Cajal course on

Brain Homeostasis and Neurovascular Coupling

Keynote Speakers

David Attwell, PhD (Department of Neuroscience, Physiology & Pharmacology, University College London, UK)

Biosketch:

David Attwell did a first degree in physics and a PhD on the electrophysiology of nerve and muscle cells (with Julian Jack) in Oxford, before spending 2 years in Berkeley studying the retina with Frank Werblin. On returning to the UK, he moved to the Department of Physiology at University College London, where he has remained ever since. He has worked on a wide range of subjects including the properties of glial cells, glutamate transporters, stroke, the formation of myelin by oligodendrocytes, how neuronal computation is powered and the control of cerebral blood flow. He was made a Fellow of the Royal Society in 2001.

Selected publications:

Hall, C.N., Reynell, C., Gesslein, B., Hamilton, N.B., Mishra, A., Sutherland, B., O'Farrell, F.M., Buchan, A.M., Lauritzen, M. & Attwell, D. (2014) Capillary pericytes regulate cerebral blood flow in health and disease. Nature 508, 55-60

Mishra, A., Reynolds, J.P., Chen, Y., Gourine, A.V., Rusakov, D.A. & Attwell, D. (2016) Astrocytes mediate neurovascular signaling to capillary pericytes but not to arterioles. Nature Neurosci. 19, 1619-1627

Cheng, J., Korte, N., Nortley, R., Sethi, H., Tang, Y. & Attwell, D. (2018) Targeting pericytes for therapeutic approaches to neurological disorders. Acta Neuropathologica 136, 507-523

Jerome Badaut, PhD (Brain Molecular Imaging Lab, INCIA, University of Bordeaux)

Biosketch:

Jerome Badaut's laboratory is currently investigating the roles of the astrocyte-endothelium-neuron interactions within the neurovascular unit in pathological processes after traumatic brain injury and stroke. His goal is to use the enhanced understanding of functional and molecular changes in the neurovascular unit after injury to generate new target-specific drugs to promote functional recovery of individuals affected by brain injury. Investigations of molecular mechanisms are performed in preclinical models with the use of several appraoches such as behavioural testing paradigms, magnetic resonance imaging, histological and molecular biology techniques. Dr Badaut sets a unique international expertise on the role of the

aquaporin (water channel) in brain edema processes post-injury and on the long-term blood vessel phenotypic changes after pediatric traumatic brain injury . Dr Badaut has been able to maintain active laboratory in several institutions, first in Lausanne University (Switzerland), then in Loma Linda University (CA, USA), before to be appointed senior research officer at the National Center for Scientific Research (CNRS) at Bordeaux Neurocampus. Dr. Badaut recently edited a book on Brain edema[7] and he is associated editor of Journal of Neuroscience Research.

Selected publications:

Jullienne, A., et al. Modulating the water channel AQP4 alters miRNA expression, astrocyte connectivity and water diffusion in the rodent brain. Sci Rep 8, 4186 (2018)
Rodriguez-Grande, B., et al. Gliovascular changes precede white matter damage and long-term disorders in juvenile mild closed head injury. Glia (2018)
Badaut, J. and Plesnila, N. Brain edema. From Molecular Mechanisms to Clinical Practice. Academic Press (2017)

Anna Devor, PhD (Department of Neurosciences, UC San Diego School of Medicine)

Biosketch:

Dr. Anna Devor received her initial research training at the interface between the experimental and computational neuroscience at Hebrew University of Jerusalem, Israel. After defending her PhD thesis in 2002, she went on to specialize in microscopic brain imaging technology at Martinos Center for Biomedical Imaging at MGH. In 2005, she established an independent research laboratory at UC San Diego. Dr. Devor has a broad base of knowledge in cellular and systems-level neuroscience as well as in the development and refinement of microscopic optical technology for imaging of brain activity in live animals ("in vivo"). These tools allow dissecting neuronal, glial and vascular mechanisms that underlie signals obtained with noninvasive brain imaging modalities such as functional magnetic resonance imaging (fMRI). These multimodal measurements are combined with system-level analysis/modeling, commonly used in engineering disciplines, to understand how specific patterns of microscopic brain activity (and their pathological departures) translate into noninvasive macroscopic observables.

Selected publications:

Uhlirova H et al. 2016 The roadmap for estimation of cell-typespecific neuronal activity from non-invasive measurements. Phil. Trans. R. Soc. B 371: 20150356. http://dx.doi.org/10.1098/rstb.2015.0356
Devor A et al. Frontiers in optical imaging of cerebral blood flow and metabolism. J Cereb Blood Flow Metab. 2012 Jul;32(7):1259-76. doi: 10.1038/jcbfm.2011.195. Epub 2012 Jan 18
Devor A. et al. (2014) Functional Imaging of Cerebral Oxygenation with Intrinsic Optical Contrast and Phosphorescent Probes. In: Weber B., Helmchen F. (eds) Optical Imaging of Neocortical Dynamics. Neuromethods, vol 85. Humana Press, Totowa, NJ

Ulrich Dirnagl, PhD **(Department of Experimental Neurology,** Charité Universitätsmedizin Berlin)

Biosketch:

At the Charité Universitätsmedizin Berlin Ulrich Dirnagl is Professor for Clinical Neurosciences and serves as Director of the Department of Experimental Neurology. Since 2017 he is also the founding director of the QUEST Center for Transforming Biomedical Research at the Berlin Institute of Health. QUEST aims at overcoming the roadblocks in translational medicine by increasing the value and impact of biomedical research through maximizing the quality, reproducibility, generalizability, and validity of research.

In preclinical as well as in clinical studies Ulrich Dirnagl's research has revealed pathobiology which impact on the outcome after a stroke. These include deleterious as well as endogenous protective mechanisms, as interactions of the brain with other systems of the body after it has been injured. Several of these mechanism can be therapeutically targeted, clinical trials are under way. In addition, through meta-research he was able to identify opportunities for improving research practice and to obtain evidence for the impact of interventions targeted to increase the value of biomedical research.

Selected publications:

Yarborough M, Bredenoord A, D'Abramo F, Joyce NC, Kimmelman J, Ogbogu U, Sena E, Strech D, Dirnagl U. The bench is closer to the bedside than we think: Uncovering the ethical ties between preclinical researchers in translational neuroscience and patients in clinical trials. PLoS Biol. 2018 Jun 6;16(6):e2006343

Dirnagl U (2016) Is translational stroke research broken, and if so, how can we fix it? Stroke 47:2148-53

Dirnagl U, Villringer A, Einhaupl KM (1992) In-vivo confocal scanning laser microscopy of the cerebral microcirculation. J Microsc 165 (Pt 1): 147-157

Britta Engelhardt, PhD (Theodor Kocher Institute, University of Bern)

Biosketch:

Britta Engelhardt obtained a degree in Human Biology at the Medical School of the Philipps-University, Marburg in Germany in 1987. She performed her PhD thesis in the laboratory of Hartmut Wekerle (Max-Planck Clinical Research Group for Multiple Sclerosis, Würzburg and Max- Planck Institute for Psychiatry, Martinsried, Germany) and obtained a PhD in Human Biology (Dr.rer.physiol.) in January 1991. After a post-doctoral fellowship in the laboratory of Eugene C. Butcher at Stanford University, California, she set up her own research group at the Max- Planck Institute for Physiological and Clinical Research, Bad Nauheim, Germany in the department of Werner Risau (†December 13th, 1998) in 1993. In 1998 she obtained the Venia Legendi for Immunology and Cell Biology from the Medical Faculty of the Philipps

University Marburg, Germany. From 1999 to 2003 she headed her research group as a senior group leader at the same institute and the Max-Planck-Institute for Vascular Cell Biology, Münster, Germany. Since November 2003 Britta Engelhardt is Professor for Immunobiology at the University of Bern and the Director of the Theodor Kocher Institute. Britta Engelhardt is an expert in blood-brain barrier biology with a special focus on neuroinflammatory processes at the BBB. She has pioneered the use of intravital microscopy of the spinal cord microcirculation allowing to study leukocyte/BBB interaction in real time in live mice. For this work she has received the Herrmann-Rein Award of the Society for Microcirculation and Vascular Biology in 2001. She has published over 130 peer-reviewed papers in addition to over 80 reviews, commentaries or book chapters on this topic. Britta Engelhardt currently coordinates the Horizon 2020 funded ITN BtRAIN focusing brain barriers research. She was Vice-Cair and elected Chair of the Gordon Research Conference Barriers of the CNS in 2016 and 2018. Furthermore, she is the current president of the Swiss Society for Microcirculation and Vascular Research (SSMVR).

Selected publications:

Engelhardt B, P Vajkoczy, RO Weller. Movers and shapers of immuneprivilege of the CNS. 2017. Nature Immunol 18(2):123-131

Tietz, Silvia and Britta Engelhardt. 2015. Brain Barriers: Crosstalk between complex tight junctions and adherens junctions. J Cell Biol 209: 493-506

Coisne Caroline, Ruth Lyck and Britta Engelhardt. 2013. Live cell imaging techniques to study T cell trafficking across the blood-brain barrier in vitro and in vivo. *Fluids and Barriers of the CNS* 10:7 doi:10.1186/2045-8118-10-7; 21 January 2013

Jean-François Ghersi-Egea, PhD (Fluids and barriers of the CNS, Lyon Neuroscience Research Center)

Biosketch:

Dr Jean-François Ghersi-Egea is Research director at INSERM, leading the "Fluids and barriers of the CNS" - FLUID - team at the Lyon Neuroscience Research Center. He graduated from pharmaceutical school and obtained his PhD in Pharmacological Sciences in France. Pioneer in the discovery of the blood-CSF barrier as a detoxifying site for the brain, Dr Ghersi-Egea studied the dynamic of cerebrospinal fluid flow and choroid plexus transport and metabolism for several years at the State University of New York, Stony Brook, USA and at the Pasteur Institute in Lille, France. His current research interests include neuroprotective mechanisms acting at the blood-brain and blood-CSF barriers to protect the developing brain in normal and adverse perinatal conditions, and the implication of the choroid plexus-cerebrospinal fluid system in neuroinflammation.

Selected publications:

Kratzer I, Strazielle N, Saudrais E, Mönkkönen K, Malleval C, Blondel S, Ghersi-Egea JF. Glutathione Conjugation at the Blood-CSF Barrier Efficiently Prevents Exposure of the Developing Brain Fluid Environment to Blood-Borne Reactive Electrophilic Substances. J Neurosci. 2018 Apr 4;38(14):3466-3479

Ghersi-Egea JF, Strazielle N, Catala M, Silva-Vargas V, Doetsch F, Engelhardt B. Molecular anatomy and functions of the choroidal blood-cerebrospinal fluid barrier in health and disease. Acta Neuropathol. 2018 Mar;135(3):337-361

Strazielle N, Creidy R, Malcus C, Boucraut J, Ghersi-Egea JF. T-Lymphocytes Traffic into the Brain across the Blood-CSF Barrier: Evidence Using a Reconstituted Choroid Plexus Epithelium. PLoS One. 2016 Mar 4;11(3):e0150945

Edith Hamel, PhD (Montréal Neurological Institute, McGill University, Canada)

Biosketch:

Edith Hamel obtained her PhD degree from l'Université de Montréal, and performed post-doctoral training in cerebrovascular pharmacology and physiology in California (City of Hope Research Institute) and France (Synthélabo) and in electron microscopy in Canada (Montreal Neurological Institute). She was Project leader at Synthélabo for 2 years before establishing her Laboratory of Cerebrovascular Research at the Montreal Neurological Institute at McGill University. Dr Hamel received several national and international awards including her election as President of the International Society of Cerebral Blood Flow and Metabolism (2013-2015) and her nomination as a Fellow of the Royal Society of Canada in 2017. Dr Hamel has published 149 original articles, 14 peer-reviewed reviews, edited one book and contributed to two teaching books and several book chapters. She seats on grant review panels, editorial boards, international research advisory committees and Meeting organizing committees.

Hamel's research focuses on the interactions between neurons, astrocytes and blood vessels that assure a proper blood supply to activated brain areas, a phenomenon commonly referred to "neurovascular coupling". These interactions are at the basis of several brain imaging techniques that use hemodynamic signals to map changes in brain activity under physiological and pathological conditions. An important part of her research is dedicated to the understanding of the relationships between cerebrovascular alterations and cognitive failure. Particularly, she investigates how pharmacotherapy or life style habits can impact cerebrovascular reactivity, brain perfusion and cognitive performance in animal models of vascular cognitive impairment and dementia (VCID) or Alzheimer's disease. She uses behavioral testing, laser doppler flowmetry, classic biochemical and anatomical techniques as well as imaging of optical intrinsic signals, laser speckle, electrophysiological recordings and electrical or optogenetic stimulation of specific brain neurons to investigate their hemodynamic responses.

Selected publications:

Cauli B, *Hamel E*. Brain Perfusion and Astrocytes. Trends Neurosci. 2018 Jul;41(7):409-413. PMID: 29933772

Royea J, Zhang L, Tong XK, *Hamel E.* Angiotensin IV receptors mediate the cognitive and cerebrovascular benefits of losartan in a mouse model of Alzheimer's disease. J Neurosci. 2017 May 31;37(22):5562-5573. PMID: 28476949

Lecrux C, Sandoe CH, Neupane S, Kropf P, Toussay X, Tong XK, Lacalle-Aurioles M, Shmuel A, *Hamel E*. Impact of altered cholinergic tones on the neurovascular coupling response to whisker stimulation. J Neurosci 2017 Feb 8;37(6):1518-1531. PMID: 27574304

Costantino Iadecola, PhD (Feil Family Brain & Mind Research Institute, Weill Cornell Medicine, New York, USA)

Biosketch:

Costantino Iadecola, M.D. is the Director and Chair of the Feil Family Brain and Mind Research Institute and the Anne Parrish Titzell Professor of Neurology at Weill Cornell Medicine. His research focuses on the basic mechanisms of neurovascular function and on the cellular and molecular alterations underlying ischemic brain injury, neurodegeneration and other conditions associated with cognitive impairment. A pioneer in establishing the concept of Neurovascular Unit, Dr. Iadecola has championed the involvement of neurovascular dysfunction in neurodegenerative diseases, and the role of innate immunity and the microbiome in ischemic brain injury. He has published over 300 papers in peer-reviewed journals and plays a leadership role in research organizations and funding agencies in the US and abroad. He has been involved, as editor or editorial board member, in several journals including *Circulation research, Hypertension,* the *Journal of Neuroscience,* and the *Annals of Neurology.* Dr. Iadecola has received the McHenry Award from the American Academy of Neurology, two Jacob Javits Awards from the National Institutes of Health, the Willis Award - the highest honor in stroke research bestowed by the AHA, the Zenith Fellow Award from the Alzheimer's Association, the Excellence Award in Hypertension Research (Novartis) from the Hypertension Council of the AHA, and the Chancellor's Award in Neuroscience from Louisiana State University. In 2015, he was elected to the Association of American Physicians.

Selected publications:

Park L et al. Brain Perivascular Macrophages Initiate the Neurovascular Dysfunction of Alzheimer Aβ Peptides. Circ Res. 2017 Jul 21;121(3):258-269. doi: 10.1161/CIRCRESAHA.117.311054. Epub 2017 May 17

Iadecola C. The Neurovascular Unit Coming of Age: A Journey through Neurovascular Coupling in Health and Disease. Neuron. 2017 Sep 27;96(1):17-42. doi: 10.1016/j.neuron.2017.07.030

Faraco G et al. Dietary salt promotes neurovascular and cognitive dysfunction through a gut-initiated TH17response. Nat Neurosci. 2018 Feb;21(2):240-249. doi: 10.1038/s41593-017-0059-z. Epub 2018 Jan 15

Martin Lauritzen, PhD (Department of Neuroscience, University of Copenhagen, Denmark)

Biosketch:

Martin Lauritzen is an MD from the University of Copenhagen (UCPH) from 1978 and got his DMedSci degree from in 1988 after spending a year with Charles Nicholson at New York University. Martin is a certified specialist in and professor of Clinical neurophysiology and Translational neurobiology at the National Hospital and UCPH. Martin has spent the main part of his professional life as a translational neurobiologist. His main interests are mechanisms of acute brain damage, brain blood flow, aging and the blood brain barrier.

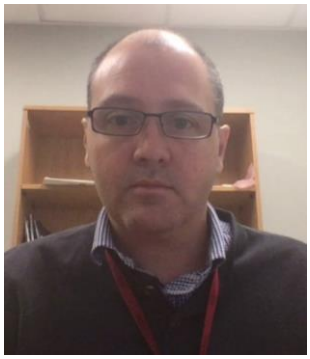
Selected publications:

Khennouf L, Gesslein B, Brazhe A, Octeau JC, Kutuzov N, Khakh BS, Lauritzen M. Active role of capillary pericytes during stimulation-induced activity and spreading depolarization. Brain 2018, July, 141 (7); 2032–2046. https://doi.org/10.1093/brain/awy143

Cai C, Fordsmann J, Jensen SH, Hald BO, Gesslein B, Lønstrup M, Brodin B, Lauritzen M. Conducted vascular responses in brain capillaries by synaptic activity and ATP in mouse cerebral cortex. Proc Natl Acad Sci USA 2018, https://doi.org/10.1073/pnas.1707702115

Kutuzov N, Flyvbjerg H, Lauritzen M. Contributions of the glycocalyx, endothelium, and extravascular compartment to the blood-brain barrier. Proc Natl Acad Sci U S A. 2018 Oct 2;115(40):E9429-E9438. doi: 10.1073/pnas.1802155115. Epub 2018 Sep 14

Frédéric Lesage, PhD (Department of Electrical Engineering, Polytechnique Montréal, Canada)



Biosketch:

Prof. Lesage has developed expertise in optical imaging. His activities include human brain imaging with work on the analysis of optical signals that is robust to physiological background noise, time-domain optical parameter recovery and multimodal imaging (fMRI-Optical, EEG-Optical). He also works on understanding the microscopic underpinnings of brain physiology using Optical Coherence Tomography, Two-photon microscopy and MRI. He leads a laboratory of around 20 people working on imaging technology development.

Selected publications:

P. Pouliot, L. Gagnon, T. Lam, P. K. Avti, C. Bowen, M. Desjardins, A. K Kakkar, É. Thorin, S. Sakadzic, D.A. Boas, F. Lesage, Magnetic resonance fingerprinting based on realistic vasculature in mice, Neuroimage. 2017 Apr 1;149:436-445. doi: 10.1016/j.neuroimage.2016.12.060. Epub 2016 Dec 31.

C. Zhang, M. Tabatabaei, S. Bélanger, K. Peng, F. Lesage, Astrocytic endfoot Ca2+ modulates both arteriolar dilation and constriction during epilepsy in vivo with two-photon lifetime microscopy, J Cereb Blood Flow Metab. 2017 Jan 1:271678X17725417. doi: 10.1177/0271678X17725417

M. Moeine, X. Lu, P.K. Avti, R. Damseh, S. Bélanger, F. Picard, D.A. Boas, A. Kakkar, F. Lesage, Compromised microvascular oxygen delivery increases brain tissue vulnerability with age. Sci Rep. 2018 May 29;8(1):8219. doi: 10.1038/s41598-018-26543-w

Mickael Tanter, PhD (French National Institute for Health and Medical Research, Institut Langevin, ESPCI, Paris, France)

Biosketch:

Mickael Tanter is a research professor of the French National Institute for Health and Medical Research (INSERM) and distinguished professor of ESPCI Paris. He is heading the laboratory "Physics for Medicine" at ESPCI Paris, France. He is also the director of the first INSERM Technology Research Accelerator created in 2016 and dedicated to Biomedical Ultrasound. Mickael Tanter is a world-renowned expert in biomedical ultrasound and wave physics. He authored more than 300 peer-reviewed papers and book chapters (hIndex 61 from Isi Web of knowledge) and is the recipient of 50 international patents. He co-invented several major innovations in Biomedical Ultrasound: Transient Elastography, Ultrafast Ultrasound and Shear Wave Elastography for cancer and cardiovascular diagnosis, functional Ultrasound imaging of brain activity and Super-Resolution Ultrasound. M. Tanter is also the co-founder of several MedTech companies in Biomedical Ultrasound (Supersonic Imagine, CardiaWave, Iconeus).

Selected publications:

C. Errico, J. Pierre, S. Pezet, Y. Desailly, Z. Lenkei, O. Couture*, M. Tanter*. Ultrafast ultrasound localization microscopy for deep in vivo super-resolution vascular imaging. Nature, September 2015

Demene C, Baranger J, Bernal M, Delanoe C, Auvin S, Biran V, Alison M, Mairesse J, Harribaud E, Pernot M, Tanter M* & Baud O*. Functional ultrasound imaging of brain activity in human newborns. Science Translational Medicine 201

M.E. Fernandez-Sanchez et al. Mechanical induction of the tumorigenic beta-catenin pathway by tumour growth pressure. Nature, July 2015

Robert G. Thorne, PhD (Denali Therapeutics, South San Francisco, California, U.S.A./ Pharmaceutical Sciences Division, Neuroscience Training Program, Clinical Neuroengineering Training Program, and Cellular & Molecular Pathology Graduate Training Program, University of Wisconsin-Madison, U.S.A.)

Biosketch:

Robert Thorne studies diffusive and convective transport within the extracellular and perivascular spaces of the central nervous system – his work aims to leverage knowledge of physiology, CNS structure, and the blood-brain and blood-cerebrospinal fluid barriers with a variety of methods in order to identify how best to deliver antibodies, oligonucleotides, and gene therapy vectors to the brain following intraparenchymal, intrathecal, or intranasal administration. Recently, as a Denali Fellow, his interests have expanded to technologies that will allow a variety of macromolecules, antibodies and enzymes to be transported into the brain across the CNS barriers. Among his achievements are pioneering measurements of extracellular diffusion in the brain to determine the width of brain extracellular spaces in vivo,1 elucidation of physiologic determinants governing perivascular space access and transport from the CSF,2,3 and the identification of transport pathways allowing large molecule entry into the brain from the nasal mucosae. Robert has had teaching roles in systems neuroscience, drug delivery, research ethics and other graduate and professional courses. He previously chaired the 2016 'Barriers of the CNS' Gordon Research Conference and is a member of the editorial boards of both Fluids and Barriers of the CNS and the Journal of Cerebral Blood Flow and Metabolism. He was recently elected Vice President (President-elect) of the International Brain Barriers Society, a global organization responsible for leadership and directing worldwide initiatives related to the CNS barriers and drug delivery fields.

Selected publications:

Thorne & Nicholson. (2006) PNAS 103:5567-5572
Pizzo et al. (2018) Journal of Physiology 596:445-475
Abbott et al. (2018) Acta Neuropathologica 135(3):387-407

Bruno Weber, PhD (Institute of Pharmacology and Toxicology, University of Zurich)

Biosketch:

Bruno Weber did his undergraduate and graduate studies at the University of Zurich. Before obtaining an assistant professorship supported by the Swiss National Science Foundation, he was a postdoctoral fellow at the Max Planck Institute for Biological Cybernetics in Tübingen with Nikos Logothetis. He holds now a full professorship at the University of Zurich (Medical Faculty and Science Faculty) since 2013. He is deputy director of the Institute of Pharmacology and Toxicology and is a Steering Committee Member of the Center for Neuroscience of the University and ETH Zürich. His main research topics are brain energy metabolism, astrocyte signaling, neurovascular biology and neuroimaging methodology.

Selected publications:

Maechler P, Wyss MT, Elsayed M, Stobart J, Gutierrez R, Zuend M, San Martin A, Romero-Gómez I, Baeza-Lehnert F, Lengacher S, Schneider B, Aebischer P, Magistretti PJ, Barros LF, Weber B (2016). In vivo evidence for a lactate gradient from astrocytes to neurons. Cell Metab, 23:94-102

Schmid F, Tsai P, Kleinfeld D, Jenny P, Weber B (2017). Depth-Dependent Flow and Pressure Characteristics in Cortical Microvascular Networks. PLoS Computational Biology, 13(2):e1005392

Stobart J, Ferrari KD, Barrett MJ, Glück C, Stobart MJ, Zuend M, Weber B (2018). Cortical circuit activity evokes rapid astrocyte calcium signals on a similar time scale to neurons. Neuron, 98(4):726-735