 was non-significant for CTOPP Nonword Repetition (unstandardized β = .435; t [80] = .929; p = .356) and MABC (unstandardized β = .326; t [80] = .652; p = .516). After inclusion of the mediators, the direct effect of Group predicting TEMA-3 is no longer significant (t = .489, p = .626), indicating that mediation has occurred since the relationship between Group and TEMA-3 score is no longer significant with the mediators in the model, as it was in the total effects model shown in Figure 1, part a. This final step satisfies step 4 of the requirements of mediation.

Discussion

The present study evaluated mathematics ability in preschoolers born VPT and their term-born peers. We sought to expand on previous literature on VPT born children by examining these skills together in one model. In line with previous studies, we found that although the group mean scores were in the average range, VPT born children performed significantly worse than their full-term born peers on a measure of early mathematics ability. In the correlation analysis, we found that mathematics ability was significantly correlated with verbal reasoning abilities, visual-motor integration, phonological working memory, phonological awareness, and motor skills. In contrast, parent ratings of executive functioning on the BRIEF-P and spatial working memory were not significantly correlated with mathematics ability in this cohort. While there was a significant group difference on the Global Executive Composite of the BRIEF-P, neither group had mean scores in the clinically significant range. The limited range of scores across the groups, as well as group means in the non-clinically significant range, may explain why this measure of executive functioning was not a significant mediator in the model. The mediation analysis indicated that while many of the variables were significantly correlated with mathematics, general verbal abilities, visual-motor integration, and phonological awareness were significant in explaining the relationship between Group and TEMA-3 when all were entered into the model simultaneously. It is important to note that a variety of skills were significantly correlated with mathematics, but these three were the most important for explaining the difference between VPT and FT children in mathematics at preschool age and represent possible criteria for detecting children at risk for difficulties.

The majority of these results are consistent with our hypothesized relationships between mathematics and preterm birth. A previous study of 7- to 9-year-old children concluded that phonological awareness (CTOPP-Elision) and simple arithmetic are highly correlated and likely have overlapping neural basis (De Smedt et al., 2010). Evidence of a shared neural basis comes from a recent functional MRI study of children and young adults. In this study, the left superior temporal and right middle temporal regions were activated during both reading and mathematics tasks (Evans, Flowers, Luetje, Napoliello, & Eden, 2016). There is also evidence of shared mechanisms between reading and mathematics via the commonalities in cognitive profiles as well as comorbidity of mathematics and reading disabilities (Simmons & Singleton, 2008). Additionally, studies have demonstrated overlap in the functional activation networks that are disrupted in both reading and math disabilities (Ashkenazi, Black, Abrams, Hoeft, & Menon, 2013). De Smedt et al. (2010) also found no correlation among mathematics and phonological working memory using the CTOPP-2 Nonword Repetition, the same task as in the current analysis. In that study, the lack of correlation was attributed to the children using a "retrieval strategy" and solving the math problems by relying on having previously memorized the answer. This is in contrast to a "problem-solving strategy" where they needed to use mathematics skills to find the solution for the majority of the large problems, which was correlated with phonological awareness. We also found that phonological awareness, and not phonological working memory, was predictive of mathematics. This may be because the types of items on the TEMA-3 cause the younger children to employ a similar strategy, "problem solving", as the previous study found older children were using for more complex problems. This would indicate that preschoolers are using a similar strategy for simple mathematics as older children are for more complex problems, hence why we found the same lack of significant correlation between Nonword Repetition and TEMA-3. General verbal abilities and phonological processing have also been linked to mathematics via processing of linguistic symbols and linking of numeric values with linguistic equivalents during development (Pinel & Dehaene, 2010). A previous study also found that motor skills and a measure of attention and executive function did not explain a significant amount of variance in mathematics in children born very preterm (Simms et al., 2013), as seen in the current study. Overall, the current analysis indicates that general verbal skills, visual-motor integration, and phonological awareness are the most important for explaining the observed group differences in TEMA-3 scores. Scores on the VMI task have been shown to be significantly related to mathematics (Verdine, Irwin, Golinkoff, & Hirsh-Pasek, 2014). One study has suggested that relative strengths in motor control and ability to reproduce the spatial aspects of the figures on the VMI are indicators of underlying numerical processing abilities (Carlson, Rowe, & Curby, 2013). Once we better understand the relationship between measures of specific skills and mathematics, they can be used as markers to determine if a child may be at risk for falling behind their term-born peers in mathematics. For example, if a teacher or parent is concerned that a very preterm born child is struggling with reading or not performing well in verbal or spatial tasks, it may be appropriate to assess further for possible difficulties in mathematics. This study also demonstrated that these types of effects can be found as early as preschool.

This study does have some limitations. A previous study found poorer performance on the CANTAB SWM task in VPT compared to FT born children at seven to nine years of age (Luciana, Lindeke, Georgieff, Mills, & Nelson, 1999). In our study, the VPT group did not perform significantly worse than the FT born group. This may be due to the difficulty of this task for children who are of preschool age. This task will continue to be administered each year of the study, and as these children get older, the differences seen in other studies may emerge. In addition, we used a single parent-report measure of executive functioning, rather than a direct measure of executive functioning. Therefore, our judgment of the functioning of these children is dependent on their parent's responding honestly and accurately on this measure. A teacher report version of this measure would be informative in future studies. In the future to provide additional evidence of current executive functioning, a direct measure of the children’s behavior related to executive functioning, such as the Test of Everyday Functioning for Children (TEA-Ch) (Manly et al., 2001) or Head-Toes-Knees-Shoulders task (Ponitz, McClelland, Matthews, & Morrison, 2009) should be used in further examining the relationship between executive function and mathematics. The group of FT born children in this study perform well on the measures, and tend to have highly educated parents. The FT born group was recruited from the same area, and often attended the same schools as the VPT born children. There were no significant differences between the Groups on SES, income, or maternal education. Therefore, we do not have any reason to believe that these children are not representative controls. Lastly, as part of the intentional design of the larger study, this investigation included children who were born preterm with a relatively uncomplicated prenatal and neonatal history. Health-related inclusion criteria previously mentioned as well as the requirement that participants obtain a VCI of at least 80, intentionally excluded children with severe cognitive impairment and the most serious health and developmental consequences of preterm birth. Therefore, the VPT children in this study are not expected to have scores in the severely impaired or intellectual disability range. Despite this, these children performed significantly worse than their term-born peers who were recruited as part of the study. Therefore, this is not necessarily a limitation to the current study, but it may limit the current study’s generalizability to other populations of children who were born very preterm and have more complicated histories or frank deficits.

Future directions for this study include correlating the behavioral and neuropsychological results with neuroanatomical data. The children in this study undergo structural magnetic resonance imaging as well as diffusion-tensor imaging each year of the study. In addition, as previously mentioned, this data is part of an ongoing, longitudinal study and this analysis includes only the first of three yearly visits. We also plan to expand the current investigation by performing the same analysis at the completion of the study, when these children have completed 2-years of formal schooling.

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Table 1.1

Participant Characteristics

Variable	VPT	FT	*p*-value
Total subjects (*n*)	58	29	
Sex: M/F (% female)	35/23 (39.7%)	15/14 (48.3%)	.819
Age: Mean (SD)	5.21 (.41)	5.29 (.31)	.420
GA at Birth: Mean (min-max)	29.51 (24 - 32)	39.96 (38 - 41)	<.001
Birth Weight (g): Mean (SD)	1320.40 (428.85)	3452.10 (504.23)	<.001
SES Composite: Mean (min-max)	5.12 (2 - 8)	5.38 (2 - 7)	.501
Maternal Education	Portion of Whole Sample		
High school or less	12.1%	10.3%	
1 to 3 years college	34.5%	20.7%	
College graduate	34.5%	34.5%	
Professional (MA, MS, MD, PhD, etc.)	19.0%	34.5%	
Family Annual Income			
$0 - $49,999	15.5%	3.8%	
$50,000-$99,999	32.8%	50.0%	
$100,000-$199,999	34.5%	46.2%	
$200,000 and above	17.2%	0%	

Note. VPT: Very preterm born; FT: Full term born; M/F: Male/Female; SD: Standard deviation; GA: gestational age at birth in weeks; min-max: minimum to maximum; g: grams

Table 1.2

Correlations Among Cognitive and Behavioral Measures

Measure	VCI	VMI	BRIEF-GEC	CANTAB SWM	CTOPP-Elision	CTOPP-Nonword Repetition	MABC-2
TEMA-3	.508 (<.001)	.482 (<.001)	-.136 (.223)	-.047 (.674)	.549 (<.001)	.302 (.006)	.296 (.007)
VCI	---	.422 (<.001)	-.202 (.069)	-.124 (.269)	.586 (<.001)	.269 (.014)	.137 (.221)
VMI		---	-.195 (.080)	.012 (.915)	.332 (.002)	.178 (.110)	.328 (.003)
BRIEF-GEC			---	.037 (.744)	-.217 (.050)	-.079 (.480)	-.189 (.089)
CANTAB SWM				---	-.057 (.610)	.035 (.755)	-.083 (.460)
CTOPP-Elision					---	.306 (.005)	.276 (.012)
CTOPP-Nonword Repetition						---	.159 (.155)

Note. Values presented as *r* (*p*-value); TEMA-3: Test of Early Mathematics Ability – Third Edition; std: Standard score; WPPSI-IV: Wechsler Preschool and Primary Scale of Intelligence - Fourth Edition. VMI: Beery-Buktenica Developmental Test of Visual-Motor Integration; BRIEF GEC: Behavior Rating of Executive Function Global Executive Composite; CANTAB SWM: Cambridge Automated Neuropsychological Test Battery Spatial Working Memory; CTOPP-2: Comprehensive Test of Phonological Processing – Second Edition; MABC-2: Movement Assessment Battery for Children – Second Edition.

Table 1.3

Summary of Scores on Cognitive and Behavioral Measures

Measure	VPT M (SD)	FT M (SD)	Group Differences: *F* (*p*)
TEMA-3 std	96.93 (14.78)	106.65 (14.05)	8.00 (.006)***
WPPSI-IV			
FSIQ std	100.38 (13.17)	109.31 (8.93)	9.88 (.002)***
FRI std	97.95 (14.85)	110.92 (8.62)	17.18 (<.001)***
PSI std	102.24 (12.68)	101.72 (12.67)	.03 (.864)
VCI std	102.38 (14.17)	109.65 (10.62)	5.46 (.022)*
VMI std	96.95 (9.83)	102.85 (6.30)	7.87 (.006)***
BRIEF GEC T-score	51.60 (12.24)	46.15 (6.92)	4.49 (.037)*
CANTAB SWM	68.64 (12.17)	65.00 (8.98)	1.86 (.177)
CTOPP-2			
Elision scaled	8.81 (2.74)	10.27 (2.78)	5.05 (.027)*
NWR scaled	7.26 (2.85)	9.27 (3.11)	8.45 (.005)***
MABC-2 scaled	6.31 (2.57)	9.69 (3.22)	26.48 (.001)***

Note. Significant group differences: *: $p < .05$; ***: $p < .005$; VPT: Very preterm born; FT: Full term born; M: Mean; SD: Standard Deviation; TEMA-3: Test of Early Mathematics Ability – Third Edition; std: Standard score; WPPSI-IV: Wechsler Preschool and Primary Scale of Intelligence - Fourth Edition; FSIQ: Full Scale IQ; FRI: Fluid Reasoning Index; PSI: Processing Speed Index; VCI: Verbal Comprehension Index; VMI: Beery-Buktenica Developmental Test of Visual-Motor Integration; BRIEF GEC: Behavior Rating of Executive Function Global Executive Composite; CANTAB SWM: Cambridge Automated Neuropsychological Test Battery Spatial Working Memory; CTOPP-2: Comprehensive Test of Phonological Processing – Second Edition; NWR: Nonword Repetition; MABC-2: Movement Assessment Battery for Children – Second Edition.

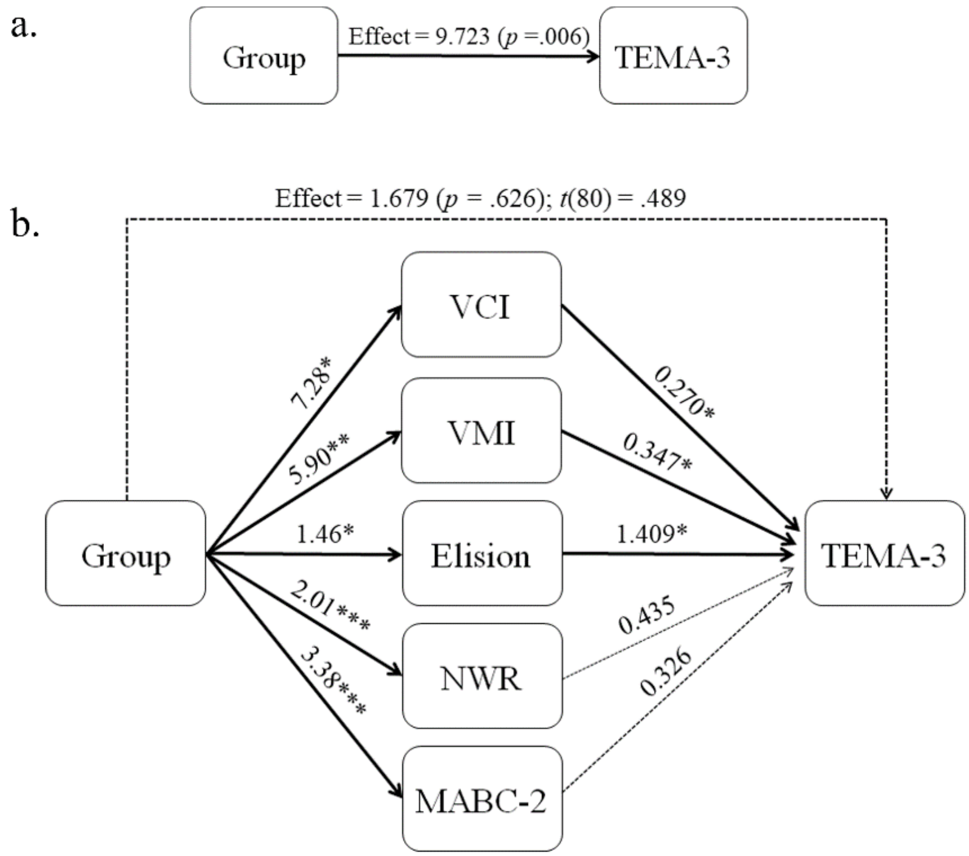

Figure 1.1

Mediation Model and Path Values

Note. Values represent unstandardized coefficients. Direct (a) values and indirect (b) models of the mediation analysis and path estimates. *p< .05, **p< .01, ***p< .005. TEMA-3: Test of Early Mathematics Ability–Third Edition; VCI: Wechsler Preschool and Primary Scale of Intelligence–Fourth Edition Verbal Comprehension Index; VMI: Beery-Buktenica Developmental Test of Visual–Motor Integration; Elision: Comprehensive Test of Phonological Processing–Second Edition (CTOPP-2) Elision subtest; NWR: (CTOPP-2) Nonword Repetition subtest; MABC-2: Movement Assessment Battery for Children–Second Edition total score.

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Chapter 3:

Study 2

Variations in Brain Morphometry Among Healthy Preschoolers Born Very Preterm

The content within this section, titled "Chapter 3: Study 2" reflects material from a paper that has been submitted for publication in the journal *Early Human Development*. The proper citation is as follows:

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Abstract

Background. Preterm birth is associated with an increased risk of neonatal brain injury, which can lead to alterations in brain maturation. Advances in neonatal care have dramatically reduced the incidence of the most significant medical consequences of preterm birth. Relatively healthy preterm infants remain at increased risk for subtle injuries that impact future neurodevelopmental and functioning. **Aims.** To investigate the gray matter morphometry measures of cortical thickness, surface area, and sulcal depth in the brain using magnetic resonance imaging at 5 years of age in healthy children born very preterm. **Study design.** Cohort study. **Subjects.** Participants were 52 children born very preterm (VPT; less than 33 weeks gestational age) and 37 children born full term. **Outcome measures.** Cortical segmentation and calculation of morphometry measures were completed using FreeSurfer version 5.3.0 and compared between groups using voxel-wise, surface-based analyses. **Results.** The VPT group had a significantly thinner cortex in temporal and parietal regions as well as thicker gray matter in the occipital and inferior frontal regions. Reduced surface area was found in the fusiform area in the VPT group. Sulcal depth was also lower in the VPT group within the posterior parietal and inferior temporal regions and greater sulcal depth was found in the middle temporal and medial parietal regions. Results in some of these regions were correlated with gestational age at birth in the VPT group. **Conclusions.** The most widespread differences between the VPT and FT groups were found in cortical thickness. These findings may represent a combination of delayed maturation and permanent alterations caused by the perinatal processes associated with very preterm birth.

Keywords: very preterm birth, preschool, gray matter, cortical thickness, surface area, sulcal depth

Variations in Brain Morphometry Among Healthy Preschoolers Born Very Preterm

Preterm birth is associated with an increased incidence of brain injury at birth that involves primarily the periventricular white matter and subcortical structures. This has been termed the “encephalopathy of prematurity” and is the primary determinant of neurodevelopmental difficulties in childhood (Volpe, 2009). Despite dramatic advances in neonatal care and increased survivability, individuals born very preterm (VPT), at less than 33 weeks gestation, continue to show differences in development of brain structures throughout childhood and as adults. These differences may be attributed to complex processes that involve brain injury at birth as well as longer term neurodevelopmental differences (Ortinau & Neil, 2015). Early injury has been shown to affect proximal and distal structures as the brain develops into childhood and beyond. The pattern of these complex findings suggests permanent cortical changes in some regions (perhaps due to neuronal loss in the perinatal period) and delayed development of later maturing cortical regions and white matter tracts. Preschool age is a time of rapid development of the brain, characterized by expansion of cortical surface area and contraction of gray matter thickness (Brown et al., 2012). Little is known about how these processes are affected in preschool age children who were born VPT.

Previous studies have demonstrated changes in cortical morphometry as a consequence of preterm birth. These studies have demonstrated some areas where thickness is greater in individuals born VPT, and other areas with lower thickness compared to individuals born full term (FT). Cortical thickness was lower in middle temporal, anterior cingulate, and posterior inferior parietal regions during middle childhood and adolescence (Lax et al., 2013; Martinussen et al., 2005; Nagy, Lagercrantz, & Hutton, 2011). Other areas have been found to have greater thickness in VPT children, adolescents, and young adults, primarily within the temporal pole and medial and lateral frontal brain regions (Martinussen et al., 2005; Mürner-Lavanchy et al., 2014; Nam et al., 2015) as well as medial occipital and anterior cingulate regions (Lean, Melzer, Bora, Watts, & Woodward, 2017).

Previous studies have found mixed results regarding the effect of preterm birth on measures of cortical surface area. In school-age children born with very low birthweight (VLBW), smaller surface area was found in the bilateral medial and lateral temporal lobes, inferior frontal lobes, and parietal/occipital regions (Sripada et al., 2018). Reduced surface area was also found in a group of 3- to 4-year-old VLBW children in orbitofrontal and transverse temporal regions (Phillips et al., 2011), as well as in studies of VLBW older children and young adults (Grunewaldt et al., 2014; Skranes et al., 2013; Solsnes et al., 2015).

Sulcal depth may also be sensitive to the effects of preterm birth. There is evidence that preterm birth may alter the timing and trajectory of the deepening of sulci (Dubois et al., 2008). In a study of cortical folding, VPT-born infants showed more shallow sulci than FT infants at term-equivalent age (Engelhardt et al., 2015). Shallower sulci have been reported in the superior temporal sulci and inferior portion of the pre and post-central sulci in children born VPT (Zhang et al., 2015).

The purpose of this study was to characterize the brain structural properties of a group of healthy preschoolers born VPT with relatively benign neonatal health history. This same sample was included in two of our previous papers (Hasler & Akshoomoff, 2019; Hasler et al., Submitted). Here we compared measures of surface area, cortical thickness, and sulcal depth between VPT and FT children at preschool age. Based on results from previous studies of older children, we hypothesized that the VPT group would have lower cortical thickness in the temporal and parietal lobes and greater thickness in the medial and lateral frontal lobes. We also predicted that areas of differences in surface area were likely to overlap with cortical thickness, with the VPT group having smaller surface area in the temporal and parietal regions. Finally, we hypothesized that the VPT group would have shallower sulci in the temporal lobe and medial occipital regions.

Method

Participants

The final sample was composed of 52 children born VPT and 37 children born FT. Children were enrolled in the study within 6 months of beginning kindergarten. The VPT group was recruited primarily from the follow-up program for two neonatal intensive care units in San Diego (UC San Diego and Sharp Mary Birch). The purpose of this study was to investigate the development of children born VPT without significant neonatal brain injury. Therefore, children were excluded from the study if they had a history of severe neonatal complications (i.e., Grade 3-4 intraventricular hemorrhage, cystic periventricular leukomalacia, moderate-severe ventricular dilation), known genetic abnormalities likely to affect development, and/or acquired neurological disorder unrelated to preterm birth. The children born FT were recruited via the UC San Diego Center for Human Development database of parents who consented to be contacted if their children might qualify for a study. Children born FT had no history of neurological, psychiatric, or developmental disorders. All children enrolled in the study were primarily English speaking with a Wechsler Preschool and Primary Scale of Intelligence – Fourth Edition (WPPSI-IV) (Wechsler, 2012) Full Scale IQ > 75. Additional exclusionary criteria included significant auditory or visual deficits and contraindications to MRI (e.g., pacemaker, metallic implants, recent dental procedures). The Institutional Review Board at UC San Diego approved all procedures, and each participant's legal guardian gave written informed consent.

Brain Imaging

Data were collected on a General Electric Discovery MR750 3.0 Tesla scanner with an 8-channel phased-array head coil at the Center for Functional MRI at UC San Diego. The full imaging protocol included: 1) a three-plane localizer; 2) a 3D T1-weighted inversion prepared RF-spoiled gradient echo scan using real-time prospective motion correction (PROMO) (White et al., 2010); 3) a 3D T2-weighted variable flip angle fast spin echo scan for detection and quantification of white matter lesions and segmentation of CSF; 4) a high angular resolution diffusion imaging (HARDI) scan with 30-diffusion directions, and integrated B_0 distortion correction (DISCO). All data were inspected for quality during collection and at all stages of processing.

Data were processed at the UC San Diego Center for Multimodal Imaging and Genetics (CMIG). Structural T1-weighted images were processed using gradient nonlinearity correction. Cortical and subcortical segmentation was completed using FreeSurfer automated segmentation in version 5.3.0 (Fischl et al., 2002). The imaging protocol and data processing stream was developed specifically for data collection and analyses for studies involving young children as part of the Pediatric Imaging Neurocognition and Genetics project (PING) (see Jernigan, Brown, Hagler, et al. (2016) for full details). Briefly, non-linear transformation was used to correct for distortions caused by nonlinearity of the spatial encoding gradient fields and nonparametric nonuniform intensity normalization method was used to reduce the non-uniformity of signal intensity. The automated FreeSurfer pipeline was used for extraction of gray matter cortical thickness, cortical surface area, and sulcal depth (Fischl, Sereno, & Dale, 1999). Sulcal depth is measured as the distance fron the deepest point of a sulcas to the mean height of the crown of the two adjacent gyri. Images were checked for movement or other scanner artifacts as well as errors in segmentation and registration by 2 trained experts. All images were assigned a number from 0 to 2 to quantify the amount of motion in the scan by a technician blinded to group membership. A value of 0 indicated no motion artifact in the scan, up to a value of 2 that indicated some motion artifact but image quality still within acceptable limits.

The final sample was composed of all the children enrolled in the study that were able to successfully complete the MRI scanning session and whose images were of acceptable quality. Of the 105 children originally enrolled in the study, five VPT- and one FT-born participants were unable to attempt the scanning procedure. Significant motion artifacts were present in the images of three VPT- and four FT-born children, therefore these were removed from the analyses. Additional subjects were removed due to significant errors in the FreeSurfer segmentation/reconstruction, which included two VPT- and one FT-born participant. All scans were reviewed by a neuroradiologist to inspect for brain abnormalities which led to one additional FT-born participant necessitating removal from the sample because of a brain abnormality. After these participants were removed from the sample, the final sample consisted of a total of 52 VPT and 37 FT children. Of those removed, 7 of the VPT and 3 of the FT were boys.

Statistical Analyses

Statistical analyses were completed in SPSS, version 25 (Corporation, 2017). Demographic variables were compared between groups using Pearson χ^2 and *t*-tests. A single socioeconomic status (SES) value was calculated for each child as a combination of parent-reported household income (4 levels) and years of maternal, or primary guardian, education (4 levels). This resulted in a value from 2 to 8 for each child; see our previous publication for full explanation of these levels (Hasler & Akshoomoff, 2019).

Surface area, sulcal depth, and cortical thickness were compared between groups using a surface-based, voxel-wise generalized linear model (GLM) with sex and age at scan as covariates. This method uses FreeSurfer tools as well as custom processing tools to calculate a voxel-wise general linear model of groups. The model is false discovery rate corrected for $p = 0.05$. The GLM results are then overlaid on a FreeSurfer standard average brain surface. Follow-up analyses utilized values derived from regions of interest (ROI) from the FreeSurfer automatic, sulcal-based parcellation (Desikan et al., 2006) corresponding to the areas of significant difference on the voxel-wise surface map. ROI values were compared between groups using ANCOVA controlling for sex and age at scan. Additional partial correlations were conducted to determine the relationship between the gray matter metrics and birth characteristic of the VPT group including GA and birth weight.

Results

Group characteristics and mean values are presented in Table 1. The groups did not differ on sex ($\chi^2 = .067$, $p = .795$), age ($t = -.447$, $p = .656$), or SES ($t = -.452$, $p = .655$). As expected, there was a significant difference between groups in birthweight ($t = -20.13$, $p < .001$) and gestational age at birth ($t = -26.75$, $p < .001$). Mean WPPSI-IV Full Scale IQ was significantly different between groups ($t = -2.36$, $p = .020$), however the group mean scores were in the average range. Groups did not differ significantly on motion artifact ratings ($\chi^2 = 3.72$, $p = .155$).

Figure 1 depicts the differences between groups on each of the metrics of interest. Overall, the measure showing the most widespread differences between groups was cortical thickness. Children born VPT had significantly lower cortical thickness in the bilateral supramarginal and angular gyri, bilateral superior and middle temporal lobes, and bilateral superior and medial middle frontal regions. Additional areas of lower cortical thickness in the

VPT group were found in the right hemisphere in lateral aspects of the frontal lobe. Children born VPT showed significantly greater cortical thickness in the cuneus and frontal pole. Total surface area was not significantly different between groups ($F[1,85] = .081$, $p = .776$). Surface area was significantly smaller in the VPT group in the fusiform gyrus. The VPT group also had significantly larger surface area in the right medial frontal, occipital pole, and anterior cingulate regions. Sulcal depth was significantly lower in the VPT group in the superior parietal lobe and medial orbital frontal regions. In summary, gray matter thickness showed the most widespread differences among the groups, with children born VPT showing significantly lower thickness in many regions of the temporal, parietal, and frontal lobes. The occipital lobe was also greatly affected in children born VPT, with significant differences across measures of thickness, and sulcal depth. Group comparisons and mean values for ROIs corresponding to regions on surface maps are displayed in Table 2.

Follow-up analyses were conducted to determine if gestational age at birth in the VPT group was correlated with the gray matter metrics of interest. Partial correlations were calculated using values extracted from regions of interest (ROI) from the FreeSurfer automatic parcellation based on areas with significant group differences on the voxel-wise surface maps. After controlling for sex and age at scan, there was a significant partial correlation between GA and thickness in the right middle temporal ($r[48] = .370$, $p = .008$) and left middle temporal ($r[48] = .314$, $p = .026$) regions. For sulcal depth, there were significant partial correlations between GA and the right precuneus ($r[48] = -.322$, $p = .022$) and right middle temporal ($r[48] = -.438$, $p =.001$) regions. Significant partial correlations between GA and surface area were found in the left fusiform region ($r[48] = .330$, $r = .019$).

Discussion

We found a number of differences in gray matter cortical morphometry between this group of preschool age children born VPT and children born FT, particularly in cortical thickness. The VPT group had thinner cortex bilaterally within the temporal, superior middle frontal, and parietal/occipital junction and thicker cortex within the dorsal medial occipital cortex bilaterally. The VPT group showed greater sulcal depth in regions of the right medial temporal, and medial partial lobes, and shallower sulcal depth in regions of the bilateral dorsal parietal lobes and ventral inferior frontal lobes compared with the FT group.

Previous studies have demonstrated a similar pattern of thicker cortex in the medial frontal and parietal lobes in children born VPT. These differences were observed from childhood through to adolescence. It may be that in adolescence, brain maturation in children born VPT continues at a slower pace and these areas undergo the regressive processes (e.g., synaptic pruning) typically seen in FT children at younger ages (Mürner-Lavanchy et al., 2014). Therefore, the areas of thicker cortex in our study of 5-year-old VPT children may represent areas where they are lagging behind in this phase of development (i.e., apparent regressive gray matter changes in thickness, and surface area). We replicated some of the previous findings of thinner cortex in the parietal and temporal lobes seen in older children born VLBW (Sripada et al., 2018). These results may indicate that the VPT group is lagging behind in some progressive/proliferative developmental processes that cause gray matter to measure thicker on MRI (e.g., cell production, dendritic arborization, synapse elaboration) that should ordinarily be occurring at this age, based on studies of typical development (Jernigan, Brown, Bartsch, & Dale, 2016). Another possible explanation is that thinner cortex may be related to early “hyper pruning” that occurred during the neonatal period (Zhou et al., 2018). Overall, it is likely that the findings of areas of thinner and areas of thicker cortex in the VPT group compared to the FT group represents interruptions or delays in the typical processes of cell proliferation, dendritic arborization, and/or cell pruning that occur across different brain regions in early childhood. The results from previous studies of older children and adolescents suggest that the neuroanatomical differences we see in this group of 5-year-olds are likely to continue as these children mature.

In contrast to previous studies of older children and young adults, we did not find smaller cortical surface area in in the prefrontal, lateral and ventral temporal, and lateral and medial parietal regions (Lax et al., 2013; Rimol et al., 2016; Sripada et al., 2018). We found that the VPT group had smaller surface area only in the bilateral fusiform region and greater surface area in the right medial frontal cortex and left occipital pole. During typical development, surface area is in the process of expansion during the preschool period (Brown & Jernigan, 2012). These results may indicate that this healthy VPT group is showing the same expansion in cortical surface area as the FT group across most of the cortex, at least at this stage of their development. These discrepancies may also reflect the inclusion of children with a greater number of birth-related risk factors, including lower gestational age at birth in those studies.

This study did not find much overlap in the regions where there were group differences in cortical thickness and surface area. Most early imaging studies of typically developing children have reported initial increases in gray matter thickness followed by thinning later in childhood, but these observations are now in serious doubt given improvements in measuring cortical thickness. Our data are consistent with the observations of Walhovd and colleagues (Walhovd, Fjell, Giedd, Dale, & Brown, 2017) who found that cortical thickness decreases from the earliest ages that were studied (i.e., starting age 3) through early adulthood, including the age range we studied here. Our group of VPT preschoolers were generally similar to the FT group in terms of surface area and sulcal depth measurements. Additional studies, particularly using longitudinal data, would likely be helpful in elucidating these results by measuring the trajectories of cortical morphometry as these children mature (Rimol et al., 2016; Sripada et al., 2018).

Increased gray matter in the occipital lobe has been demonstrated previously in older children born VPT (Lean et al., 2017). Early exposure to visual stimuli because of early exit from the womb, among other factors, puts preterm children at increased risk for visual problems, and associated effects can be seen in the complex network of cortical and subcortical areas associated with visual development (Ramenghi et al., 2010). All children in the study were screened and all were found to have grossly normal vision. However, it is possible that group differences in occipital cortex growth are related to these early differences in visual experiences, as well as the impact of early periventricular disruption.

Additional differences between the groups were found in sulcal depth and cortical thickness in the right middle temporal regions. These measures were also significantly correlated with GA at birth. This finding has been demonstrated in young adults born VPT (Bjuland, Lohaugen, Martinussen, & Skranes, 2013). This area may be vulnerable to damage in the third trimester, and thus structural differences when children are older may correspond to early damage or developmental difference within this region related to preterm birth (Nosarti et al., 2008).

The current study does have some limitations. The children included in this study were recruited to be “low-risk”, without significant neonatal brain injury. Therefore, these results may not generalize to a VPT-born population with more serious brain injury or more serious health complications related to premature birth. Also, these children have a relatively restricted range of GA at birth, with a mean of 29.5 weeks. More significant effects on gray matter morphometry may be present in children with lower GA, particularly those born at < 28 weeks. An additional limitation is the cross-sectional nature of this study. The current analyses cannot answer the question of developmental trajectory and the changes that occur as a child develops in each of the metrics included in this study.

In summary, the results of this study indicated differences in cortical morphometry between preschool-age children who were born VPT and children born FT. At age 5, the most widespread differences were found in measures of cortical thickness. Measures of surface area and sulcal depth were also different between VPT and FT groups. Given the limited research at this age, these results may help elucidate the pattern of brain development in this preterm population from early infancy to the outcomes reported in older children and young adults.

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Table 2.1

Participant Characteristics

Variable	VPT	FT
Total subjects (*n*)	52	37
Sex: M/F (% female)	30/24 (44.4%)	19/17 (52.7%)
Age: Mean (SD)	5.29 (.40)	5.33 (.31)
GA: Mean (range)	29.50 (24 - 32)*	39.66 (38 - 41)
Birth Weight (g): Mean (SD)	1354.80 (450.07)*	3416.11 (512.38)
WPPSI-IV FSIQ	101.85 (12.87)^	107.86 (9.46)
SES Composite: Mean (range)	5.04 (2 - 8)	5.19 (2 - 8)
Ethnicity (*n*)		
African American	2	1
Asian	4	6
Caucasian	26	12
Hispanic/Latino	14	8
Mixed	6	9
African American/Caucasian	--	2
American or Alaskan Native/Caucasian	1	2
Asian/Caucasian	5	3
Native Hawaiian or Pacific Islander/Caucasian	--	1

Note. VPT: Very preterm born; FT: Full term born; M/F: Male/Female; SD: Standard deviation; GA: gestational age at birth in weeks; WPPSI-IV FSIQ: Wechsler Preschool and Primary Scale of Intelligence – Fourth Edition Full Scale IQ; * significant difference between groups, $p < .005$; ^ significant difference between groups, $p < .05$. Ethnicity based on self-report (1 FT family declined to state).

Table 2.2

ROI Values for Areas Shown to Have Significant Between-Group Differences on the Vertex-wise Maps

Thickness	VPT (M, sd)	FT (M, sd)	*F*	*p*	η_p^2
L inf parietal	2.88 (.12)	2.96 (.12)	11.875	.001	.123
R inf parietal	2.94 (.13)	3.02 (.12)	9.502	.003	.101
L supramarginal	2.98 (.14)	3.07 (.12)	10.752	.002	.112
R supramarginal	3.01 (.14)	3.08 (.12)	6.036	.016	.066
L middle temporal	3.21 (.16)	3.32 (.14)	11.670	.001	.121
R middle temporal	3.25 (.13)	3.37 (.14)	16.547	<.001	.163
L sup temporal	3.18 (.14)	3.23 (.14)	2.713	.103	.031
R sup temporal	3.20 (.13)	3.27 (.13)	6.877	.010	.075
L sup frontal	3.30 (.15)	3.35 (.14)	2.318	.132	.027
R sup frontal	3.22 (.18)	3.30 (.15)	4.845	.030	.054
R caudal middle frontal	2.86 (.17)	2.94 (.12)	5.140	.026	.057
L cuneus	2.32 (.26)	2.22 (.22)	3.699	.058	.042
R cuneus	2.35 (.24)	2.23 (.20)	6.957	.010	.076
Surface Area			*F*	*p*	η_p^2
Total L hemisphere	82097.65 (7921.16)	81644.73 (7239.12)	0.095	.758	.001
Total R hemisphere	82266.15 (8009.99)	81864.22 (7421.82)	0.068	.796	.001
L fusiform	3083.79 (400.62)	3292.35 (390.85)	6.779	.011	.074
R fusiform	2973.06 (356.88)	3220.38 (400.02)	11.430	.001	.119
L lateral occipital	4981.50 (641.81)	4699.46 (472.21)	6.175	.015	.068
R superior frontal	7070.23 (895.38)	6736.43 (749.70)	4.155	.045	.047
R caudal middle frontal	2217.31 (398.32)	2041.84 (365.52)	5.016	.028	.056
Sulcal Depth			F	*p*	η_p^2
L superior parietal	-.0015 (.055)	.0317 (.033)	10.661	.002	.111
R superior parietal	-.0521 (.053)	-.0070 (.041)	18.075	<.001	.175
L inferior parietal	.0953 (.046)	.0880 (.039)	.589	.445	.007
R inferior parietal	.0880 (.037)	.0787 (.034)	1.353	.248	.016
L supramarginal	.0512 (.050)	.0269 (.032)	6.845	.011	.075
R supramarginal	.1269 (.059)	.0987 (.048)	5.800	.018	.064
L middle temporal	-.1056 (.064)	-.1480 (.056)	11.486	.001	.119
R middle temporal	-.1070 (.067)	-.1548 (.045)	14.339	<.001	.144
L inferior temporal	-.1154 (.050)	-.0646 (.054)	20.748	<.001	.196
R inferior temporal	-.1225 (.054)	-.0756 (.049)	17.547	<.001	.171
L lateral orbitofrontal	.0057 (.051)	.0272 (.047)	3.983	.049	.045
R lateral orbitofrontal	.0286 (.050)	.0494 (.043)	4.200	.044	.047
R cuneus	-.3297 (.073)	-.3622 (.071)	4.317	.041	.048
L precuneus	.1782 (.055)	.1550 (.041)	5.003	.028	.056
R precuneus	.2115 (.056)	.1724 (.049)	12.168	.001	.125

Note. Group comparisons controlling for sex and age at scan. ROI values extracted from the FreeSurfer Desikan parcellation; M: mean; sd: standard deviation; R: Right; L: Left, inf: inferior, sup: superior, thickness and sulcal depth measured in mm, area measured as mm^2

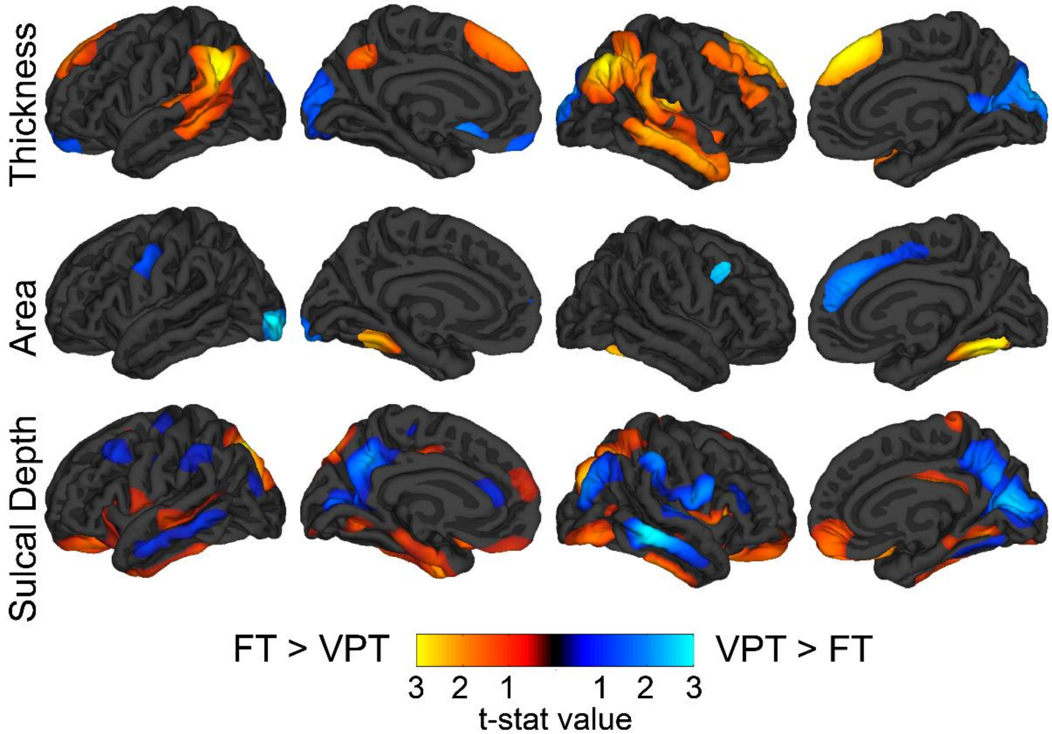

Figure 2.1

Vertex-wise Comparison of Gray Matter Measures

Note. Mean difference between VPT and FT groups corrected for false discovery rate = .05, projected onto the FreeSurfer average surface. Minimum threshold of $p = .01$ based on the t-statistic. FT: Full Term group; VPT: Very Preterm group

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Chapter 4:

Study 3

The content within this section, titled "Chapter 4: Study 3" reflects material from a paper that has been submitted for publication in the journal *Brain Imaging and Behavior*. The proper citation is as follows:

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Abstract

This paper aims to examine how healthy preschoolers born very preterm (VPT) with and without significant movement impairments differ from full term (FT) controls in subcortical brain volume measures and white matter diffusion properties. A case-control, observational study of fifty-four VPT-born and 32 FT-born children were administered the Movement Assessment Battery for Children – Second Edition (MABC-2) and underwent MRI within 6-months of starting kindergarten. Selected subcortical structural volumes, fractional anisotropy (FA), and mean diffusivity (MD) of selected white matter tracts were compared across VPT children with movement impairments (VPT-abnormal), and VPT and FT children without movement impairments. The VPT-abnormal group had higher MD in the corpus callosum and inferior frontal-occipital fasciculus and lower FA in the anterior thalamic radiations, corpus callosum, and cingulum than the FT group. The forceps major was particularly affected in the VPT-abnormal group compared with the VPT and FT groups without movement impairments. Both VPT groups had reduced brainstem and cerebellar white matter volumes and larger lateral ventricles compared to the FT group. Movement impairments in healthy VPT preschoolers were associated with more abnormalities in white matter integrity and reduced subcortical brain volumes most likely reflecting a greater extent of white matter damage associated with their very preterm birth.

Keywords: movement abilities, very preterm, white matter diffusion, subcortical volumes

Movement Abilities and Brain Development in Preschoolers Born Very Preterm

Children born very preterm (VPT), at gestational age less than 33 weeks, are at increased risk for health problems, behavioral difficulties, and cognitive impairments. Motor deficits are prominent with some studies reporting almost 40% of extremely preterm (< 28 weeks) children displaying mild motor deficits and up to 10% developing cerebral palsy (Adams-Chapman et al., 2018; de Kieviet, Piek, Aarnoudse-Moens, & Oosterlaan, 2009; Edwards et al., 2011; Spittle, Cameron, Doyle, Cheong, & Victorian Infant Collaborative Study, 2018; Williams, Lee, & Anderson, 2010).

Preterm birth increases the risk for periventricular white matter injury in the neonatal period which can contribute to more diffuse alterations in white matter pathways and distal gray matter (Volpe, 2009). Compared to their full term (FT) born peers, reduced volumes of the thalamus, cerebellar white matter, and anterior cingulate were reported in one study of toddlers born VPT (Lowe et al., 2011). In a number of studies of older VPT children and adolescents, reduced volumes of the corpus callosum, basal ganglia, thalamus, brainstem, ventral diencephalon, and cortical white matter regions volumes are commonly found (J. F. de Kieviet et al., 2014; de Kieviet et al., 2012; Lax et al., 2013; Solsnes et al., 2016).

Injury to the regions that are typically most affected by preterm birth may help explain the prevalence of motor dysfunction in children born VPT. White matter integrity and injury severity in infants scanned near-term equivalent age have been shown to be related to motor abilities assessed later in development (Rose et al., 2015; Schadl et al., 2018; Spittle et al., 2011). In toddlers, fractional anisotropy (FA) of the corpus callosum, cingulum, fornix, and uncinate fasciculus were correlated with movement skills (Counsell et al., 2008). Movement abilities in older children and adolescents have been shown to be correlated with the volume of the corpus callosum, cerebellar white matter, and cerebellar gray matter (de Kieviet et al., 2012). In a study of white matter integrity at 8-years of age, VPT children who scored <15th percentile on the Movement Assessment Battery for Children (MABC) showed FA differences in widespread white matter tracts including in the cingulum, corticospinal tract (CST), forceps major, and forceps minor (Jorrit F. de Kieviet et al., 2014).

Motor skill assessments at age 4 have been shown to be more reliable than assessments conducted at age 2, which tend to underestimate movement difficulties in VPT children without cerebral palsy (Griffiths et al., 2017; Spittle et al., 2013). Assessment of motor skills just prior to entering kindergarten may identify persistent motor difficulties that may be associated with cognitive and academic challenges (Brostrom, Vollmer, Bolk, Eklof, & Aden, 2018; Maggi, Magalhaes, Campos, & Bouzada, 2014).

The objective of this study was to examine the movement skills and differences between subcortical volumes and white matter fiber volume and diffusion properties between VPT-born preschoolers with impaired movement assessments and VPT and FT preschoolers with movement assessments in the normal range. Given previous study findings, investigating the difference between children born VPT with movement difficulties and those without may help identify brain regions most at risk in these children. To date no published studies have examined how movement abilities relate to brain structure when both are measured at preschool age in VPT children without major neurodevelopmental disorders or other significant functional impairments.

Method

Participants

Participants were healthy children born VPT (*n* = 54) and FT (*n* = 32) who were part of an ongoing, longitudinal study of cognitive and academic skills (Hasler & Akshoomoff, 2017). Demographic characteristics are shown in Table 1. A convenience sample of VPT children was recruited primarily from the neurodevelopmental follow-up program of a tertiary NICU (UC San Diego). Exclusion criteria included history of severe neonatal brain injury (i.e., Grade 3-4 intraventricular hemorrhage, cystic periventricular leukomalacia, moderate-severe ventricular dilation), known genetic abnormalities likely to affect development, and/or acquired neurological disorder unrelated to preterm birth. Children born FT were recruited from the UC San Diego Center for Human Development database of parents who consented to be contacted for research studies and had no history of neurological, psychiatric, or developmental disorders. VPT and FT born children were primarily English speaking with a WPPSI Full Scale IQ > 75, without significant auditory or visual deficits, or contraindications to MRI. One child born FT was excluded due to a brain abnormality identified after review by our study neuroradiologist. Three children born VPT and two children born FT were excluded who had excessive movement artifacts in their diffusion-weighted images or errors in MRI segmentation. Six children born FT were excluded for MABC-2 scores in the impaired range.

The Institutional Review Board at UC San Diego approved all procedures, and each participant's legal guardian gave written informed consent.

Movement Assessment Battery for Children – Second Edition (MABC-2)

The MABC-2, (Henderson, Sugden, & Barnett, 2007) a norm-referenced assessment that measures manual dexterity, balance, and visual-motor coordination through a series of motor tasks, was administered to all children by a single examiner (MGF). The three MABC-2 subscale scores (Aiming and Catching, Balance, and Manual Dexterity) are combined to form a Total Score. Scaled scores for the individual subscales and the Total Score range from 1 to 19, with higher scores representing better performance. It is recommended that children with Total Scores at or below the 15^{th} percentile receive ongoing monitoring of their movement skills. For this study, impairment was defined by a Total Score of ≤ 6, equivalent to performance below the 15^{th} percentile for age. Subscale scores of ≤ 6 are at or below the 9^{th} percentile for age.

Wechsler Preschool and Primary Scale of Intelligence - Fourth Edition (WPPSI - IV)

The WPPSI-IV is a broad measure of cognitive abilities used in children and includes indices of verbal comprehension, visual spatial abilities, fluid reasoning, working memory, and processing speed (Wechsler, 2012). The WPPSI-IV was administered by trained, reliable examiners to assess overall cognitive functioning for inclusion in the study.

Brain Imaging

Each child underwent a mock MRI to familiarize them with the procedure, with the study MRI on a separate day.

Data were collected on a General Electric Discovery MR750 3.0 Tesla scanner with an 8-channel phased-array head coil at the Center for Functional MRI at UC San Diego. The imaging protocol included 1) a three-plane localizer; 2) a 3D T1-weighted inversion prepared RF-spoiled gradient echo scan using prospective motion correction (PROMO) for cortical and subcortical segmentation; 3) a 3D T2-weighted variable flip angle fast spin echo scan for detection and quantification of white matter lesions and segmentation of CSF; 4) a high angular resolution diffusion imaging (HARDI) scan with integrated B_0 distortion correction (DISCO), for segmentation of white matter tracts and calculation of diffusion parameters. All data were inspected for quality during collection and at all stages of processing.

Data were processed at the UC San Diego Center for Multimodal Imaging and Genetics (CMIG) using gradient nonlinearity correction, co-registration of images, and EPI B_0 distortion correction. In addition, images were processed using and automated probabilistic, atlas-based analysis of white matter tracts (Hagler et al., 2009) and cortical and subcortical segmentation was performed using FreeSurfer version 5.3.0 (Fischl et al., 2002). The imaging protocol was developed specifically for data collection with children as part of the Pediatric Imaging Neurocognition and Genetics project (PING) (Jernigan, Brown, Hagler, et al., 2016).

Statistical Analyses

All statistical analyses were completed in SPSS, version 23 (SPSS, 2014). Children were categorized into three groups by their Total MABC-2 score: "VPT-abnormal" with scores in the impaired range (scaled score ≤ 6 and $<15^{th}$ percentile); "VPT-normal" and FT children with scores in the normal range (scaled scores ≥ 7 and $> 15^{th}$ percentile).

Demographic variables were compared between groups using Pearson χ^2 and *t*-tests. A single SES value was calculated as a combination of parent-reported household income (4 levels) and years of maternal education (4 levels). This resulted in a value from 2 to 8 for each child.

Group whole brain and ventricle volumes were inspected for outliers using boxplots; none were found. MANCOVAs were used to compare values derived from brain measures between groups. Brain structure and white matter tract volumes were compared controlling for sex, SES, and FreeSurfer-derived intracranial volume (ICV). Diffusion measure comparisons (FA and MD) controlled for sex and SES. When evaluating the assumptions of the MANCOVA, Box's M was significant for both models. Therefore, Pillai's Trace (*V*), was used as a more robust estimation of overall effect. Individual neuroanatomical regions were entered simultaneously into the model. Bonferroni corrected, *a priori* pair-wise t-tests were conducted to elucidate differences among groups. There were no *a priori* hypotheses regarding left versus right hemisphere differences, therefore values were summed across hemispheres for volumes and averaged for DTI values to reduce the number of multiple comparisons. However, some previous studies have reported hemispheric differences; thus, follow-up group comparisons of each hemisphere separately were conducted using t-tests with Bonferroni correction.

Results

The three groups did not differ in age (F [2,81] = .681, p =.509) or SES (χ^2 = 9.90, p = .630). The VPT-abnormal and VPT-normal groups did not differ in gestational age (t [52] = -.647, p = .521) or birthweight (t [52] = -.678, p = .501). The total VPT group (VPT-abnormal + VPT-normal) was 48.1% female, which is similar to the FT group (χ^2 = .013, p = .909, 46.9% female). However, the VPT-abnormal and VPT-normal groups differed significantly in proportion of females (χ^2 = 7.42, p = .006). Subsequent analyses were conducted with sex as a covariate in order to better account for possible sex differences. FSIQ was not a significant factor in the omnibus MANCOVA for brain volumes (p = .705, ηp^2 = .116), or the diffusion model (p = .719, ηp^2 = .170), including all pair-wise comparisons. In addition, FSIQ was not a significant between-subject predictor in either model. Therefore, FSIQ was not included in the final model as a covariate.

Results of the one-way ANOVA demonstrated Total MABC-2 scores as well as the three subtest scores were significantly different between the three groups (Table 2). In the post-hoc pairwise analyses, after Bonferroni correction, each subtest score was significantly lower in the VPT-abnormal group compared to VPT-normal (all ps < .001) and FT groups (all ps < .001).

Additionally, the VPT-normal group performed significantly worse on the Balance subtest (p = .01) than the FT group. The VPT-abnormal group had significantly lower Full Scale IQ scores (FSIQ) than the FT group, although all three group mean scores were within the average range (see Table 2). Total MABC-2 scaled score was significantly correlated with FSIQ across all the children in the study (r = .252, p = .019).

There was a statistically significant OMNIBUS difference across the brain volume measures (V = .614, F (24, 140) = 2.58, p < .001, $\eta p^2 = .307$). Post-hoc analyses indicated group differences for volumes of the brainstem (F(2, 84) = 10.25, p < .001, $\eta p^2 = .204$), lateral ventricles (F(2, 84) = 7.17, p = .001, $\eta p^2 = .152$), forceps major (F(2, 84) = 6.48, p = .002, p = .002, $\eta p^2 = .139$), thalamus (F(2, 84) = 4.44, p = .015, $\eta p^2 = .100$), and cerebellar white matter (F(2, 84) = 5.78, p = .005, $\eta p^2 = .126$). Follow-up testing between groups is presented in Table 3. The FT group had a higher brainstem, lateral ventricle, and cerebellum volume than both VPT groups. FT had higher volume than only the VPT-normal group. Both the VPT-normal and FT groups had higher forceps major volume than the VPT-abnormal group. Volume of the other white matter regions entered in the model (corpus callosum, forceps minor, anterior thalamic radiations (ATR), and cortical-spinal tract), and subcortical structures (ventral diencephalon and basal ganglia) were not significant predictors of group.

The omnibus MANCOVA revealed a significant group difference across the diffusion measures (V = .617, F (34, 132) = 1.73, p = .015, $\eta p^2 = .309$). Post-hoc analyses indicated group differences for FA (F(2, 84) = 6.85, p = .002, $\eta p^2 = .145$) and mean diffusivity (MD) (F(2, 84) = 9.99, p < .001, $\eta p^2 = .198$) of the forceps major, MD of the corpus callosum (F(2, 84) = 4.27, p = .017, $\eta p^2 = .095$), FA of the ATR (F(2, 84) = 3.89, p = .024, $\eta p^2 = .088$), and FA of the cingulate (F(2, 84) = 7.35, p = .001, $\eta p^2 = .154$). Follow-up testing between groups is presented in Table 3. VPT-abnormal group had significantly higher MD and lower FA in the forceps major than the VPT-normal and FT groups. The VPT-normal group had significantly higher MD and lower FA in the corpus callosum, ATR, and cingulum, compared to the FT group. Diffusion measures of the inferior frontal-occipital fasciculus, thalamus, basal ganglia, superior cortical striatal fibers, and CST were not significant predictors of group.

Planned, follow-up group comparisons of separate hemispheres were conducted. Regions that were found to have significant associations with group in follow-up testing are presented in Table 4. Compared with the FT group, the volume of the left thalamus was significantly smaller in the VPT-abnormal (p = .021) and VPT-normal (p = .027) groups and the right thalamic volume (p = .007) was significantly smaller in the VPT-normal group. The remaining measures were significant for both left and right hemispheres. Cerebellar white matter volume was significantly smaller in both the left (p = .003) and right (p = .005) hemisphere for the VPT-abnormal group, as well as in the left (p = .027) and right (p = .007) hemisphere for the VPT-normal group. With regard to the diffusion measures, both left (p = .02) and right (p = .04) FA of the ATR as well as left (p = .001) and right (p = .02) cingulum FA were significantly reduced in the VPT-abnormal group relative to both the VPT-normal and FT groups.

Discussion

Half of this sample of healthy, preschool-aged children born VPT had significant deficits on a standardized test of movement abilities. The VPT-abnormal children in this study demonstrated deficits in movement abilities across all subsections of the MABC-2 including gross motor (Balance), visual-motor coordination (Aiming & Catching), and fine motor dexterity skills (Manual Dexterity). Despite having normal MABC-2 total scores, the children in the VPT-normal group had significantly lower scores on the Balance subscale compared with the FT group, a concerning finding that requires additional evaluation. The higher proportion of males in the VPT-abnormal group adds further evidence that boys born preterm tend to be at higher risk for motor difficulties than girls (Arnaud, Daubisse-Marliac, White-Koning, & et al., 2007; Kuban et al., 2016).

Previous studies have demonstrated a difference in birth characteristics between children born VPT with and without movement difficulties (de Kieviet et al., 2009), though these studies often included children with more risk factors than in this study. Our cohort of VPT children were intentionally selected as “healthy” based on a relatively benign neonatal course. There were no differences in gestational age, birth weight, or NICU course between the VPT-abnormal and VPT-normal groups. The VPT children had no significant neurologic or medical complications related to prematurity and no significant cognitive deficits.

Abnormal motor skills were associated with decreased subcortical volumes and abnormal diffusion measures (higher MD and lower FA) across many white matter tracts. Significant brain region volumes and white matter diffusion property differences were found bilaterally between VPT-born preschoolers with motor impairments, compared to VPT without motor impairments and their FT-born peers. The areas related to motor problems are those that are most vulnerable to the effects of preterm birth (Volpe, 2009) and included subcortical structures, corpus callosum, anterior thalamic radiations, and cingulum fibers.

The abnormalities in white matter microstructure and subcortical brain volumes found in the VPT-abnormal group (i.e., forceps major, cingulum, cerebellum) have been demonstrated in older children with motor impairments who were born VPT (Jorrit F. de Kieviet et al., 2014; de Kieviet et al., 2012). We demonstrated many of the same findings here, though de Kieviet et al. (Jorrit F. de Kieviet et al., 2014) found a more extensive network of association tracts were related to motor impairments in 7- to 8-year-old children born VPT. The younger children in the current study have not yet reached the peak of the myelination process for association fibers (Brown et al., 2012) which may explain why some group differences were not found in our young sample.

In our study the white matter properties of the corpus callosum, anterior thalamic radiations, and cingulum were significantly different between the VPT-abnormal and the FT group. The VPT-normal group were found to have values between the VPT-abnormal and FT groups, but their values were not significantly different. This is in contrast to previous findings that have demonstrated differences between all three groups. This may indicate that while white matter is affected by preterm birth, greater damage to these fibers may be associated with later motor deficits.

A major finding of this study is the relationship between corpus callosum anatomy and the MABC-2 in VPT-born children with motor impairment. A study using comparable methods demonstrated a relationship between diffusion properties of the corpus callosum and MABC-2 scores in typically developing preschoolers (Grohs, Reynolds, Dewey, & Lebel, 2018). They concluded that a more a mature corpus callosum, as reflected by higher FA and lower radial diffusivity, may account for better motor skills in typically developing children. The lower FA and higher MD in the forceps major fibers found in the VPT-abnormal group in the current study may therefore reflect less mature white matter. The higher FA and lower MD in the FT and VPT-normal groups may indicate that these children have increased myelination and/or a decrease in extracellular space associated with a more typical developmental trajectory (Qiu, Mori, & Miller, 2015).

We also demonstrated lower brain stem volume and higher ventricle volumes across VPT groups compared to the FT group. This finding is in line with previous findings in older children who were born preterm (de Kieviet et al., 2012; Solsnes et al., 2016) and likely represents areas that are vulnerable to damage caused by early birth, rather than specific to movement abilities.

The current study does have limitations. This was a small convenience sample of low-risk VPT children without significant medical complications, thus limiting the generalizability of these results to the overall population of VPT-born children. The children also had a range of gestational ages and birthweights. Studies performed in higher risk populations (e.g., > 28 weeks gestation or < 1000 gm birthweight) may reveal more significant abnormalities.

We have shown that healthy preschool children born VPT who demonstrate motor deficits have neuroanatomical differences compared to their age-matched normal VPT-born peers. These neuroanatomical regions may be important markers for predicting longer term outcomes. It is possible that the motor impairments present at preschool age and the correlations between movement skills and measures of brain structures and integrity will persist as children grow. It is also possible that motor deficits may become more profound as older children are expected to complete become more complex motor tasks.

Early motor development has been demonstrated as an important predictor of future cognitive skills (Oudgenoeg-Paz, Mulder, Jongmans, van der Ham, & Van der Stigchel, 2017). Motor skill weaknesses may thus provide clues regarding which VPT children are at risk for future cognitive challenges. This study emphasizes the importance of longitudinal neurodevelopmental follow-up of VPT children since motor difficulties in VPT children without previously identified neurodevelopmental impairments may not become evident unless formally assessed in the preschool period. Further follow-up studies are needed to examine the relationship between motor skills at preschool age and scores on measures of movement, academic, and cognitive function in later childhood and adolescence. Early recognition of motor deficits may enable early intervention that can improve motor and academic outcomes in children born very preterm (Litt, Glymour, Hauser-Cram, Hehir, & McCormick, 2017).

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Table 3.1

Participant Characteristics

Variable	VPT-abnormal	VPT-normal	FT
Total subjects (*n*)	27	27	32
Sex: M/F (% female)	19/8 (29.6%)	9/18 (66.7%)	17/15 (46.9%)
Age: Mean (SD)	5.34 (.40)	5.27 (.43)	5.37 (.32)
GA: Mean (range)	29.13 (25 - 32)	29.54 (24 - 32)	39.60 (38 - 41)
Birth Weight (g): Mean (SD)	1269.39 (444.39)	1390.62 (451.55)	3473.76 (489.43)
SES Composite: Mean (range)	4.78 (2 - 8)	5.33 (2 - 8)	5.16 (2 - 8)
Maternal Education (%)		Portion of Whole Sample	
High school or less	15	11	9
1 to 3 years college	52	26	31
College graduate	15	41	34
Professional degree	19	19	25
Family Annual Income (%)			
$0 - $49,999	19	15	6
$50,000-$99,999	33	26	47
$100,000-$199,999	37	41	47
$200,000 and above	11	19	0
Ethnicity (*n*)			
African American	1	1	1
American or Alaskan Native	1	1	2
Asian	1	3	6
Caucasian	11	15	12
Hispanic/Latino	10	5	5
Mixed	3	--	4
African American/Caucasian	--	--	2
American or Alaskan Native/Caucasian	--	--	--
Asian/Caucasian	3	--	2

Note. VPT: Very preterm born; FT: Full term born; M/F: Male/Female; SD: Standard deviation; GA: gestational age at birth in weeks; min-max: minimum to maximum; g: grams; percentages rounded to the nearest whole number

Table 3.2

Performance on Movement Measure and FSIQ by Group

	VPT-abnormal	VPT-normal	FT	ANOVA	η^2
	M (SD)	M (SD)	M (SD)	*F* (*p*)	
MABC-2					
Aim & Catch	6.70 (2.74) [a, b]	9.96 (2.19)	10.31 (3.02)	15.28 (<.001)	.269
Balance	5.48 (1.81) [a, b]	8.74 (2.86) [a]	10.71 (3.24)	27.00 (<.001)	.394
Manual Dexterity	4.74 (2.14) [a, b]	9.67 (2.42)	9.63 (3.20)	31.40 (<.001)	.431
Total	4.26 (1.51) [a, b]	9.11 (1.74)	10.13 (2.93)	57.16 (<.001)	.579
WPPSI-IV					
FSIQ	99.48 (12.83) [a]	103.52 (12.76)	108.31 (9.77)	4.17 (.019)	.091

Note. Pairwise comparisons: [a]: Significantly different from FT Group; [b]: significantly different from VPT-normal Group; VPT: Very preterm born; FT: Full term born; M: Mean; SD: Standard Deviation; MABC-2: Movement Assessment Battery for Children – Second Edition; Aim & Catch: Aiming and Catching; WPPSI-IV: Wechsler Preschool and Primary Scale of Intelligence - Fourth Edition; FSIQ: Full Scale IQ. Two FT-born children were administered the WPPSI-III, therefore their scores are not included

Table 3.3

Regional brain Volume and Diffusion Measures by Group

Region	VPT-abnormal	VPT-normal	FT
Vol Brainstem	16026.27 (265.25) [a]	16131.93 (265.76) [a]	17430.02 (236.58)
Vol Lateral Ventricles	14145.22 (1572.12) [a]	13044.51 (1575.14) [a]	6943.41 (1402.18)
Vol Thalamus	13353.89 (161.70)	13228.88 (162.01) [a]	13826.30 (144.22)
Vol Cerebellum WM	21230.03 (516.92) [a]	21566.21 (517.92) [a]	23361.36 (461.05)
Vol Forceps Major	10045.89 (305.54) [a, b]	11299.65 (306.13)	11442.70 (272.51)
MD Forceps Major	.977 (.009) [a, b]	.934 (.009)	.923 (.008)
MD Corpus Callosum	.913 (.008) [a]	.895 (.008)	.881 (.007)
FA Forceps Major	.492 (.008) [a, b]	.520 (.008)	.533 (.007)
FA ATR	.338 (.004) [a]	.347 (.004)	.353 (.004)
FA Cingulum	.375 (.006) [a]	.392 (.006)	.406 (.005)

Note. Marginal means calculated from the MANCOVA controlling for SES, sex, and ICV for volumes and SES and sex for MD and FA; Volume measures presented as adjusted mean mm^3 after controlling for total intracranial volume (standard error); Post-hoc comparisons using Bonferroni correction for multiple comparisons: [a]significantly different from FT group; [b]significantly different from VPT-normal group; ICV: intracranial volume; Vol: volume; WM: white matter; MD: mean diffusivity; FA: fractional anisotropy;

Table 3.4

Estimated Marginal Means for Follow-up Separate Hemisphere Analyses of Significant Pairwise Group Comparisons

Region	VPT-abnormal	VPT-normal	FT
Vol R Thalamus	6739.65 (92.19)	6598.95 (92.36) [a]	6944.45 (82.22)
Vol L Thalamus	6614.24 (84.97) [a]	6629.93 (85.14) [a]	6881.86 (75.79)
Vol R Cerebellum WM	10693.16 (267.08) [a]	10738.68 (267.60) [a]	11732.21 (238.21)
Vol L Cerebellum WM	10536.87 (265.21) [a]	10827.53 (265.72) [a]	11629.15 (236.54)
FA R ATR	.331 (.004) [a]	.339 (.004)	.345 (.004)
FA L ATR	.344 (.005) [a]	.354 (.005)	.361 (.004)
FA R Cingulum	.363 (.006) [a]	.371 (.006)	.385 (.006)
FA L Cingulum	.387 (.008) [a]	.412 (.008)	.426 (.007)

Note. Marginal means calculated from the MANCOVA controlling for SES, sex, and ICV for volumes and SES and sex for MD and FA; Volume values presented as adjusted mean mm^3 after controlling for intracranial volume (standard error); Post-hoc comparisons using Bonferroni correction for multiple comparisons: [a]: significantly different from FT group; [b]: significantly different from VPT-normal group; ICV: intracranial volume; Vol: volume; WM: white matter; MD: mean diffusivity; FA: fractional anisotropy.

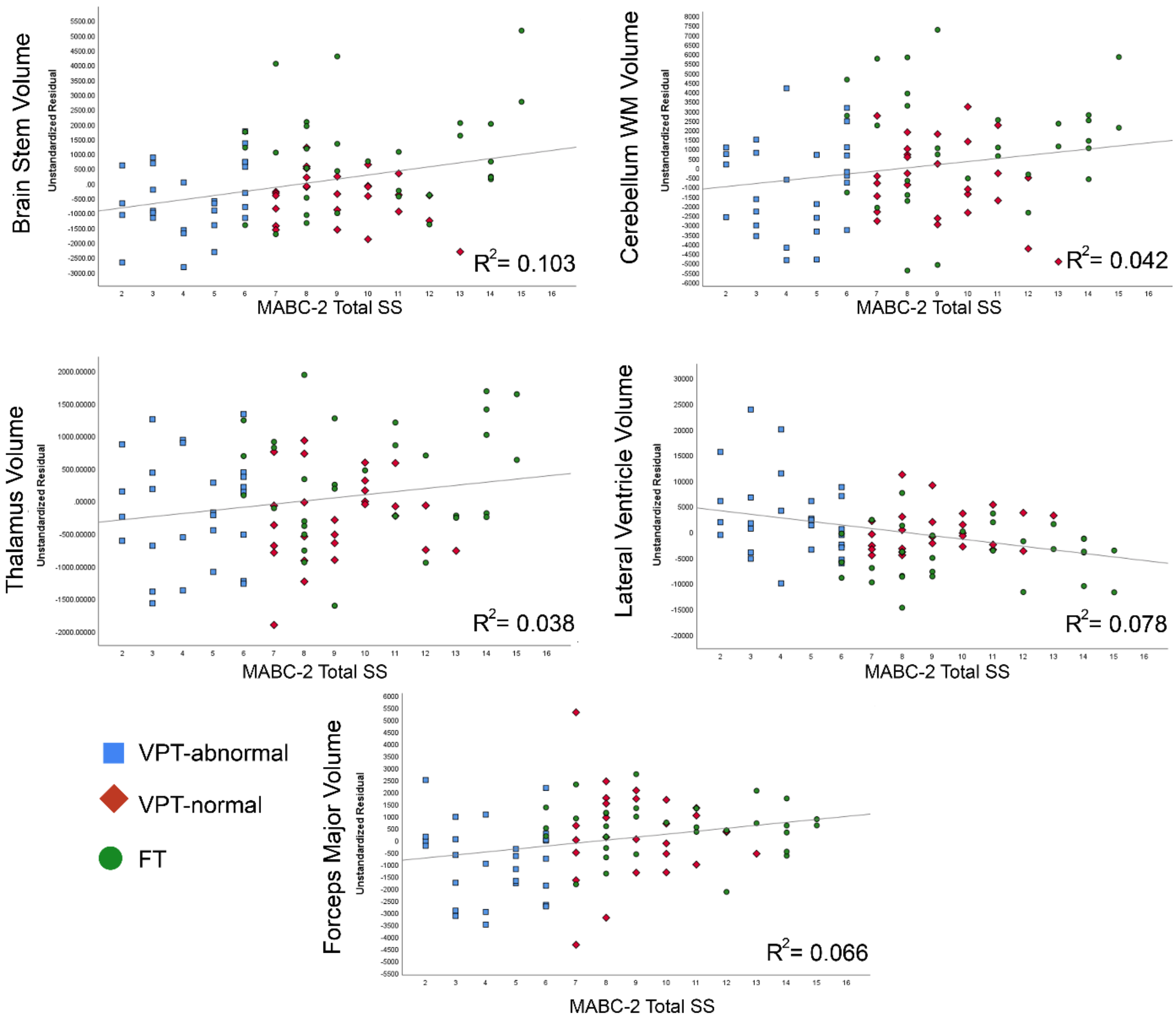

Figure 3.1

Scatterplots of Regional Volumes with Significant Between-Group Differences

Note. Unstandardized residuals after controlling for intracranial volume, sex, and socioeconomic status. WM: white matter; MABC-2: Movement Assessment Battery for Children – Second Edition; SS: scaled score.

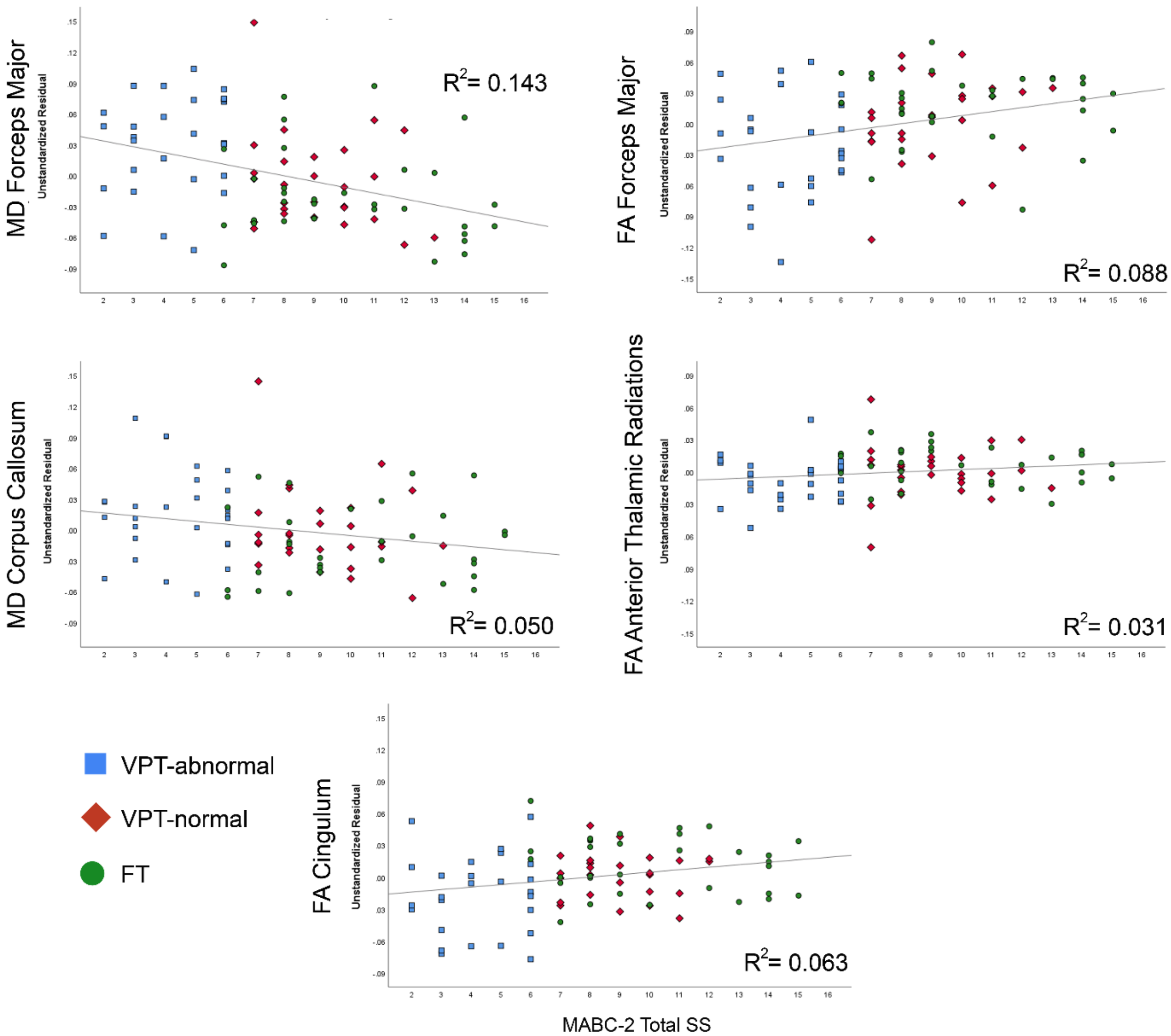

Figure 3.2

Scatterplots of Regional White Matter Fibers with Significant Between-Group Differences

Note. Unstandardized residuals after controlling for sex and socioeconomic status. MD: mean diffusivity; FA: fractional anisotropy MABC-2: Movement Assessment Battery for Children – Second Edition; SS: scaled score.

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Chapter 5:

Summary and Concluding Discussion

There has been a recent rise in incidence of preterm birth, despite previous decades of declining preterm birth rates. Medical care continues to advance and therefore infant mortality and the most serious neurologic consequences of due to premature birth continue to decline. However, children born very preterm with a relatively benign early health history often demonstrate difficulties at school age. These difficulties are related to subtle differences in neuroanatomical areas often affected by very preterm birth. The current project, and the three studies included therein, used a multi-modal approach to assessment of a group of "low-risk" children born VPT at preschool age.

Study 1 examined early mathematics skills in children born VPT and a group of FT born peers. This study examined the skills that mediate the difference in performance between VPT and FT groups. Findings included that VPT children performed significantly worse than their FT-born peers on a preschool mathematics measure, the TEMA-3. In addition, the VPT group obtained significantly lower scores on the WPPSI-IV Full-Scale IQ (though both groups were within the average range), verbal skills, non-verbal reasoning, visual-motor integration, phoneme awareness, phonetic working memory, and movement abilities. However, only verbal skills, visual-motor integration, and phoneme awareness were significant mediators of the group differences in mathematics ability.

Study 2 sought to characterize gray matter morphometry in children who were born VPT compared to their FT-born peers. This study compared the gray matter measures of cortical thickness, surface area, and sulcal depth. Cortical thickness showed the most widespread differences between the groups. Cortical thickness was lower in the VPT-born group in lateral parietal, middle frontal, and temporal lobe regions. The VPT-born group showed higher values for thickness and sulcal depth (to some extent) in the medial occipital regions. These findings expand upon previous studies that have found mixed results, showing greater effects in either surface area or thickness, in older children through adults. These findings could indicate that at preschool age, these children have not yet undergone the developmental processes (e.g., neuron proliferation and subsequent cortical pruning), or that they have completed the same process as their peers but that they simply did not grow as much indicating a reduced growth in normal processes (e.g. neuron proliferation, arborization, etc.)

Study 3 investigated the relationship between movement abilities and brain structure. This study investigated movement abilities as measured by the MABC-2, an area of clear weakness for VPT-born children that is likely related to measurable differences in their brain. The key finding in this study were that the VPT-born children performed significantly worse than their FT-born peers across each subscale (i.e., Balance, Aiming and Catching, and Manual Dexterity). In this sample, 50% of the children born VPT who completed the measure performed in the impaired range. Of those performing poorly on the motor assessment, the majority were boys. Many brain regions were correlated with poor performance on the MABC-2. Lower volume of the forceps major and lower FA/higher MD in the corpus callosum, anterior thalamic radiations, and cingulum were all associated with the group of VPT children performing poorly on the movement measures. Overall, the volume of the brainstem, lateral ventricles, and cerebellum white matter were broadly associated with VPT birth, rather than specific to poor movement abilities. Therefore, this study concluded that subtle brain findings in the areas known to be vulnerable to the effects of early birth were related to motor abilities, and boys were particularly vulnerable.

Collectively, these aims and conclusions from the three included studies demonstrate a profile of skills deficits and neuroanatomical differences in a group of “low-risk” VPT-born children compared to their FT born peers. The present findings may help focus areas that should be monitored by providers when a child has a history of preterm birth, even if they had a relatively benign neonatal course.

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