Neurology

Division Details

Division Data Summary

Research and Training Details

Number of Faculty	27
Number of Joint Appointment Faculty	2
Number of Research Fellows	1
Number of Research Students	2
Number of Support Personnel	46
Direct Annual Grant Support	\$7,001,275
Direct Annual Industry Support	\$234,375
Peer Reviewed Publications	49

Clinical Activities and Training

Number of Clinical Staff	77
Number of Clinical Fellows	17
Number of Other Students	13
Inpatient Encounters	1,895
Outpatient Encounters	23,254

Cincinnati Children's

Division Photo



Row 1: B Wong, D Gilbert, J Vannest, J Xiang, A Hershey

Row 2: M Williams, D Krueger, K Wesselkamper, J Tenney, T Glauser

Row 3: C Vorhees, D Franz, C Thomas, M Skelton

Significant Accomplishments

Headache Center

The Headache Center celebrated its 15th year with continued growth in the management, treatment and understanding of children, adolescents and young adults. The multidisciplinary outpatient clinic, acute treatment center, young adult headache program and a focused inpatient service provide the basis for the research and educational activities, including an UCNS-certified Headache Medicine fellowship. Headache Center research includes clinical trials, outcome studies and understanding the molecular and neurophysiological basis of migraine. Recent blood genomic studies identified the gene expression patterns for medication overuse and menstrual-related migraine. An NIH-sponsored study of acute migraine has demonstrated cortical dysfunction in children during a migraine and has been extended to the effects of chronic migraine. In collaboration with the Division of Behavioral Medicine and Clinical Psychology, an NIH study examining the role of coping skills training in the management of chronic migraine will be completed this fall. We have entered into a significant additional collaborative effort with Scott Powers, PhD, Center for Clinical and Translation Research and the Department of Biostatistics and Clinical Trials Statistical and Data Management Center at the University of Iowa in launching our 40-site study investigating the comparative effectiveness of amitriptyline and topiramate in preventing pediatric and adolescent migraine (CHAMP) study.

Epilepsy Center

The Comprehensive Epilepsy Center includes multiple epilepsy clinics including New Onset Seizure (with separate clinics for infants and older children), Advanced Therapies, Epilepsy Surgery, Epilepsy and Sleep Clinic. Multiple clinical and translational research activities are underway, including investigation of the role of drug-gene interactions on the individual variation in anti-epileptic drug clinical response; observational and interventional adherence research; examination of the differential gene expression patterns in blood and brain; a study examining the effect of sleep medications on EEG patterns; research on the effect of spikes on language development; functional MRI/magnetoencephalographic imaging of generalized spike discharges; and application of advanced technologies to develop epilepsy clinical decision support algorithms.

There are six individual NIH-funded epilepsy researchers in the Comprehensive Epilepsy Center. The NIHfunded, 29-center U01 trial based out of Cincinnati Children's is the largest pediatric epilepsy trial ever funded in the United States. The study is designed to better identify the pharmacokinetic, pharmacodynamic and pharmacogenetic factors that impact response to therapy. The research on epilepsy adherence was recently published in *JAMA*. The varied research efforts continue to generate highly significant information on the management of children with epilepsy.

Tuberous Sclerosis Program

The Tuberous Sclerosis Program had another very productive year. Our clinic is the largest in the world, and the only one that manages every aspect of the disorder in both adults and children. We receive increasing numbers of referrals from throughout the United States and internationally. Research conducted here or led by our clinic physicians has resulted in a new FDA indication for renal tumors associated with condition, and has identified new therapies for epilepsy, cognitive impairments, lung disease, and skin tumors. mTOR inhibition, the main focus of our research, is also applicable to non-TSC patients with epilepsy, movement disorders, autism, sporadic lymphangioleiomyomatosis and Alzheimer's disease. Darcy Krueger, MD, PhD, received two RO1 grants from the National Institutes of Health last year, totaling more than 15 million dollars. One of these grants, which received a perfect score from reviewers, will form an autism research network based at Cincinnati Children's using TSC as paradigm. Our research has been accepted by numerous high profile publications, including the *New England Journal of Medicine, The Lancet,* and *Annals of Neurology*. We also offer unique social and emotional support to patients and families, the highlight of which is our TSC summer camp, the first and only one of its kind in the world.

Division Highlights

Neuromuscular Program

The Pediatric Neuromuscular program assumed overall coordination and direction of the Comprehensive Neuromuscular Care Center in July 2011. The following accomplishments are noted with increase in total number of outpatient visits and encounters (with 60% of all neuromuscular families and 80% of DMD families from outside Cincinnati Children's service areas – i.e. other states and cities in the US and other countries):

- 1. Establishment of an interdisciplinary cardiac-pulmonary clinic for the extended neuromuscular evaluations
- 2. Provision of additional DMD/BMD carrier clinics with Cardiology, ophthalmology evaluations, health psychologist and neuromuscular neuropsychology services
- 3. Initiation of muscle and nerve ultrasound services in the outpatient clinic is expected in the fall 2012

The pediatric NM clinic was one of the 3 (with Asthma and Rheumatology) clinics at Cincinnati Children's to successfully engage in the EHR process for review of history and Peds QL, thereby laying the infrastructure for

efficient use of electronic medical records for monitoring patient outcomes.

Preclinical neuroscience

Skelton lab: The development of a brain specific CrT knockout mouse to understand CNS specific effects of the loss of Cr has demonstrated that female carrier mice did not have learning and memory deficits despite having significantly lower Cr than WT, providing insight into the necessary levels of Cr for proper brain function. CrT knockout mice were found to have an exaggerated response to serotonin releasing drugs, expanding the role of Cr in serotonin signaling.

Vorhees lab: Hypothesizing that inhibiting the serotonin reuptake transporter would prevent the adverse effects of MDMA (Ecstasy), the selective serotonin reuptake inhibitor (SSRI) antidepressant, citalopram caused long-term reductions in hippocampal 5-HT and impairments in learning and memory for both allocentric and egocentric abilities. Animals were exposed during a stage of brain development approximating human 3rd trimester, raising concerns about the safety of antidepressants when used during pregnancy.

Williams Lab: Focusing on understanding the brain regions involved in egocentric learning and memory, specific dopaminergic lesions in rats demonstrated that lesions in the lateral portion of the dorsal striatum ,but not the medial portion dorsal striatum lesions produced 30-40% increases in errors during egocentric learning with increases in latency to escape, improving our understanding of regional specificity for egocentric learning and memory.

Neonatal Neurology Program

The Neonatal Neurology team provides consultation services to Newborn Intensive Care Units at Cincinnati Children's Hospital, Good Samaritan Hospital and University Hospital of Cincinnati for the acute management of seizures and other neurological disorders of the newborn. We have worked closely with neonatology to develop protocols for EEG monitoring and treatment of neonatal seizures. We are in the process of expanding neonatal electrophysiology services to neonatal intensive care units in Dayton and Northern Kentucky.

We have also created and continue to expand a multi-disciplinary follow up clinic including participants from Occupational Therapy, Speech Therapy, Nutrition, Neonatology and Neurology which provides subsequent care for these infants following discharge from the Neonatal Intensive Care Unit and continuing through the first several years of life. This consistent and comprehensive outpatient care facilitates longitudinal identification of risk factors for poor neurologic development and areas where targeted interventions may improve long term outcomes.

Using lessons learned from our experiences creating multi-disciplinary care for patients from the neonatal intensive care period through early childhood, we are also working with Cardiology to develop similar cardiac intensive care protocols and outpatient follow up for survivors of complex congenital heart disease requiring cardiac surgery.

Movement Disorder and Tourette Syndrome Program

The Movement Disorders and Tourette Syndrome Clinic has a regional and national reputation and we see referrals from multiple states in the region for second opinions. The clinic program offers a full spectrum of pharmacological services for movement disorders, collaboration with and referral to neurosurgery for deep brain stimulation, and collaboration with psychology for behavioral treatments for Tourette Syndrome. Clinic director Donald Gilbert is a member of the NIH taskforce on Pediatric Movement Disorders and of the Medical Advisory Board for the Tourette Syndrome Association. He has also been a visiting professor and speaker at conferences on Movement Disorders in Children in Minneapolis, Savannah, and Boston. The clinic is active in

multiple phases of research, with 14 publications in the last year and with two clinical trials of new medications for Tourette Syndrome. The research program includes studies of the physiology of motor cortex and brain neuroplasticity in children and adults. We currently have 3 NIH grants active for studies in Tourette Syndrome and ADHD.

Division Publications

- 1. Adkin CF, Meloni PL, Fletcher S, Adams AM, Muntoni F, Wong B, Wilton SD. Multiple exon skipping strategies to by-pass dystrophin mutations. *Neuromuscul Disord*. 2012; 22:297-305.
- Austin JK, Perkins SM, Johnson CS, Fastenau PS, Byars AW, deGrauw TJ, Dunn DW. Behavior problems in children at time of first recognized seizure and changes over the following 3 years. *Epilepsy Behav*. 2011; 21:373-81.
- 3. Bagic Al, Barkley GL, Rose DF, Ebersole JS. American Clinical Magnetoencephalography Society Clinical Practice Guideline 4: qualifications of MEG-EEG personnel. *J Clin Neurophysiol.* 2011; 28:364-5.
- Bagic AI, Knowlton RC, Rose DF, Ebersole JS. American Clinical Magnetoencephalography Society Clinical Practice Guideline 1: recording and analysis of spontaneous cerebral activity. J Clin Neurophysiol. 2011; 28:348-54.
- Chung TK, Lynch ER, Fiser CJ, Nelson DA, Agricola K, Tudor C, Franz DN, Krueger DA. Psychiatric comorbidity and treatment response in patients with tuberous sclerosis complex. *Ann Clin Psychiatry*. 2011; 23:263-9.
- Dabora SL, Franz DN, Ashwal S, Sagalowsky A, DiMario FJ, Jr., Miles D, Cutler D, Krueger D, Uppot RN, Rabenou R, Camposano S, Paolini J, Fennessy F, Lee N, Woodrum C, Manola J, Garber J, Thiele EA. Multicenter phase 2 trial of sirolimus for tuberous sclerosis: kidney angiomyolipomas and other tumors regress and VEGF- D levels decrease. *PLoS One*. 2011; 6:e23379.
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- 8. Ducharme S, Hudziak JJ, Botteron KN, Albaugh MD, Nguyen TV, Karama S, Evans AC. Decreased regional cortical thickness and thinning rate are associated with inattention symptoms in healthy children. *J Am Acad Child Adolesc Psychiatry*. 2012; 51:18-27 e2.
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- 10. Fountain-Capal JK, Holland KD, Gilbert DL, Hallinan BE. When should clinicians order genetic testing for Dravet syndrome?. *Pediatr Neurol.* 2011; 45:319-23.
- 11. Franz DN. Everolimus: an mTOR inhibitor for the treatment of tuberous sclerosis. *Expert Rev Anticancer Ther.* 2011; 11:1181-92.
- 12. Franz DN, Weiss BD. Molecular therapies for tuberous sclerosis and neurofibromatosis. *Curr Neurol Neurosci Rep.* 2012; 12:294-301.
- Fujiwara H, Greiner HM, Hemasilpin N, Lee KH, Holland-Bouley K, Arthur T, Morita D, Jain SV, Mangano FT, Degrauw T, Rose DF. Ictal MEG onset source localization compared to intracranial EEG and outcome: Improved epilepsy presurgical evaluation in pediatrics. *Epilepsy Res.* 2012; 99:214-24.
- 14. Gilbert DL. Training the next generation of child neurologists: a child health-based approach. J Child

Neurol. 2012; 27:270-2.

- 15. Gilbert DL. The relationship between group A streptococcal infections and Tourette syndrome. *Dev Med Child Neurol.* 2011; 53:883-4.
- 16. Glauser TA. Biomarkers for antiepileptic drug response. Biomark Med. 2011; 5:635-41.
- 17. Greiner HM, Holland K, Leach JL, Horn PS, Hershey AD, Rose DF. Nonconvulsive status epilepticus: the encephalopathic pediatric patient. *Pediatrics*. 2012; 129:e748-55.
- 18. Greiner HM, Lynch ER, Fordyce S, Agricola K, Tudor C, Franz DN, Krueger DA. Vigabatrin for childhood partial-onset epilepsies. *Pediatr Neurol.* 2012; 46:83-8.
- Greiner HM, Park YD, Holland K, Horn PS, Byars AW, Mangano FT, Smith JR, Lee MR, Lee KH. Scalp EEG does not predict hemispherectomy outcome. Seizure. 2011; 20:758-63.
- 20. Greiner HM, Tillema JM, Hallinan BE, Holland K, Lee KH, Crone KR. Corpus callosotomy for treatment of pediatric refractory status epilepticus. *Seizure*. 2012; 21:307-9.
- 21. Hershey A, Horn P, Kabbouche M, O'Brien H, Powers S. Genomic expression patterns in menstrual-related migraine in adolescents. *Headache*. 2012; 52:68-79.
- 22. Hershey AD. Pediatric headache: update on recent research. Headache. 2012; 52:327-32.
- 23. Hershey AD, Winner P, Linder S, Gladstein J, Yonker M, Mack K, Pearlman E, Rothner AD. In memoriam: Donald W. Lewis, MD (1951-2012). *Headache*. 2012; 52:720-1.
- Jacola LM, Byars AW, Chalfonte-Evans M, Schmithorst VJ, Hickey F, Patterson B, Hotze S, Vannest J, Chiu CY, Holland SK, Schapiro MB. Functional magnetic resonance imaging of cognitive processing in young adults with Down syndrome. *Am J Intellect Dev Disabil*. 2011; 116:344-59.
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- 26. Kabbouche M, O'Brien H, Hershey AD. **OnabotulinumtoxinA in pediatric chronic daily headache**. *Curr Neurol Neurosci Rep.* 2012; 12:114-7.
- Korostenskaja M, Pardos M, Kujala T, Rose DF, Brown D, Horn P, Wang Y, Fujiwara H, Xiang J, Kabbouche MA, Powers SW, Hershey AD. Impaired auditory information processing during acute migraine: a magnetoencephalography study. *Int J Neurosci.* 2011; 121:355-65.
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- Miles MV, Miles L, Horn PS, DeGrauw TJ. Enzyme inducing antiepileptic drugs are associated with mitochondrial proliferation and increased cytochrome c oxidase activity in muscle of children with epilepsy. Epilepsy Res. 2012; 98:76-87.
- 31. O'Brien HL, Kabbouche MA, Hershey AD. **Treating pediatric migraine: an expert opinion**. *Expert Opin Pharmacother*. 2012; 13:959-66.
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- 40. Tillema JM, Leach JL, Krueger DA, Franz DN. **Everolimus alters white matter diffusion in tuberous** sclerosis complex. *Neurology*. 2012; 78:526-31.
- 41. Vannest J, Eaton KP, Henkel D, Siegel M, Tsevat RK, Allendorfer JB, Schefft BK, Banks C, Szaflarski JP. Cortical correlates of self-generation in verbal paired associate learning. *Brain Res.* 2012; 1437:104-14.
- 42. Vorhees CV, He E, Skelton MR, Graham DL, Schaefer TL, Grace CE, Braun AA, Amos-Kroohs R, Williams MT. Comparison of (+)-methamphetamine, +/--methylenedioxymethamphetamine, (+)-amphetamine and +/--fenfluramine in rats on egocentric learning in the Cincinnati water maze. *Synapse*. 2011; 65:368-78.
- 43. Vorhees CV, Morford LR, Graham DL, Skelton MR, Williams MT. Effects of periadolescent fluoxetine and paroxetine on elevated plus-maze, acoustic startle, and swimming immobility in rats while on and offdrug. Behav Brain Funct. 2011; 7:41.
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- Wang Y, Xiang J, Vannest J, Holroyd T, Narmoneva D, Horn P, Liu Y, Rose D, deGrauw T, Holland S. Neuromagnetic measures of word processing in bilinguals and monolinguals. *Clin Neurophysiol*. 2011; 122:1706-17.
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- 47. Wu SW, Shahana N, Huddleston DA, Gilbert DL. Effects of 30Hz Theta Burst Transcranial Magnetic Stimulation on the primary motor cortex. *J Neurosci Methods*. 2012; 208:161-164.
- Zafar M, Kashikar-Zuck SM, Slater SK, Allen JR, Barnett KA, Lecates SL, Kabbouche MA, Hershey AD, Powers SW. Childhood abuse in pediatric patients with chronic daily headache. *Clin Pediatr (Phila)*. 2012; 51:590-3.
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Faculty, Staff, and Trainees

Faculty Members

Andrew Hershey, MD, PhD, Professor

Leadership Interim Division Director; Director Headache Center

Research Interests Migraine, blood genomics
Todd Arthur, MD, Assistant Professor Research Interests Brain concussion
Anna W Byars, PhD, Associate Professor Research Interests Cognitive effects of epilepsy
James Collins, MD, PhD, Assistant Professor Research Interests Congenital Muscular Dystrophy; Neuromuscular Disease
David Franz, MD, Professor Leadership Director Tuberous Sclerosis program
Research Interests Tuberous sclerosis
Donald Gilbert, MD, Professor Leadership Director Movement Disorders program; Director Neurology Residency Program
Research Interests Tourette syndrome, Transcranial Magnetic Stimulation (TMS)
Tracy A Glauser, MD, Professor Leadership Director Comprehensive Epilepsy program
Research Interests Epilepsy, pharmacology
Hansel Greiner, MD, Assistant Professor Research Interests Epilepsy
Barbara Hallinan, MD, PhD, Assistant Professor Research Interests CSF steroid profiles
Katherine Holland-Bouley, MD, PhD, Assistant Professor Research Interests Ion channels and epilepsy
Sejal Jain, MD, Assistant Professor Research Interests Epilepsy, sleep
Marielle A Kabbouche, MD, Assistant Professor Research Interests Migraine
Darcy Krueger, MD, PhD, Assistant Professor Research Interests Tuberous Sclerosis
Diego Morita, MD, Assistant Professor Research Interests Epilepsy, pharmacology
Hope O'Brien, MD, Assistant Professor Research Interests Headaches
Douglas Rose, MD, Professor Leadership Director, MEG lab
Research Interests Magneto-Encephalography (MEG)
Mark Schapiro, MD, Professor Research Interests Neurodevelopmental disorders
Mary Sutton, MD, Assistant Professor Research Interests Neuro-oncology

Shannon Standridge, DO, Assistant Professor Research Interests Outcomes study, epilepsy
Cameron Thomas, MD, Assistant Professor Research Interests Neonatal neurology
Jennifer Vannest, PhD, Assistant Professor Research Interests Speech and language development
Charles Vorhees, PhD, Professor Leadership Director Animal Neurobehavior Core
Research Interests Drugs/toxicants and brain development
Kristen Wesselkamper, MD, Assistant Professor Research Interests Improvement science
Michael Williams, PhD, Associate Professor Research Interests Drugs/toxicants and brain development
Brenda Wong, MD, Professor Leadership Director Neuromuscular program
Research Interests Duchenne's Muscular Dystrophy, Spinal Muscular Atrophy
Steve Wu, MD, Assistant Professor Research Interests Movement Disorder; Transcranial Magnetic Stimulation (TMS)
Jing Xiang, MD, PhD, Associate Professor Leadership Director MEG Research program

Research Interests MEG

Clinical Staff Members

• Irina Rybalsky, MD

Trainees

- Alice Lawrence, MD, PGYVI, Milton S. Hershey Medical Center
- Jan-Mendelt Tillema, MD, PGYV, St. Radboud University Nijmegen, The Netherlands
- Laura Lehman, MD, PGYV, University of Cincinnati
- Jeffrey Tenney, MD, PGYV, University of Massachusetts Medical School
- Jamie Capal, MD, PGYV, Albany Medical College
- Holly Hoenes, MD, PGYIV, Mercer University
- Andrea Pardo, MD, PGYIV, Universidad del Rosario
- John Pugh, MD, PGYIV, Boston University
- Tanishia Williams, MD, PGYIV, University of Medicine & Dentistry of New Jersey
- Thomas Dye, MD, PGYIII, St. Louis University
- Nina Natarajan, MD, PGYIII, University of Cincinnati
- Katrina Peariso, MD, PGYIII, University of New Mexico
- Sarah Weatherspoon, MD, PGYIII, University of Texas Southwestern

Grants, Contracts, and Industry Agreements

Grant and Contract Awards		Annual Direct
COLLINS, J		
Phase 3 Trial of Coenzyme Q10 in Mitocho	ondrial Diseases	
National Institutes of Health(University of Flor	ida)	
R01 FD 003032	09/20/06-05/31/12	\$20,000
2/2 Anomalous Motor Dhysiology in ADUS		
National Institutes of Health		
R01 MH 095014	05/01/12-04/30/17	\$175,000
4/8-Collaborative Genomic Studies of Tou	rette Disorder	<i> </i>
National Institutes of Health		
R01 MH 092520	09/15/11-06/30/14	\$50,000
GLAUSER, T		
Cincinnati Neuroscience Clinical Trials Re	search Center	
National Institutes of Health(University of Cin		¢400.000
UTUINS 077311	09/30/11-08/31/18	\$100,000
National Institutes of Health	Long term outcome in children with CAE	
U01 NS 045911	09/01/10-08/31/14	\$4,007,367
Outcome in Pediatric Status Epilepticus		÷ 1,001,001
Epilepsy Foundation(Children's Hospital Bost	on)	
	07/01/11-06/30/12	\$18,206
HERSHEY, A		
Female Hormones and Their Role in Provo	ocation of Migraine Headaches in Adolescent Girls	
University of Cincinnati(National Headache F	OUNDATION)	¢47.150
	08/29/11-01/01/13	\$47,150
HERSHEY, A / POWERS, S		
Amitriptyline and Topiramate in the Preve	ntion of Childhood Migraine	
National Institutes of Health	C C	
U01 NS 076788	09/30/2011-08/31/2016	\$1,600,626
HOLLAND-BOULEY, K		
Sodium Channel Gene Variation in the Tre	atment of Epilepsy	
National Institutes of Health	04/04/00 00/04/44	0044075
RU1 NS 062756	04/01/09-03/31/14	\$214,375
VANNEST. J		
Imaging the Effect of Centrotemporal Spik	es and Seizures on language in Children	
National Institutes of Health		
R01 NS 065840	09/15/2011-06/30/2016	\$348,997
VORHEES, C		
Training Grant in Teratology		
National Institutes of Health		
T32 ES 07051	07/01/07-06/30/12	\$297,054
XIANG J		
Motor Cortex Dysfunction in Migraine		
National Institutes of Health		
R21 NS 072817	09/01/10-08/31/12	\$122.500
	Current Year Direct	\$7.001.275
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Industry Contracts

	Total	\$7,235,650
	Current Year Direct Receipts	\$234,375
DART Therapeutics, LLC		\$6,399
GlaxoSmithKline LLC		\$134,717
WONG, B		
Novartis Pharmaceuticals		\$39,185
KRUEGER, D		
VirtualScopics, Inc.		\$21,913
HOLLAND-BOULEY, K		
Psyadon Pharmaceuticals, Inc.		\$5,230
Otsuka Pharmaceutical Development & Commercialization Inc.		\$10,660
GILBERT, D		
Novartis Pharmaceuticals		\$16,271