How is it that some children grow up to be autistic or schizophrenic, while others do not? Increasingly, people are interested in understanding the developmental origins of health and disease (DOHaD). This avenue of study exploring the fetal origins of adult disorders began with human epidemiological studies and more recently has been expanded by basic research. The DOHaD concept proposes that chronic diseases are biologically “programmed” in utero (during pregnancy). Programming refers to the process by which a stimulus or insult at a critical period of development induces long lasting changes in cells which in turn changes the structure of organs, tissues or body systems. Common and powerful insults—or adverse events—include maternal infections (viral or bacterial) during pregnancy, maternal stress and depression, and exposure to drugs and toxic substances. These have been shown to increase the risk of developing metabolic and mental disorders such as autism, attention deficit disorder, schizophrenia or even major depression in the offspring, diseases that manifest many years after their onset.

Although evidence from multiple epidemiological studies is solid and increasing, the molecular and physiological mechanisms by which DOHaD events ‘program’ the offspring to develop diseases later in life are poorly understood. Years of clinical research suggest that maternal-fetal interactions, which take place through the placenta, are central components of this “fetal programming” of diseases. In support of this, placental dysfunction during pregnancy is associated with increased risk for the offspring of developing diseases, including mental disorders.

ZNI Faculty Profile

Alexandre Bonnin PhD
Assistant Professor, Cell & Neurobiology

Serotonin is a neurotransmitter that is involved in the transmission of nerve impulses. Serotonin can trigger the release of substances in the blood vessels of the brain that in turn cause the pain of migraine. Serotonin is also key to mood regulation; pain perception; gastrointestinal function, including perception of hunger and satiety; and other physical functions. More recently, serotonin was also shown to be an important trophic factor during brain development.

ZNI Hosts LA-Irvine Area Brain Bee

In late January, nearly 100 high school students from the Southern California region were buzzing around the USC Health Sciences Campus, as they participated in the LA-Irvine Brain Bee. Sponsored by the Society for Neuroscience, the Brain Bee is designed to engage kids between the ages of 14 and 19 in conversations and hands-on demos to stimulate their interest in the brain sciences, and otherwise encourage them to explore neuroscience as a field of study and perhaps their future vocation.

In the months leading up to the event—this year held on Saturday, January 30, 2016 at the Zilkha Neurogenetic Institute—more than 50 graduate students, faculty, postdocs and staff from USC, University of California Los Angeles (UCLA), University of California at Irvine (UCI) and Los Angeles Community College (LACC) attended meetings. Led by Amy Nelson, PhD from ZNI, these volunteers shared ideas on how to contact area high schools to recruit students, choose speakers and create publicity materials. The teams including InterAxon groups from all schools reviewed test questions, planned and coordinated with multiple departments and institutions and otherwise

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A growing research effort is now focused on exploring the possibility that insults such as maternal infections or stress and depression may in fact primarily alter placental function, with downstream consequences for fetal brain development, and brain dysfunctions later in life.

Alexandre Bonnin, PhD, and his lab are attempting to understand how maternal-fetal interactions shape fetal brain development during pregnancy. Focusing on relationships between the placenta and fetal neuronal development, Dr Bonnin and his group aim to discover new molecular pathways by which prenatal insults influence the onset of mental diseases in the adult offspring. Their efforts provide new directions to study the developmental origin of mental health-related disorders such as autism and schizophrenia in humans.

To this end, Bonnin and his team developed a new technology to study the molecular, neurochemical and metabolic details of the maternal-fetal interaction in mice. This technology, based on the ex vivo dual perfusion of live mouse placenta at different stages of gestation enables the researchers to test how changes in placental metabolism impact the supply of serotonin and other important neurogenic molecules to the fetus during early brain development. A central hypothesis of Bonnin’s research is that serotonin produced by the placenta during pregnancy modulates axon guidance mechanisms and therefore is critical for the refinement of neuronal circuits formation in utero. Therefore, if adverse prenatal insults alter this particular placental metabolic pathway, the impact on placentally-derived serotonin could alter normal fetal brain neuronal wiring.

**What are the effects of maternal depression and use of antidepressant drugs on fetal brain development?**

While increasing numbers of women are prescribed selective serotonin reuptake inhibitor (SSRI) antidepressants to treat depression during pregnancy, pharmacological treatment presents a conundrum. The use of SSRIs in early pregnancy has been associated with increased risk of adverse effects, including autism spectrum disorder. Importantly, the long-term effects of prenatal SSRI exposure on the development of offspring brain circuitry involved in modulating mood and anxiety-related behavior are unknown. Conversely, maternal stress generated by untreated depression and/or the underlying mechanisms of depression are associated with adverse neurological outcomes for offspring.

So is it more harmful for a fetus if a pregnant woman suffering from depression is treated with SSRIs or not? The Bonnin lab deploys a mouse model to examine and dissociate mechanistically the short- and long-term effects of exposure to maternal stress and SSRIs on fetal brain development and function, using several methods:

- a newly developed methodology for studying placental drug transport and drug safety during fetal development;
- whole fetal brain diffusion magnetic resonance imaging (dMRI) to investigate the effects of maternal stress and SSRI exposure on fetal brain structure;
- high-speed in vivo neurochemical measurements of adult brain neurotransmission, measuring the long-term effects of prenatal SSRI and/or stress exposure on offspring serotonergic neurotransmission.

These projects will advance our understanding of maternal-fetal SSRI transfer, fetal brain drug exposure, and the short- and long-term consequences of SSRI exposure alone and combined with maternal stress on the development and function of brain circuits that are implicated in psychiatric disorders. For these studies, Bonnin was recently awarded a 5-year R01 grant from the National Institutes of Mental Health (NIMH).
Do maternal infections and inflammation have an effect on fetal brain development?

Mechanistic links between maternal infections and inflammation during pregnancy and the risk for developmental disorders in the offspring, including autism spectrum disorders, cognitive delay, and schizophrenia, are being intensively investigated. Intra-uterine bacterial infection is an independent risk factor for early autistic features, and systemic maternal viral infections (e.g. influenza) are reported as a risk factor for autism and schizophrenia in the offspring. These associations are observed for both vertically (from mother to fetus) and non-vertically transmitted pathogens, suggesting that maternal inflammation resulting from exposure to these pathogens in and of itself is sufficient to alter fetal neurodevelopment.

Bonnin’s research recently identified a novel molecular pathway (involving placentally-derived serotonin) by which maternal inflammation during pregnancy alters specific aspects of fetal brain development. For these studies, Bonnin was awarded a 3-year grant by the US Department of Defense. These results are particularly important in view of recent infectious diseases outbreaks (such as H1N1 influenza or Zika virus) suggesting that pregnant women and their fetuses are high-risk groups for severe and long-lasting complications. Recently, Dr Bonnin initiated a collaboration with Jae Jung, PhD, (chair, Molecular Microbiology & Immunology, who has a laboratory in ZNI) to further study the effects of infectious agents such as the Zika virus on placentally-derived modulators of neurodevelopment.

ZNI Sees Rise in Number of Grants

Despite the current difficult funding climate, the number of ZNI researchers awarded more than one R01 from the National Institutes of Health (NIH) has increased significantly for the first time in several years. Six principal investigators (PIs) at ZNI now hold two or more R01 grants across seven different institutes within the NIH.

The Research Project Grant (R01) is the original and historically oldest grant mechanism used by NIH. An R01 provides support for health-related research and development based on the mission of the NIH. Grants can be investigator-initiated or can be in response to a program announcement or request for application. In general, awards are for $250,000 in direct costs annually, for a maximum of five years.

Six ZNI PIs Hold More Than Two RO1s across Seven Institutes

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Legend:

- NINDS: National Institute of Neurological Disorders & Stroke
- NIGMS: National Institute of General Medical Sciences
- NHGRI: National Human Genome Research Institute
- NIMH: National Institute of Mental Health
- NIA: National Institute on Aging
- NIDDK: National Institute of Diabetes & Digestive & Kidney Diseases
- NEI: National Eye Institute
pieced together the many details necessary to construct an engaging agenda of multiple overlapping activities for this day-long exploration of the wonders of the brain.

The agenda for the participants included hands-on demonstrations, including sheep brain dissections, optical illusions, sensory demonstrations, a rope neuron model, and functional magnetic resonance software to view the brain in 3-D. There were also poster sessions about neurodegenerative diseases, brain computer interfaces, the evolution of the brain, a written exam, as well as a brain anatomy test administered via a timed slide show. After the results were tabulated, 10 finalists received prizes and the top three students played two rounds of a fun, yet challenging, Jeopardy-style game, providing questions to the answers on the screen until a first place winner was announced.

Giveaways were raffled off, items donated by the Brain Research Institute of UCLA, the USC Laboratory of Neuro Imaging (LONI, part of the USC Mark & Mary Stevens Neuroimaging and Informatics Institute), USC Credit Union, Keck Medicine of USC and the Keck School of Medicine. Parking was graciously provided free of charge by USC Transportation and USC Facilities Management covered all of our maintenance needs. Everyone enjoyed a complementary light breakfast, and throughout the day, snacks and fresh fruit donated by Einstein’s Bagels and ZNI. Courtesy of LONI and ZNI, a plentiful lunch was served to over 250 people.

Families were escorted on tours around campus and everyone was open to attend a number of professional panels, where experts discussed college and career options. Overflow crowds listened to a presentation on “Concussion in Youth Sports” given by David Baron MD (assistant dean of international relations at Keck School of Medicine of USC), followed by a cinematic review of “Hollywood and the Brain,” by Amy Sweetman, (professor of psychology at LACC and founder of the LA Brain Bee).

It was a day most will not soon forget, especially Jacob, who we learned at press time finished in 9th place in the national Brain Bee held in Bethesda, MD in late March. A very impressive feat, considering there were 58 competitors! The winner of the nationals goes on to compete in the International Brain Bee in Copenhagen later in 2016.

Zlokovic named as Fellow of Academia Europaea

Berislav Zlokovic MD PhD, director of the Zilkha Neurogenetic Institute and professor and chair of the Department of Physiology and Biophysics, was recently elected as a Fellow of the Academy of Europe (Academia Europaea), the premier academic body of the entire European continent. Academia Europaea was founded in 1988 as an international, nongovernmental association of individual scientists and scholars from all disciplines, who are experts and leaders in their own subject areas as recognized by their peers. The organization supports a range of activities, including plenary meetings, study groups and expert workshops, as well as publishing the Academia’s quarterly journal, the European Review.

Membership in the Academy is limited to only 2,600 scholars, 54 of which are current Nobel Prize winners.