Neural White Matter Distinctions in Biologically Classified Psychosis

Courtney Burton, B.S. Jackson, D.A. Parker, E.S. Gershon, M.S. Keshavan, G.D. Pearlson, C.A. Tamminga, B.A. Clementz, and J.E. McDowell, Cognitive and Clinical Neuroscience, University of Georgia

Psychotic disorders share common phenomenology and genetic risk factors, but the specific etiologies and therefore targeted pharmacological treatments for these disorders remain elusive. Schizophrenia (SZ), schizoaffective disorder (SZA), and bipolar disorder with psychosis (BPP) are all diagnosed based on clinical symptoms, which in their lack of diagnostic specificity, evidence homogeneity between disorders historically considered distinct. Separating probands based on neurobiology rather than clinical symptoms alone may yield more meaningful classifications which then offer better targets for study of disease mechanisms and treatments. The Bipolar and Schizophrenia Network for Intermediate Phenotypes (BSNIP) consortium has collected brain and behavioral data from probands with these three disorders and used k-means clustering and multivariate discriminant analysis to regroup probands into three "Biotypes" based on electrophysiological, oculomotor, and cognitive measures; this gave two linear discriminant functions that were termed cognitive control and sensorimotor reactivity. The present study examines measures of neural white matter, which were not included in the original Biotypes analysis, in order to determine whether Biotypes provide better group separation than diagnostic classification. Diffusion-weighted imaging data were acquired from probands with SZ (n=30), SZA (n=39), and BPP (n=10), as well as healthy comparison (HC) subjects (n=76); fractional anisotropy (FA) values indexing white matter structure were calculated and compared between these three diagnostic groups, as well as between the three Biotypes previously derived. Between diagnoses, FA measures were lower for SZ probands than HC across several white matter tracts, but often not different between BPP probands and HC. In contrast, FA measures were lower across several tracts for Biotype 2, which includes probands from all three diagnostic categories, than for HC or the other Biotypes. Given that probands within Biotype 2 rate highly on sensorimotor reactivity, this decrease in white matter structure may be related to possibly compensatory, elevated neural activity. These results suggest that white matter differences between Biotypes may reflect true biological alterations in psychosis, which ultimately provide better classification and possible targets for etiological

mechanisms and treatments.

Computational and Predictive Models for Medical Image Analysis

Yi Hong, Computer Science, University of Georgia

In medical research, time-varying images or their derived shapes have been playing an important role in understanding and monitoring human health, including aging, disease progression, and development of critical organs such as the brain. Computational methods based on regression are widely used to summarize changes in such data over time. However, Euclidean models often result in blurry or unsmooth predictions, due to the ignorance of the intrinsic geometry of images and shapes. In this talk, I present our models for image and shape regression developed in non-Euclidean spaces, particularly in the manifold of diffeomorphisms and in the Grassmann manifold. These models use optimal control and can capture both linear and non-linear time-varying geometrical changes; they are also efficient as the regression can be decomposed as a collection of pairwise image registrations. Experiments on brain MRI scans and corpus callosum shapes from the OASIS dataset demonstrated the advantages of our models in both prediction accuracy and computational cost.

Differentiating Independent Brain Activity Patterns by Cognitive Skills

Ling-Yu Huang, David A. Parker, Scot K. Hill, Matcheri S. Keshavan, Godfrey D. Pearlson, Carol A. Tammiga, John A. Sweeney, and Brett A. Clementz, Cognitive and Clinical Neuroscience, University of Georgia

Electroencephalogram (EEG) captures electrical activity in the cortex via sensors pasted on the scalp. A whole-brain functional measure with high temporal resolution, it is the technique of choice for identifying and differentiating abnormalities in localized or collective brain response to controlled sensory stimuli. Auditory oddball task, with common standard tones (1000Hz, 85% of trials) randomly interspersed with rare target tones (1500Hz, 15%

of trials), is a robust measure of subjects' sensory acuity, salience detection, and working memory. In oddball tasks, P300 ERP (event-related potential around 300ms after stimulus onset) in response to the rare target tones is believed to be a combination of responses from the brain's frontal, parietal, and temporal regions. Decreased general P300 amplitudes have been observed in clinical populations. The present study examined amplitudes of P300 components in subjects with various cognitive profiles, in healthy control group as well as a psychosis group. Data was collected as part of the BSNIP (Bipolar Schizophrenia Network on Intermediate Phenotypes) consortium, and the cognitive measure selected for this analysis was the Penn Conditional Exclusion Test (PECT), a computerized analog of the Wisconsin Card Sorting Task. 2X2 General Linear Model found that on average, psychosis probands produced lower late P300 amplitudes than control subjects (F(1,743)=21.47, p¡0.0001), and there was also an observable group difference between subjects with high versus low rule deduction skills (F(1,743)=15.27, p=0.0001), however, there was no interaction between psychosis presentation and rule deduction (F(1,743)=1.12, p=0.2906). To identify functional markers for cognitive deficits in psychosis, further investigation on how sub-components of P300 ERP are related to different PCET parameters will be performed.

Examining Context-Dependent Changes to Behavior and Brain Functioning in Psychosis

Brooke Jackson, Courtney R. Burton, Emma Auger, Amanda L. Rodrigue, and Jennifer E. McDowell, Cognitive and Clinical Neuroscience, University of Georgia

Saccadic eye movements have been widely implemented to examine behavioral and neural processes involved in executive functioning. Populations with psychosis show impairments to various aspects of cognitive control, including inhibition and attention, but it is still unclear what underlying neural functioning is implicated in these impairments. The current study utilizes fMRI and saccadic eye movement tasks to examine behavior and context-dependent brain modulation in populations with psychosis. We recruit subjects with schizophrenia, schizoaffective disorder, bipolar disorder with psychosis, and comparison subjects in order to examine both brain and behavioral differences when task complexity is modulated. Participants perform single task runs of prosaccades and antisaccades, as well as two mixed tasks (one event-related and one block-designed) which contain both prosaccades and antisaccades. Brain and behavioral changes will be compared for more basic contexts (single task runs) versus more complex contexts (mixed task runs), as well as changes that occur as the task changes within these runs. We expect more errors and longer reaction times for more complex, mixed contexts. Additionally, we expect that psychotic participants will exhibit higher error rates and longer reaction times for these complex tasks compared with control subjects. The study aims to identify specific brain regions implicated in the modulation between easier tasks (prosaccades) and tasks that require higher levels of cognitive control (antisaccades) within the same run and how these might functionally differ between psychotic populations and comparison subjects.

Statistical Modeling of fMRI Data for Pre-Surgical Planning

Timothy Johnson, Biostatistics, University of Michigan

Spatial smoothing is an essential step in the analysis of functional magnetic resonance imaging (fMRI) data. The standard method is to convolve the image data (at each point in the time-series) with a three-dimensional Gaussian kernel that applies a fixed amount of smoothing to the entire image. In pre-surgical planning, using fMRI to determine functionally eloquent, peritumoral regions of the brain image, spatial accuracy is paramount. Thus methods that rely on global smoothing may not be reasonable as global smoothing can blur the boundaries between activated and non-activated regions of the brain. Moreover, in a standard fMRI analysis strict false positive control is desired. For pre-surgical planning false negatives may be of greater concern. In this talk, we present two Bayesian models that allow spatially adaptive smoothing that circumvent the problem with global smoothing. For both models, with start with the unsmoothed Z-statistic image obtained from standard software, such as SPM or FSL, and segment the image into three classes: deactivated, activated, and null classes. The first model is based on a Pott's prior model for image segmentation that does not smooth over sharp boundaries in the Z-statistic image. The Pott's model favors image configurations where neighboring voxels belong to the same class. We adopt a Bayesian decision theoretic approach to determine which voxels belong to each of the three classes. In this approach, false negatives and false positives are penalized asymmetrically in the loss function allowing false negatives to be penalized more heavily than false positives. Our second model is a spatially adaptive, conditionally autoregressive model. Similar to the Potts model, this model reduces smoothing at boundaries between regions of no activation and activation in the Z-statistic image. After we fit the model to the data, we again take a Bayesian decision theoretic approach that allows false negatives and false positives to be penalized differently. We apply both models to pre-surgical fMRI data from a patient with an Oligodendroglioma. During surgery, electrical stimulation mapping (EMS) was performed to determine functionally eloquent, peritumoral, regions of the brain responsible for speech. Post-surgery assessment of our modeling results with EMS show promise for these models and fMRI in pre-surgical planning.

Multiple Paths Issues in Neuroimaging and Topological Data Analysis

Chul Moon, Statistics, University of Georgia

Functional magnetic resonance imaging (fMRI) has been used to discover functional connectivities and diagnose disorders. The recent projects that share fMRI data have increased the needs of a large-scale neuroimaging analysis methods. The multiple path issues, related to a large number of potential pre-processing paths, is one of the biggest challenges for the big data neuroimaging analysis. In this talk, we will introduce two methods using topological data analysis that can enable the neuroimaging analysis with minimal pre-processing steps.

Scalable Estimation for Genetic Components of High-Dimensional Imaging Data

Benjamin Risk, Emory University

It is of great interest to quantify the contributions of genetic variation to brain structure and function, which are typically measured by high-dimensional imaging data (e.g., structural magnetic resonance imaging data). However, existing methods cannot efficiently handle high-dimensional functional phenotypes, such as cortical thickness with 60,000 vertices. Several major big-data challenges arise from estimating the genetic and non-genetic (or environmental) covariance functions of functional phenotypes extracted from high-dimensional imaging data. We develop a scalable method to estimate these high-dimensional and non-stationary covariance components while preserving their positive semi-definiteness. Positive semi-definite functions are estimated using kernel regression with geodesic distance. Simulation studies demonstrate large improvements over existing approaches, both with respect to covariance estimation and heritability estimates. We have successfully applied the proposed method to a cortical thickness data set obtained from around 1,200 subjects in the young adult Human Connectome Project. This is joint work with Hongtu Zhu.

BrainPack: A Suite of Advanced Statistical Techniques for Multi-Subject and Multi-Group FMRI Data Analysis

Arunava Samaddar, Nicole A. Lazar, Jennifer E. McDowell, Cheolwoo Park, University of Georgia

We aim to evaluate brain activation using functional Magnetic Resonance Imaging (fMRI) data and activation changes across time associated with practice related cognitive control during tasks. FMR images are acquired from participants engaged in 1 block design and 5 probability event related designs at two scan sessions: 1) pre-practice before any exposure to the task, and 2) post-practice, after 4 days of daily practice on either general antisaccade (generating a glance away from the cue) tasks or specific probability related event runs, which are a mixture of antisaccade and prosaccade (generating a glance towards the cue) task. The clustering technique is composed of several steps: detrending, data aggregation, wavelet transform and thresholding, the adaptive pivotal thresholding test, principal component analysis and K-medoids clustering. We use the structural similarity index to compare similarity between pre- and post- scan session images on the probability event related runs. Also, we apply the semiparametric model under shape invariance to test the differences between the two sessions and the two practice groups in regions of interest for the block run.