Results: By modelling connectivity as complex networks, this talk will shed some light on whether functional connectomics based on resting state fMRI could 1) reveal symptoms-associated brain network changes; 2) detect early changes in prodromal stage of the disease; 3) predict clinical outcomes in psychosis. Particularly, work from our group and others on persons at-risk for psychosis will be discussed. Moreover, accumulating evidence suggests the influence of vigilance, motion, and physiological noise on functional connectivity measures. I will provide some tips on how to minimize these confounds and increase the reliability and reproducibility of functional connectomics measures.
Discussion: Resting state fMRI provides a novel network-sensitive, immediately repeatable, non-invasive tool to examine human functional connectome. Future directions such as dynamic or time-varying functional connectivity which captures neural dynamics at a finer time scale will be briefly discussed. Further developed and integrated with brain structural connectivity measures, brain network functional connectomics may help us better understand heterogeneity in psychosis, reveal disease mechanism, predict and track disease progression, and monitor treatment response.

7. RETINAL FUNCTIONS EXPRESSED IN RETINAL IMAGING, CONTRAST PROCESSING AND ELECTRORETINOGRAPHY MAY DECRYPT EARLY RISK MECHANISMS AND PATHOPHYSIOLOGY OF SCHIZOPHRENIA AND MOOD DISORDERS AND ACCELERATE TRANSLATION TO THE CLINIC

Michel Maziade
Centre de recherche CIUSSS de la Capitale-Nationale

Overall Abstract: The rationale of this symposium is twofold. First, true understanding of the neurobiological and environmental causes of schizophrenia and mood disorders will require the investigation of the human neuronal tissue in function. As an external and accessible extension of the brain, the retina opens this avenue. Existing technologies such as retinal imaging, computerized psychophysical assessment, and electroretinography (ERG) have recently provided evidence that the microanatomy of the retina and strength of rod, cone, and bipolar cell responses to light stimuli can distinguish patients from healthy individuals (Adams & Nasrallah, Schizophr Res 2017; Silverstein & Rosen, Schizophr Res Cogn 2015; Bubl, Biol Psychiatry, 2010; Plos ONE, 2015, Meier, Am J Psychiatry 2014). Second, the search for indicators of brain dysfunction that are detectable both in adult patients and in children at genetic risk is the cornerstone of genetic high-risk research into the neurodevelopmental origins of serious mental disorders and prevention (Maziade, New Eng J Med 2017). In this regard, it has been shown that children at genetic risk show many of the retinal anomalies that adult patients display (Hébert et al., 2010, Biol Psychiatry). Studies of the retina can therefore contribute to clarifying illness pathophysiology and its developmental roots.
This symposium objectives are to: 1) present findings from retinal imaging, visual processing and electroretinography in patients with schizophrenia or mood disorders, and in young healthy offspring of affected parents; 2) to discuss the data in terms of their implications for understanding psychotic and mood disorders; and 3) to clarify the similarities and differences between retinal findings in psychotic and mood disorders and their early developmental trajectories.
Participating scientists: Professor Michel Maziade will be the chair, with Professor Steven Silverstein as the co-chair of the symposium. Professor Anne Giersh, INSERM Strasbourg, France, will act as the discussant.
Professor Emanuel Bubl, Saarland University, Germany, will present findings on the potential of ERG measured retinal background noise as neurobiological correlate for cognitive deficits in ADHD and schizophrenia.
Professor Maziade, Laval University, Canada, will present new ERG findings in young offspring of parents affected by schizophrenia or bipolar disorder and the implications for the illness developmental origin and later transition to illness.
Professor Madeline Meier, Arizona State University, USA, will present results showing phenotypic and genetic associations between schizophrenia and retinal vessel diameter. Findings suggest that individuals with schizophrenia are at increased risk of microvascular complications.
Professor Silverstein, Rutgers University, USA, will present new ERG findings in schizophrenia, and data on the relationships between ERG anomalies, symptoms, retinal structural abnormalities as measured with optical coherence tomography, and antipsychotic medication use.
Based on empirical data, the symposium will offer an integrated view as to: i) how non-invasive measurements of retinal structure and function show consistent anomalies in schizophrenia, bipolar disorder, major depression and ADHD; ii) how findings from children and adolescents at high genetic risk not only indicate a neurodevelopmental process, but also suggest that retinal anomalies in patients are not due to medication use or degenerative effects; iii) how ERG can be administered to adults and children at low cost in clinical studies; iv) how to integrate findings in the staging of the risk status of children at genetic risk.

7.1 ELECTRORETINOGRAPHIC ANOMALIES IN SCHIZOPHRENIA AND THEIR RELATIONSHIPS WITH RETINAL STRUCTURE, VISUAL FUNCTIONS, CLINICAL SYMPTOMS, AND MEDICAL COMORBIDITIES

Steven Silverstein*[,1], Docia Demmin[1],
Molly Erickson[1], Judy Thompson[1],
Danielle Paterno[1], Roni Netser[1]
[1]*Rutgers University*

Background: Although several studies have documented retinal cell dysfunction in schizophrenia (Silverstein & Rosen, Scz Res: Cogn, 2015), the extent to which these abnormalities contribute to, and/or result from, other features of the condition is unclear. Thus we sought to: 1) evaluate associations between retinal signaling anomalies as measured with flash electroretinography (fERG) and previously reported changes in visual evoked potentials (VEPs), contrast sensitivity, visual acuity, and contour integration in people with schizophrenia (Silverstein, Neb Symp Motiv, 2016); 2) determine whether fERG anomalies are related to retinal structural abnormalities as indicated by optical coherence tomography (OCT); 3) examine relationships between fERG changes and psychiatric symptoms; 4) determine relationships between fERG anomalies and frequent medical comorbidities in schizophrenia that are known to affect the retina (e.g., diabetes, hypertension); and 5) examine potential medication effects on these findings.
Methods: We have assessed 25 patients with schizophrenia and 25 controls who are free of medical comorbidity with fERG and measures of visual function and symptom severity, and data collection is ongoing with patients and controls with diabetes and/or hypertension using these same measures. In addition, we are in the process of completing data collection with two additional groups of patients and controls, one with fERG and OCT (n=12 to date), and another with fERG and VEPs (n=13 to date). fERG data are being collected under both light- and dark-adapted conditions, using a range of flash intensities, backgrounds, and temporal frequencies. The primary fERG variables of interest are a-wave and b-wave amplitudes, which reflect photoreceptor and bipolar cell responses, respectively, and the photopic negative response (PhNR), which reflects ganglion cell activity.
Results: On photopic fERG tests, patients with schizophrenia demonstrated significantly weaker photoreceptor response when a flash was presented against an unlit background ($p<.05$), and during a steady-state flicker test ($p<.005$). On scotopic tests, the rate of response gain per unit of intensity increase was significantly weaker for patients than controls ($p=.001$). In both light- and dark-adapted conditions, patients demonstrated weaker

signaling of bipolar cells (ps < .005). The schizophrenia group was also characterized by a weaker PhNR (p<.05). Weaker retinal cell responses were related to contrast sensitivity impairments in the schizophrenia group (ps < .05 and .001), but not to visual acuity or contour integration. Reduced responsiveness to low-intensity light was related to more severe negative symptoms, suggesting a reduced dynamic range within which environmental events (i.e., salience) are represented. Measures of retinal cell function were not related to antipsychotic medication dose. Preliminary findings indicate that attenuated fERG signals are not associated with weaker visual cortical responses (EEG-measured VEPs), presumably due to gain control mechanisms. We will report on the extent to which fERG anomalies are related to retinal structural changes and comorbid medical conditions.
Discussion: Reduced signaling of photoreceptor, bipolar, and ganglion cells are characteristics of schizophrenia, and are not related to extent of antipsychotic medication use. These changes are related to reduced contrast sensitivity and increased negative symptoms, and may reflect an attenuated ability to accurately represent changes in the intensity of environmental stimuli. Data collection is ongoing for studies examining relationships between ERG indices and VEPs and medical comorbidities.

7.2 ELECTRORETINOGRAPHIC ANOMALIES SEEN IN PATIENTS AFFECTED BY SCHIZOPHRENIA OR BIPOLAR DISORDER ARE DETECTABLE EARLY IN CHILDREN BORN TO AN AFFECTED PARENT: IMPLICATIONS FOR THE STAGING OF RISK STATUS IN CHILDHOOD-ADOLESCENCE

Michel Maziade*[,1], Thomas Paccalet[2], Anne-Marie Gagné[1], Elsa Gilbert[3], Daphné Lussier[4], Marc Hébert[3], Valérie Jomphe[1], Nathalie Gingras[3]
[1]Centre de recherche CIUSSS de la Capitale-Nationale; [2]Université de Québec à Trois-Rivières et Centre de recherche CIUSSS-CN; [3]Université Laval & Centre de recherche CIUSSS-CN

Background: Adult patients having schizophrenia, bipolar disorder or major depression display indicators of brain dysfunctions that may be detectable in healthy children-adolescents at genetic risk, such as those born to an affected parent (Maziade, New Eng J Med 2017; Schizophr Res 2013). For instance, cognitive deficits are displayed by both adult patients and children at risk (Maziade, Schizophr Bull 2011). We had reported that schizophrenia patients present diminished amplitudes and delayed latencies of rod and cone photoreceptor responses (Hébert, Schizophr Res, 2015) and we recently found that bipolar patients have similar ERG anomalies. We had also reported preliminary data in a small sample of 29 children born to an affected parent showing that young offspring had rod diminished amplitudes (Hébert, Biol Psychiatry 2010).
The present objectives were i) under the hypothesis that offspring would display many of the ERG anomalies that schizophrenia or mood disorder patients carry (Hébert, Schizophr Res 2015; Prog Neuropsychopharmacol Biol Psychiatry 2017), to look for cone and rod response anomalies in a large sample of young high-risk offspring; ii) to describe the relationship between ERG anomalies and other risk endophenotypes in the offspring; and iii) look at the relationship between ERG anomalies and the risk clusters already shown to predict later transition to illness.
Methods: The sample consisted of 84 young offspring (aged 6 to 27) of a parent affected by schizophrenia or bipolar disorder, compared to 224 healthy controls balanced for age and sex. Full-field cone and rod ERG was measured in non-dilated eyes for all subjects. In the young offspring, we also collected measures of different cognitive domains, attenuated symptoms of psychosis, non-psychotic DSM diagnosis and/or an episode of poor GAF functioning in childhood-adolescence, childhood trauma, and cannabis use (Paccalet, Schizophr Res 2016).
Results: In comparison to controls the offspring displayed three ERG anomalies that were observed in adult patients: prolonged cone b-wave latency (p=0.04), diminished rod b-wave amplitude (p=0.04) and prolonged rod b-wave latency (p=0.006). These ERG anomalies were shared by offspring of a parent with schizophrenia or bipolar disorder, an observation of ERG commonality that we had made in adult patients. The three ERG amplitude and latency anomalies tended to aggregate in a child at risk, a trend we also observed in another endophenotype modality such as deficits in different cognitive domains. However, in these high-risk children and adolescents, the patterns of aggregation suggest that ERG anomalies would depict another risk pathway than that marked by cognitive deficits.
Discussion: First, ERG anomalies in high-risk children have neurobiological implications for future research on the illness neurodevelopment. Second, as found for other modalities of risk endophenotypes in children at genetic risk (Maziade, New Eng J Med 2017), multiple rod and cone ERG anomalies tended to cluster together in a child. Such an aggregation may be compatible with the multifactorial polygenic theory with a threshold. Remarkably, a clustering of risk indicators is also observed in children at risk of metabolic cardiovascular disorders and is presently considered in practice guidelines for these children. The clustering of risk indicators may provide an empirical basis for the staging of the risk status of children at genetic risk and has immediate implications for their longitudinal surveillance in the clinic.

7.3 EVALUATING THE NEUROBIOLOGICAL CORRELATES AND IMPACT OF TREATMENT ON COGNITIVE DYSFUNCTION IN ADHD AND SCHIZOPHRENIA BY MEANS OF THE PATTERN ELECTRORETINOGRAM

Emanuel Bubl*[,1], Lisa Werner[2], Yumin Liang[2], Dieter Ebert[2], Evelyn Friedel[2], Anna Bubl[1], Michael Bach[2], Ludger Tebartz van Elst[2]
[1]University of Saarland; [2]University of Freiburg

Background: Problems with cognitive function are found in many major psychiatric disorders. In schizophrenia and attention deficit hyperactivity disorder (ADHD), they are among the core symptoms. Based on a growing recognition that there is little diagnostic specificity for any single cognitive impairment, there is an increasing emphasis on investigating impairments across psychiatric disorders. This approach, which is consistent with the NIMH Research Domain Criteria initiative, is expected to lead to a better understanding of the neurobiological mechanisms involved in cognitive deficits.
An increase in neuronal background noise has been identified as a neuronal correlate of inattention. Because the dopamine system has been found to play a critical role in modulating neuronal noise, dopamine dysfunction may play a substantial role in generating the excessive noise that has been found to characterize information processing in both schizophrenia and ADHD. This issue can be studied noninvasively via electrophysiological examination of the retina, a distinct neural network. Both basic research and human studies indicate that retinal information processing is under strong dopaminergic modulation (Bubl, Biol. Psychiatry, 2010; Bubl, Br J Psychiatry, 2012). We have previously demonstrated an elevated level of background noise at a very early stage in visual information processing in untreated patients with ADHD (Bubl, Plos One, 2015). Moreover, background noise was associated with inattention measures in these subjects. To further address the hypothesis that elevated retinal noise reflects dopaminergic dysfunction, we report here on a new study that compared retinal background noise in patients with ADHD both before and after therapy, as well as in patients with schizophrenia.
Methods: Neuronal noise was assessed using pattern electroretinogram (PERG), an objective electrophysiological measure for retinal network function from the photoreceptors to the retinal ganglion cells. A total of 20 patients diagnosed with ADHD were tested both before and after treatment