Cortical Connections 2018
Symposium on Brain Development
June 28, 2018
Westin South Coast Plaza
Costa Mesa, California
# Symposium Program

## 8:30 am - 8:45 am

**Welcome & Opening Remarks**

*Lynn Paul, PhD, IRC5 President*

## 8:45 am - 9:15 am

**Development of Cortical Wiring**

<table>
<thead>
<tr>
<th>Time</th>
<th>Title</th>
<th>Speaker</th>
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<tbody>
<tr>
<td>8:45 am</td>
<td>Embryonic Mechanisms of Corpus Callosum Formation</td>
<td>Linda Richards, PhD, Queensland Brain Institute, University of Queensland, Australia</td>
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<tr>
<td>9:15 am</td>
<td>Axonal Plasticity in Corpus Callosum Formation</td>
<td>Roberto Lent, MD, Federal University of Rio de Janeiro, Brazil</td>
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<tr>
<td>9:45 am</td>
<td>Human Corpus Callosum Anomaly in Fetal Life</td>
<td>Tania Attie-Bitach, MD, PhD, Hospital Necker-Enfants Malades, Université Paris, France</td>
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<tr>
<td>10:15 am</td>
<td>Morning Break</td>
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## 10:45 am - 11:15 am

**Genetics of Cortical Wiring**

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<thead>
<tr>
<th>Time</th>
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<tbody>
<tr>
<td>10:45 am</td>
<td>Interpreting the Genetic Architecture of De Novo Mutations in Structural Brain Disorders</td>
<td>Paul Lockhart, PhD, Murdoch Children’s Research Institute, Melbourne, Australia</td>
</tr>
<tr>
<td>11:15 am</td>
<td>What Can Genes Tell Us about Disorders Affecting the Corpus Callosum?</td>
<td>Christel Depienne, PhD, University Hospital Essen, Germany</td>
</tr>
<tr>
<td>11:45 am</td>
<td>Cerebral Connectivity: From Genes to Cognition</td>
<td>Elliott Sherr, MD, PhD, University of California, San Francisco, California, USA</td>
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<tr>
<td>12:15 pm</td>
<td>Lunch - Waterfall Terrace</td>
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## 1:15 pm - 1:45 pm

**Diagnosis of Cortical Wiring Disorders**

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<thead>
<tr>
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<tbody>
<tr>
<td>1:15 pm</td>
<td>Neonatal MRI and the Diagnosis of Cortical Wiring Disorders and Co-Morbidities</td>
<td>Simone Mandelstam, MB, ChB, Royal Children’s Hospital, University of Melbourne, Australia</td>
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<tr>
<td>1:45 pm</td>
<td>Crossing the Great Divide: Developmental and Genetic Landscape of Midline Crossing Defects</td>
<td>William Dobyns, MD, University of Washington, Seattle, Washington, USA</td>
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<tr>
<td>2:15 pm</td>
<td>Advances in Imaging of White Matter Microstructure and the Macroscale Connectome</td>
<td>Pratik Mukherjee, MD, PhD</td>
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<tr>
<td>2:45 pm</td>
<td>Afternoon Break</td>
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## 3:15 pm - 5:00 pm

**Compensation & Limitations in Cortical Wiring Disorders**

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<tr>
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<tr>
<td>3:15 pm</td>
<td>Mapping and Modeling Cortical Connections</td>
<td>Fernanda Tovar-Moll, MD, PhD, D’Or Institute for Research &amp; Education, UFRJ, Rio de Janeiro, Brazil</td>
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<tr>
<td>3:45 pm</td>
<td>Cognitive Syndrome of Callosal Agenesis</td>
<td>Warren Brown, PhD, Fuller Graduate School of Psychology, Pasadena, California, USA</td>
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<tr>
<td>4:15 pm</td>
<td>Impact of Diminished Cortical Connectivity on Development and Adaptive Behavior</td>
<td>Lynn Paul, PhD, California Institute of Technology, Pasadena, California, USA</td>
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<tr>
<td>4:45 pm</td>
<td>Concluding Remarks</td>
<td>Linda Richards, PhD, IRC5 Secretary</td>
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T. Attié-Bitach, Professor at Paris Descartes University, is human geneticist specialized in molecular genetics of congenital malformations and fetalpathology. She developed a clinical and genetic research on human fetal disorders at Imagine Institute, in Necker Medical School. She has driven projects leading to the identification of genes responsible for Meckel syndrome, hydrolethalus, related ciliopathies and other lethal disorders such as Matthew-Wood and Fowler syndromes, as well as a national project aiming to characterize the genetic causes of corpus callosum anomalies in humans.

Warren S. Brown is Professor of Psychology and Director of the Lee Travis Research Institute at the Graduate School of Psychology, Fuller Theological Seminary. He is a research neuropsychologist/neuroscientist studying the cognitive and psychosocial impact of a congenital brain malformation (agenesis of the corpus callosum and hemispherectomy). He is also author or editor of 4 books on neuroscience and philosophy/religion.

Christel Depienne is Associate Professor at the University Hospital of Essen, Germany. She has been responsible for genetic testing of neurological disorders (hereditary spastic paraplegia, epilepsy, intellectual disability) and, in parallel, has developed research projects as principal investigator focusing on the identification of genes involved in several neurodevelopmental disorders (epilepsies, intellectual disability, autism spectrum disorders, mirror movements and more recently agenesis of the corpus callosum) and establishment of genotype-phenotype correlations.

William B. Dobyns is Professor of Pediatrics (Genetics) and Neurology at the University of Washington, and Principal Investigator in the Center for Integrative Brain Research at Seattle Children’s Research Institute. He is a physician-scientist who studies the nature and causes of many human developmental brain disorders. While best known for studies of lissencephaly and other cortical malformations, his work also involves disorders of brain size (microcephaly and megalencephaly), brainstem and cerebellar malformations, intellectual disability, autism, and early childhood epilepsies.

Roberto Lent is Professor of Neuroscience at the Federal University of Rio de Janeiro (1992), former director of the Instituto de Ciências Biomédicas, member of the Brazilian Academy of Sciences, member of the Technical-Scientific Council for Basic Education, and president of the Council of Instituto Ciências Hoje, a social organization created by the Brazilian Society for the Progress of Science, dedicated to science popularization. At the University, RL heads a Laboratory at Instituto de Ciências Biomédicas, working in Neuroembriology, Neuroplasticity and Evolution of the Nervous System.

Associate Professor Paul Lockhart is Co-Director of the Bruce Lefroy Centre where his research activities to include gene identification utilising modern genomic technologies. He works in close collaboration with the Victorian Clinical Genetics Service to identify and characterise the genetic basis of rare Mendelian genetic disorders in families presented to the clinic. Currently he leads a laboratory group that investigates the molecular basis of neurogenetic disorders.

Simone Mandelstam is a Senior Specialist Paediatric Radiologist at the Royal Children’s Hospital in Melbourne and an Associate Professor of Radiology and Paediatrics at the University of Melbourne, Australia. She specializes in Neuroimaging and is a clinical and research epilepsy radiologist at the Florey Institute of Neuroscience and Mental Health and Honorary Research Fellow at the Murdoch Children’s Research Institute. Simone is involved in many research collaborations on the imaging of genetic epilepsies, brain malformations and paediatric stroke.

Pratik Mukherjee is Professor of Radiology and Bioengineering at the University of California, San Francisco (UCSF). He is a clinical neuroradiologist and his research is focused on technical development and neuroscience applications of mapping microstructure, function and connectivity in the human brain, with the goal of developing novel imaging biomarkers for neurological and psychiatric diseases that can be used in a Precision Medicine framework for diagnosis, prognosis and treatment selection and monitoring.

Lynn K. Paul (Sternberg) is a Senior Research Scientist at California Institute of Technology, and a licensed clinical psychologist at L.K.Paul & Associates in Pasadena, CA. Her research focuses on brain-structure, cognition and social processing in adolescents and adults with agenesis of the corpus callosum and individuals with childhood hemispherectomy. She is also conducting the first longitudinal study of behavioral development in infants with callosal dysgenesis. Dr. Paul was founding president of the NODCC in 2002 and helped found the IRC® in 2016.

Linda J. Richards is a Professor of Neuroscience and Deputy Director of the Queensland Brain Institute at the University of Queensland. She is an NHMRC Principal Research Fellow and current President of the Australasian Neuroscience Society and Chair of the Australian Brain Alliance. She is patron and scientific advisor of AusDoCC, the Australian Disorders of the Corpus Callosum support group.

Elliott Sherr is a Professor in Neurology and Pediatrics at the Weill Institute of Neurosciences and the Institute of Human Genetics at UCSF. He directs the Brain Development Research Program, a group that studies the genetics and biology autism and epilepsy (brain.ucsf.edu). Dr. Sherr also studies the genetics of disorders of brain development, including agenesis of the corpus callosum. Dr. Sherr is a board-certified Child Neurologist and co-directs the Comprehensive Center for Brain Development at UCSF, where he cares for children with neurodevelopmental disorders.

Fernanda Tovar-Moll is an Adjunct professor of the National Center of Structural Biology and Bioimaging at UFRJ and co-founder and president of the D’Or Institute for Research and Education. Her research interests include clinical/translational research, employing novel in vivo imaging techniques in human and rodents to map brain circuits in order to improve the understanding of mechanisms related to brain connectivity and plasticity, in normal and pathological conditions.
Development of Cortical Wiring

Embryonic Mechanisms of Corpus Callosum Formation
Linda Richards, PhD

The corpus callosum is the largest fiber tract in the human brain and connects the two cerebral hemispheres. The mechanisms regulating the formation of the corpus callosum are complex as they involve all of the developmental mechanisms required to form a functioning brain. Our laboratory not only investigates the mechanisms involved in the formation of the corpus callosum, but also how other seemingly unrelated structural brain malformations may be related to callosal dysgenesis via the disruption of similar cellular and molecular mechanisms. Subjects with corpus callosum agenesis/dysgenesis are currently identified based on their structural midline phenotype, a limit imposed by current clinical neuroimaging capabilities. However, these subjects are likely to represent sub-groups with more severe forms of callosal dysgenesis. More subtle changes in callosal targeting could represent a much larger and diverse group of subjects that have normal midline crossing, but disrupted targeting in the contralateral hemisphere. This area of research is in its formative stages but could offer potentially major breakthroughs in how the brain is normally wired during development and what mechanisms may be disrupted in disorders of brain connectivity.

Acknowledgment of funding: Our research is funded by project grants from the National Health and Medical Research Council, Australia, the Australian Research Council, and the National Institutes of Health, USA. LJR is supported by an NHMRC Principal Research Fellowship.

Axonal plasticity of the Corpus Callosum After Birth
Roberto Lent, MD

The corpus callosum starts to form prenatally in most mammalian species, but its full development lasts all through adolescence, until the final wave of myelination of axonal fibers. Perhaps due to this protracted development, callosal axons remain vulnerable to different forms of plasticity after postnatal insults. One of these insults is the deafferentation caused by limb amputation. I am going to show an example of this late axonal plasticity, studied with a reverse translational approach, starting with human amputees, and following up with experiments done in rats. Human lower limb amputees have been studied with MR neuroimaging, which revealed a functional expansion of the stump and intact foot representations in the cerebral cortex in both hemispheres, together with a reduction in fractional anisotropy of the callosal sector whereby somatosensory fibers cross the midline. To reveal the microstructural underpinnings of these phenomena, we placed axonal tracer injections in the somatosensory representation of the missing limb of early amputated rats, and reconstructed the labeled axons in the opposite hemisphere, revealing that the terminal callosal arbors increased in size therein, with a higher number of synaptic boutons as compared with controls. Also, we studied the ultrastructure of that callosal sector in both early and late amputated rats, using transmission electron microscopy, and showed a reduction in myelination of axons therein, in amputated as compared with control animals. Altogether, these results indicate that the corpus callosum is plastic until late in postnatal life, undergoing changes in myelination and in its synaptic input to the cortex, phenomena that possibly contribute to a misbalance of the inhibitory callosal modulation of the opposite hemisphere, and consequent expansion of the neighboring somatotopic representation, adjacent to the lost limb.

Acknowledgment of funding: Brazilian Ministry of Science, Technology and Innovation (CNPq, INNT), Ministry of Education (CAPES), and the Rio de Janeiro Foundation for the Support of Science (FAPERJ).

Human Corpus Callosum Anomalies in Fetal Life
Tania Attié-Bitach, MD, PhD

Corpus callosum (CC) is the major brain commissure connecting the homologous areas of both hemispheres at the midline. CC malformations (CCM) are the most frequent brain malformations with an incidence of 1/4000 newborn often associated with chromosomal anomalies or mendelian syndromes with recessive and dominant inheritance. Recurrence is observed in 5% of cases. Children with CCM have an uncertain neuro-developmental outcome. Therefore, counseling remains challenging, especially prenatally. We systematically reviewed the data of 142 fetuses with CCM as isolated or associated autopsy findings in our center. We first completed the cytogenetic analysis by a CGH array when the underlying etiology was not found: 108 (76%) of cases remained unsolved.

In our effort to identify the disease causing gene of CCM antenatally, we use CGH array and high throughput sequencing strategies. Interestingly some diseases were not possible antenatally due to the absence of specific signs, but reevaluation of fetopathological data (reverse phenotyping) allowed to support NGS findings. All together, combined fetal imaging, fetal exmination, cytogenetic and molecular analysis allows the identification of a genetic cause in 25-30% of fetuses.

Acknowledgment of funding: Agence Nationale pour la recherche (ANR); Agence de la Biomédecine (ABM)
Family-based Studies to Identify Genes that Influence Development of the Corpus Callosum
Paul Lockhart, PhD

Agenesis of the corpus callosum (ACC) is a genetically complex, congenital brain malformation, characterised by partial or complete absence of the corpus callosum, the structure that connects the two cerebral hemispheres. ACC is associated with diverse neurological deficits and affects ~1:4500 children. While there is considerable evidence that genetics contributes to ACC, in approximately 50% of cases the cause remains unknown.

Historically, the identification of disease-associated genes was challenging and often depended on characterising naturally occurring models, including mice and rats. The recent development of genomic technologies that enable rapid sequencing and analysis of the entire exome or genome of affected individuals has resulted in the identification of genes underlying many human disorders. These approaches are now being successfully applied to disorders of the corpus callosum. This presentation will briefly review the methodologies being applied and describe recent discoveries in the field.

Acknowledgment of funding: This research has been supported by grants from the National Health and Medical Research Council (Australia) and philanthropic donations to the Bruce Lefroy Centre.

What can Genes Tell Us About Disorders Affecting the Corpus Callosum?
Christel Depienne, PhD

Agenesis of the corpus callosum (AgCC) is a clinically and genetically variable condition characterized by a complete or a partial absence of the corpus callosum, the main commissure connecting the two brain hemispheres in mammals. Mutations in more than 300 genes have been associated with AgCC in humans, and most of them also lead to intellectual disability (ID). Interestingly, a large proportion of genes associated with AgCC and ID encodes transcription factors or chromatin remodelers, two classes of genes that regulate the expression of other target genes. For example, genes encoding subunits of the SWI/SNF complex is one of the most frequent cause of AgCC and ID. On the contrary, the cause of isolated AgCC remains unknown in most patients. Recently, we have described variants in DCC as the first cause of isolated AgCC. Interestingly, AgCC or other malformations of the corpus callosum are present in only a subset of individuals with mutations, which range from a few percent to half of the individuals. This incomplete penetrance of the AgCC phenotype suggests that AgCC is not a condition determined by genetic variants in a single gene, but on the contrary depends on additional genetic or environmental factors.

Acknowledgment of funding: The work presented was funded the Agence Nationale de la Recherche (ANR Blanc CILAXCAL), Assistance Publique des Hôpitaux de Paris (APHP), the “programme hospitalier de recherche clinique” (PHRC) AC-CREM, and the “Investissements d’Avenir” programme ANR-10-IAIHU-06 (IHU-A-ICM).

Cerebral Connectivity: From Genes to Cognition
Elliott Sherr, MD, PhD

Dr. Sherr will address advances in biology related to development of the corpus callosum, using genetics as a guide to discovery.

Acknowledgment of funding: NIH, Goldman Foundation, DDX3X Foundation, Simons Foundation
Diagnosis of Cortical Wiring Disorders

Imaging Guidance for Minimalistic Neurosurgery in Children with Focal Cortical Dysplasia
Simone Mandelstam, MB, ChB

Focal Cortical Dysplasias (FCD) in children can cause intractable epilepsy that is not controlled with antiepileptic medications and may result in significant neurodevelopmental issues affecting a child’s social, physical and learning capabilities. The ultimate aim in a high level Epilepsy Surgery Program is to identify those patients with FCD who have resectable lesions and will benefit from surgery. As a seizure focus does not exist in isolation, consideration has to be given to brain networks that may be damaged or disrupted by the operation. Multimodality imaging can help identify important structural and functional networks so that the surgical corridor can be planned to minimise harm to eloquent cortex while achieving the best surgical outcome. Meticulous imaging has obviated the need for subdural electrode implantation in most of our patients at the Royal Children’s Hospital in Melbourne. Cortical resections are now far smaller, with less collateral damage and good post surgical results.

Acknowledgment of funding: None

Crossing the Great Divide: The Developmental and Genetic Landscape of Midline Crossing Defects
William B. Dobyns, MD

The corpus callosum (CC) and other cerebral commissures are often overlooked in assessing fetuses and children with developmental brain disorders because of multiple patterns of malformation that are inconsistently defined, lack of experience in recognizing these patterns, variable severity including non-penetrance, occasional co-occurrence of atrophy, and limited understanding of the underlying causes. The spectrum of defects classified as agenesis of the corpus callosum (ACC) includes complete absence, partial absence and diffuse thinning of the CC, and can be confused with late fetal or early postnatal degeneration of the CC.

ACC has been associated with more than 30 chromosome microdeletions and duplications, at least 12 of them relatively common. ACC has also been associated with more than 40 genes, most with variable severity of the callosal defect. The major groups include ACC with developmental encephalopathies and early-life epilepsies, ACC with autism, and ACC with severe multiple anomaly syndromes. This lecture will describe the full phenotypic spectrum of ACC per se and associated brain malformations, review data on copy number variants, and review ACC associated genes from the three major phenotype groups - severe early life handicaps and epilepsy; autism; and complex syndromes such as Aicardi syndrome.

Acknowledgement of funding: NIH grant: 1R01NS058721 (Sherr and Dobyns)

Advances in Imaging White Matter Microstructure and the Macroscale Connectome with Applications to Human Brain Development and Agenesis of the Corpus Callosum
Pratik Mukherjee, MD, PhD

Diffusion MRI has made enormous strides over the past three decades and is now the primary method to probe the living human brain across orders of magnitude of scale: from tissue microarchitecture to the whole-brain structural connectome. Greatly improved gradient strength and speed, innovative pulse sequences, combined with novel biophysical modeling of diffusion MRI data, now enable the noninvasive measurement of biologically meaningful microstructural parameters such as axonal and dendritic density and fiber orientation dispersion. In this lecture, I review the development of novel diffusion MRI methods for brain microstructure and connectivity imaging with applications to human brain development and to agenesis of the corpus callosum (AgCC) as a model of human brain dysconnectivity. I also discuss two recent advances in white matter connectomics. First, I focus on mapping the anatomic embedding of the whole-brain structural network, which identifies special zones of vulnerability that are of particular importance in many white matter diseases across the lifespan, from premature infants to the elderly. Second, I review progress in applying spectral graph theory to decompose the human macroscale connectome into its fundamental "eigenmodes". These structural eigenmodes provide a robust and parsimonious basis set with which to describe functional connectivity networks from fMRI and MEG, as well as to characterize the changes of human brain development and the unique perturbations of brain network organization that occur in neurodevelopmental disorders.

Acknowledgment of funding: Not available
Compensation & Limitations in Cortical Wiring

Plasticity in the Human Brain
Fernanda Tovar-Moll, MD, PhD

Over the last two decades, structural and functional neuroimaging have promoted a great advance on the characterization of the brain connectome, and its capacity to reorganize in response to internal and environmental influences, opening new windows for the investigation of changes in brain networks in normal and pathological conditions. These new concepts and techniques will be presented, including fMRI (especially resting state fMRI) that allows us to probe functional coupling of networks, and diffusion tensor imaging, which characterizes white matter tracts interconnecting nodal structures among brain networks. We will present the use of those methods in investigating brain plasticity in the developing and adult brain. Although all these conditions are associated with brain circuitry reorganization, they exhibit different levels of changes. Our human and mice data indicates that plasticity in the developing brains can exhibit a massive white matter reorganization, leading to the formation of anomalous tracts interconnecting distant cortical areas. On the other hand, neuroimaging data supported by behavioral and clinical data also show that neuromodulation techniques, such as fMRI neurofeedback or current stimulation, can induce functional and structural plasticity in normal and pathological adult brain. We will also address how these findings are inspiring new research translational platforms to establish a more detailed view of brain plasticity mechanisms.

Acknowledgment of funding: Brazilian Ministry of Science, Technology and Innovation (CNPq, INNT), Ministry of Education (CAPES), the Rio de Janeiro Foundation for the Support of Science (FAPERJ) and intramural grants from D’Or Institute for Research and Education (IDOR)

Cognitive Syndrome of Callosal Agenesis
Warren S. Brown, PhD

Agenesis of the corpus callosum (AgCC) involves congenital absence of all or part of the corpus callosum. Because the disorder can only be firmly diagnosed via neuroradiology, it has a short research history, and only recently has the cognitive syndrome become clear. Our purpose is to review the primary deficits in AgCC that constitute the core syndrome. The core syndrome includes: (1) Reduced interhemispheric transfer of sensory-motor information; (2) Reduced cognitive processing speed; (3) Deficits in complex reasoning and novel problem-solving. These domains do not appear to reflect different neuroanatomical abnormalities, but rather different domains of expression of reduced interhemispheric communication from callosal absence. These core deficits are expressed across various domains of cognitive, behavioral, and social functioning. The impact of these deficits varies across development and may be moderated by individual factors such as co-occurrence of other neurodevelopmental conditions, general intellectual capacity, and environmental support.

Acknowledgment of funding: None

Behavioural Consequences of Callosal Malformations
Lynn K. Paul, PhD

The corpus callosum, whose roughly 200 million axons constitute the largest white matter tract in the human brain, remains enigmatic in its contribution to cognition and behavior. For two decades we have been characterizing the cognitive and behavioral features shared among individuals with agenesis of the corpus callosum (AgCC), a congenital brain malformation defined by the complete or partial absence of callosal structures. AgCC can be an isolated finding but can also co-occur with additional brain malformations and systemic conditions. Adolescents and adults with isolated AgCC and normal-range intellectual scores exhibit a shared pattern of limitations in fundamental aspects of cognition including interhemispheric transfer of complex information and processing speed, as well as higher order cognitive skills such as novel problem solving, comprehension of second-order meanings in language, and complex theory of mind and social interpretation. We have recently begun longitudinal studies of cognitive development in infants with AgCC. Our research aims to provide a foundation for more accurate cognitive and psychosocial profiling and intervention for people with corpus callosum disorders, while also informing wider central issues in neuroscience, such as functional development of the cortex and neuroplasticity.

Acknowledgment of funding: Our research on AgCC has been supported by the Simons Foundation, a NARSAD Young Investigator Grant to LKP, and the Pfeiffer Foundation. LKP is supported in part by a Conte Center grant from the NIH.
The International Research Consortium for the Corpus Callosum and Cerebral Connectivity (IRC5) is an international, multidisciplinary effort to discover the causes, consequences, and effective interventions for disorders of the corpus callosum and associated disorders of cerebral connectivity. It was established on March 20, 2015 by a group of investigators who are leading experts in corpus callosum developmental disorders and their neuropsychological and developmental outcomes and who have maintained long-standing involvement in patient support organizations.

IRC5 Mission

- Identify what causes malformation of brain connections before birth
- Discover ways to prevent or ameliorate these malformations
- Improve accuracy of predicting how child will be impacted by these malformation
- Develop effective interventions to prevent (or minimize) long-term disability from them, such as deficits in cognition and behavior, as well as neurologic conditions such as epilepsy, ataxia and spasticity

Our mission is to enhance the quality of life and promote opportunities for individuals with disorders for the corpus callosum.

The NODCC is the leading organization for disorders of the corpus callosum seeking to raise the profile, understanding and acceptance of these disorders through education, networking, advocacy, and being a catalyst for research.