The Role and Development of Applied Statistics to Advance Brain Science

In this special issue we have the pleasure of reading 18 papers on the theory and application of modern statistics in brain science. Brain-based research topics include the study of disrupted glial-neuronal interactions in HIV-associated dementia, cortical surface morphology in autism, schizophrenia and family pedigrees, serotonin receptor occupancy, mouse auditory cortex, bilateral hand movements in Parkinson's disease research, task switching, word generation, visual hemifields and resting states, visual attention, hippocampal surfaces in schizophrenia, cortical thickness, hemispheric asymmetry, and programmed stimulation of motor neurons for prosthetic robotic devices. Measurement technology and methods include brain tissue analysis, electrophysiology, electroencephalography (EEG), positron emission tomography (PET), structural magnetic resonance imaging (MRI) volumetry and surface reconstruction, functional MRI (fMRI) and functional near infrared spectroscopy (fNIRS). Several brain imaging methods used today are not represented here, including MR diffusion tensor imaging (MR-DTI), magnetoencephalography (MEG), MR spectroscopy (MRS), MR spectroscopic imaging (MRSI), and transcranial magnetic stimulation (TMS). Mathematical and statistical methods and models also vary: point processes, time series, penalized regression and inverse problems, varieties of Markov models, state-space models, principal component analysis (PCA), independent component analysis (ICA), functional connectivity, spatiotemporal power spectra, spherical harmonics and bootstrap techniques. Sample sizes range from 1 to 131 subjects, not all human. There are 13 demonstrations of new statistical methods with a data example and 5 data analyses with results that contribute to the brain science literature, a mix common to many high-quality statistical and biostatistical journals. Each paper provides accessible introductory background material on the statistical theory and practice to which they contribute and some provide background material in brain science. The scientific topics, mathematical and statistical methods and neuroscience addressed here could easily fill many undergraduate courses, graduate courses, masters theses, doctoral dissertations and research programs — they do, they should and they will.

All papers address research topics in brain structure and function that involve neurons, the main cells in the brain that help enable all our talents of mind, brain

and behavior, and aspects of blood flow, volume and oxygenation. The idea that neuronal activity is related directly to changes in brain metabolism and blood supply was perhaps first put forth by Roy and Sherrington in 1890. They conducted highly invasive experiments with dogs, cats and rabbits treated with curare to relax skeletal muscles. Interestingly, they began their report on a statistical note:

> ". . . the cause of these discrepancies [in the results of different researchers in the area] is to be found in the great difficulty of avoiding the sources of error which plentifully surround the subject, and in overcoming certain technical difficulties . . . . The ease with which one can obtain results upon certain points, on taking up the subject, is itself, we believe, apt to make the inquirer careless in controlling sources of error, which, it may be noted, are some of them not at first sight obvious. We must on this account say more about the technology of our subject than would be necessary were the subject a simpler one."

> (Roy and Sherrington (1890))

These two brain science pioneers were speaking mainly of physiological noise and the proper design and analysis of experiments. Nearly one hundred and twenty years later, we still grapple with these and many other statistical issues in our search for a deeper and wider understanding of what the brain is and how it works. It can be argued that all brain science, especially imaging, is statistical. It can also be argued, perhaps more strongly, that every one of our methods and models, calculations and cautions are meaningful to brain science only when coupled with the principles and current state of neuroscientific knowledge and its underlying physics, chemistry and clinical utility. An excellent comprehensive source in neuroscience is Kandel, Schwartz, and Jessell (2000). An equally excellent source in MR physics is Stark and Bradley (1999). In this author's view, parts of these texts are required reading for any statistician working in brain science.

This editorial is written primarily for statisticians interested in applying their skills to advance brain science in meaningful ways to help improve people's lives. In the following pages the reader will find a brief summary of each article, some connecting themes, and closing remarks.

Bai, Shen, Huang and Truong propose a supervised singular value decomposition (SVD) for ICA with application to fMRI and provide an example of bilateral finger tapping in Parkinson's disease research. Their SVD and ICA decompose the fMRI signal into its spatial and temporal components by data projections to lower dimensional subspaces. They seek to improve scientific inference by using stimulus-locked filters that match aspects of periodic experimental designs. For instance, the fundamental frequency and onset of the experimental forcing function is employed to exclude from the analysis all off-frequency and/or out-of phase fMRI time series. Such data exclusion can be useful in the pursuit of tight *a priori* goals when "noise", such as random and intermittent spikes, is well understood and characterized. But there is an incurred risk of missing important yet unanticipated brain activity that is relevant, perhaps indirectly, to the goals of the study. (This point is emphasized and expanded by Linquist, Zhang, Glover and Shepp, and by Loh, Lindquist and Wager in this issue.) When one accepts this risk, however, data filtering is best performed objectively and systematically, as advised by the authors. Such practice is certainly an improvement over the highly subjective and nonsystematic pixel surfing during the halcyon days of early fMRI, when large, darkened rooms were filled with cathode ray tubes armed by eager researchers searching for, finding and publishing a few local brain activations that matched their boxcar functions. Lower dimensional data transformations should not, however, depend too heavily on *a priori* expectations if the analysis is to escape a kind of self-fulfilling circularity. One can still read a new brain imaging research report in which the premise and conclusions rely on little sufficiently objective empirical-inductive investigation (after some digging into specifics). As we know, the development and application of objective statistical methods is an essential contribution of our field. The proposal offered by Bai et al. can be useful in this regard when applied appropriately.

Bellec, Marrelec and Benali present a circular block bootstrap for fMRI studies of "functional connectivity" that they call "Yet Another Double Bootstrap (YADB)". In imaging neuroscience, functional connectivity refers to an emerging subfield that seeks to understand relationships between interacting neuronal clusters that "talk" with each other via long- and short-range projections. There are an estimated 100 billion neurons and 100 trillion synapses in the human brain. Mappings between them are many-many, many-one, one-many and one-one. There are also important connections between neurons and non-neuronal glial ("glue") cells, as studied by Landau and Everall in this issue. The simple McCullough-Pitts neuron (McCullough and Pitts (1943)), a foundation of modern neural computation models, is a many-one mapping

of electrochemical signals from dendrites (input channels from other neurons) to synapses on the membrane and/or axon of a single neuron. The neuron fires if the weighted sum of the signals exceeds a threshold; weights and thresholds vary across neuronal ensembles. From a simple perspective, functional connectivity in fMRI statistics involves the inspection of spatial arrays of Pearson correlations of inter-voxel time series. The authors remind us that these series are not independent, identically distributed or Gaussian distributed. Their YADB, and many bootstrap predecessors, intends to address these and other distributional assumption violations to protect global false-positive error and false discovery rates. They report that YADB has coverage and power properties superior to several bootstrap alternatives in simulations and also apply it in a longitudinal motor learning study of $N = 3$ young healthy male subjects.

Chung, Hartley, Dalton and Davidson describe and extend the mathematics of weighted spherical harmonic expansions for cortical surface rendering, 1-1 hemispheric correspondence and asymmetry indices for the human brain. Spherical harmonics, pioneered in imaging neuroscience by Dr. Guido Gerig and others, use polar coordinate basis representations to span cortical surface vector spaces. The authors compute a 1-1 mapping of the cortical surface to the unit sphere assuming that the two are topologically equivalent. Model fitting is iterative. Since the PET image reconstruction work of Drs. Larry Shepp and Yehuda Vardi in the early 1980s that estimated joint probabilities from a series of marginal projections by the EM algorithm, the choice of stopping criteria that strikes a balance between bias (underfit) and variance (overfit) has been a challenge. The authors present their choice based on a generalization curve used in machine learning and elsewhere. Artifacts in estimated surfaces due to abrupt topographic changes (Gibbs ringing), at a sulcal-gyral interface for instance, are ameliorated by weighting the spherical harmonic coefficients and squared residuals to speed convergence. The classical hemispheric asymmetry index of Galaburda, Rosen, and Sherman (1990), proportional to (Left – Right) / (Left + Right), is the ratio of the positive- and negative-order harmonics of the series expansion. The authors' framework enables further study of the possible importance of other harmonic combinations. Their representation is employed to study inter-hemispheric differences in cortical thickness in autism versus typical development. They begin by applying 3D linear transformations from the image spaces of individual subjects to a common Cartesian coordinate reference frame based on a publically available structural MRI brain "template" derived from 305 subjects at the Montreal Neurological Institute (MNI). Such mapping is termed "spatial normalization", "coregistration", or "stereotaxic transformation". Im et al. (2008) have pointed out,

however, that linear mappings can cause major distortions of cortical thickness and other shape-based measures when these measures depend on size. For instance, when comparing two groups of people having differences in a global size measure, such as total brain volumes for males and females which differ by roughly 10% on average, linear stereotaxy can distort a geometric similarity measure that varies with this global scaling, introducing a source of non-biological variance that has nothing to do with any true biological differences between the two groups. Volumetric components of the healthy adult and pediatric brain, however, do not all scale proportionally with total brain volume (Kennedy, Lange et al. (1998)). Local developmental factors exist that introduce non-proportional scalings of considerable magnitudes that affect volumetric group analyses. The nonlinear stereotaxic transformation used by Zhu et al. in this issue may obviate such potential distortions of cortical thickness measurements. Despite this possible weakness, Chung et al. have contributed an excellent probe of the brain basis of autism spectrum disorders.

Eden and Brown contribute an outstanding paper in motor decoding that describes the stochastic process models and control theory used in the design of robotic prosthetic devices to control muscle movements through programmed stimulations of primary motor neurons. The authors contribute to this field by making explicit connections between adaptive filters of point processes for the analysis of neural spike trains in continuous time and a new filter for estimating state-space models from point processes. Such innovative technology may provide safe and efficacious therapies for people with spinal cord injuries and neural degeneration, possibly in tandem with neural regeneration therapy and stem cell transplantation. By use of simulated neuronal stimulation patterns derived from a previously published animal model, the authors generate smooth arm movements that compare favorably with the actual 3D arm trajectories of a Macaque monkey. The current mean squared displacement error of their system in 2D is about 2.5cm/sec in both directions, attributed to observation error. There is more work to be done and this research holds future promise to help many people with a variety of motor impairments.

In related work, Guha and Biswas present an overview of continuous-time models for local field potentials and point process models for neuronal firing patterns. Field potentials are the trans-membrane electrical currents generated by cell firings. Their application example involves the location of the auditory cortex in the mouse brain. Humans possess a tonotopic map between pitch and neuronal location in the primary auditory cortex, but mice do not. Projections from the auditory cortex to other regions

such as the caudate nucleus and putamen are more variable in primates than in rodents (Borgmann and Jürgens (1999)). Therefore a further statistical understanding of these and other connections in the mouse brain is essential in animal models of pitch discrimination, for example. The authors also provide an extensive literature review that includes seminal work by Dr. David Brillinger. We all can learn from his example, a brilliant theoretical statistician who, avoiding simplistic reductions to convenient statistical formulations, takes the time and energy needed to learn the principles and current findings in the science he engages. The authors present comparative results and choices from a wide range of Markov models, state-space models and a new ARMA-type model and find that their Markov chain model is the most robust in their context.

Jiang and Ogden present an alternative approach to the analysis of plasma kinetics via PET. As its name indicates, PET is an emission tomography method, in contrast to transmission tomography methods such as 2D X-ray and 3D computerized tomography (CT). Ionizing radiation from ligands bound to macromolecules helps locate sites with of high glucose metabolism. In the brain, these sites can be as large as tumors and as small as targeted presynaptic and postsynaptic receptors of hundreds of chemical signaling agents (neurotransmitters). Some statistical methods for PET data analysis select design matrices, one for each voxel, from a library of basis functions for use in subsequent regression analyses. The authors propose to achieve statistical gains when adopting this approach by assuming that a common parameter is shared by all voxel values and also recommend the use of spatial variance-covariance patterns generated by conditional autoregressive (CAR) models. The authors apply their proposal to a PET study of serotonin ($5HT_{1A}$), a neurotransmitter that regulates mood, where levels are manipulated by medications for treatment of depression and other biological disorders.

Keller, Roche, Tucholka and Thirion address the deleterious effects on population inferences of imperfect spatial normalization across subjects in fMRI studies. Intuitively, the spatial extents of activated regions under misalignment are larger than they would be if perfect alignment were possible. The authors present an attractive extension of the two-level empirical/full Bayes formulation that acknowledges voxel location uncertainty. Models are fit via Markov chain Monte Carlo (MCMC) sampling with conjugate priors, a separate Metropolis accept/reject rule for obtaining draws from the conditional distribution of spatial displacements, and a sign permutation test to control false positive error rate. Although the authors, and others before them, argue that their MCMC sampling time is considerably less than the total time required

to design, enroll and implement a typical fMRI study, some clinical brain imaging studies require results quickly. The authors apply their approach to an fMRI study of calculation and sentence switching to locate number processing regions. Setting a threshold that limits the global false positive rate to 1%, their Bayes factor maps detect broad activity in the posterior parietal cortex where spatial extent decreases under their spatial uncertainty model to become comparable to that detected by a common t-statistic map with 0.1% coverage. When they threshold their map at this same coverage probability, the activation pattern becomes tighter, as expected, and includes the more localized brain activity seen in other similar studies of mental calculation (Rueckert, Lange et al. (1996); Chochon, Cohen, van de Moortele, and Dehaene (1999); Dehaene, Piazza, Pinel, and Cohen (2003)).

Landau and Everall have chosen an active research area in brain tissue analysis to demonstrate their extension of semi-parametric bootstrap methods for regression models of Professor Brian Ripley's K-functions for inhomogeneous spatial point processes (SPPs) (Diggle, Lange, and Benes (1991)). They extend current approaches to multivariate (Landau, Rabe-Hesketh, and Everall (2004)) mixed-effects (Carpenter, Goldstein, and Rasbash (2003)) models. Professor Ripley's K-functions quantify divergence from complete spatial randomness and are invariant to random thinning. In contrast to employing a brain science data set as an example application of a new statistical method, the authors have provided us with an example of statistical methodology generated to answer a specific set of research questions in brain science. HIV-associated dementia (HAD) is thought to be due, in part, to disruptions of spatial interactions between astrocytes, a type of glial cell, and pyramidal neurons. Interestingly, there is no particular reason why two brain cells are in their particular locations, excluding cells that communicate by very short-range electrical fields called gap junctions. Once positioned, however, cell densities and arrangements change over time by a variety of processes including programmed cell death (apoptosis), neural generation (controversial in the human brain), tissue shrinkage not due to cell loss, and random thinning. The spatial distributions of neurons in the six layers of human neocortex diverge greatly from 3D Poisson SPPs of complete spatial randomness to include sub-Poisson SPPs (more regularly spaced patterns with exclusionary distances between cells), supra-Poisson SPPs (spatial clustering, mother-daughter processes) and other patterns. Spatial arrangements of glial cells, however, are generated by 3D Poisson SPPs. Glial cell analysis was once thought to be a research backwater when most attention was directed to understanding neuronal interactions at the synapse. Astrocytes now play a central role in molecular genetic studies of the *tripartite*

synapse (Halassa, Fellin, and Haydon (2007)). Astrocytes are coupled to one another by gap junctions. Their processes are contained within 100 µm regions contiguous to the neuronal membrane. One astrocyte makes contact with over 100,000 synapses (Bushong, Martone, Jones, and Ellisman (2002)). They regulate the availability of D-Serine, an endogenous ligand that binds to the glycine site on the predominantly glutamatergic NMDA receptor (Halassa, Fellin, and Haydon (2007)). NMDA receptor hypofunction has been implicated in schizophrenia (Tsai and Coyle (2002)). Increasing D-Serine levels, enabled by astrocytes, may decrease positive and negative symptoms in schizophrenia (Tsai, Yang, Chung, Lange, and Coyle (1998)). Astrocyte dysfunction has been associated with HAD and epilepsy, and possibly Alzheimer's disease and depression. Through their regulation of local blood flow, astrocytes make important contributions to the cellular bases of functional brain imaging (Magistretti (2000)). Hence, further understanding of correlations between the spatial arrangements of neurons and astrocytes will continue to reveal the molecular genetic etiology of major brain disorders. Landau and Everall present a clear, experienced and detailed description of their statistical machinery that enables others to use and extend their work to similar situations and know precisely what they are doing. Theirs is a well-written paper worthy of attention by anyone interested in brain tissue analysis.

Lindquist, Zhang, Glover and Shepp contribute an excellent paper on an innovative approach to functional MR image acquisition that, when brought to fruition, could revolutionize the field. As the authors point out, when we seek to use current fMRI technology to understand spatiotemporal relations between the activation sequences induced by controlled external stimuli, its poor temporal resolution makes such attempts futile. They direct our attention away from the slowly evolving post-stimulus signal peak to the transient, low magnitude negative dip immediately following the stimulus. This dip is an early component of the blood oxygen-level dependent (BOLD) response that is believed by many MR physicists and neurochemists to be due to an immediate decoupling of cerebral oxygen consumption and blood flow in the capillary bed. The existence of the negative dip remains an unproven hypothesis, yet the authors' innovation in MR image acquisition makes this controversy partially irrelevant because their new acquisition technique has potential applications in other MRI areas. In the frequency domain, instead of traversing gradient history space (*k-space*) conceived as stacks of 2D echo-planar images (EPI) in the spatial domain, the authors traverse k-space in true 3D by developing an alternative to a method proposed originally by Dr. Peter Mansfield, a pioneer inventor of MRI, that he called echo-volumnar imaging (EVI). In so doing, they reduce the time it takes

to collect a high-resolution whole head image in fMRI (the time-to-repetition or TR) drastically from 2000 ms to 100 ms. The Nyquist sampling theorem tells us that a sampling frequency of 100 ms enables reconstruction of any periodic function with frequency 200 ms or more (in other words, two points determine a straight line). The authors focus on dips instead of peaks, trade spatial resolution for temporal resolution, collect rapid snapshots to locate negative dips (if any), put the dips in correspondence with their future peaks (What goes down must go up?), and thus obtain temporal sequence orderings that are more spatially accurate. They actually start with possible peak locations identified by the general linear model options available in the widely-used Statistical Parametric Mapping (SPM) program. There are potential sources of false positives (declaring a dip, a peak, or a dip-peak correspondence when they do not exist) and false negatives (missing dips and peaks when they exist). Brain vasculature slowly overreacts to the call for more freshly oxygenated blood required to perform neural computations, memorably described by Dr. Robert Turner as "watering the garden for the sake of a single flower". This slow response is characterized by the brain's hemodynamic response function (HRF) and is a major confound in BOLD signal detection and analysis. As is customary, the authors assume a global HRF with a common delay between 5-8 seconds. Relaxation of this assumption to allow location-dependent HRFs modeled by two-parameter gamma distributions (Lange and Zeger (1997)) may improve the spatial accuracy of their technique; yet that model is nonlinear in its parameters and its iteration may be too costly. The authors address the sensitivity and specificity of their proposal by analyzing an fMRI data set generated by one subject in an audiovisual study of motor cortex. They choose a time series decomposition model with AR(2) correlation structure that separates signal, trend and seasonal components, followed by bootstrap hypothesis testing. Lindquist, Zhang, Glover and Shepp have demonstrated proof of concept for a method that addresses a major problem in fMRI data analysis directly that has until now been largely ignored. Readers seeking to learn more MR physics and help resolve temporal sequence ordering problems in fMRI should study this paper.

Loh, Lindquist and Wager address the important problem of model misspecification in fMRI. Their idea is to alert the practitioner to potential biases and statistical power losses when estimating onsets and widths of brain activations by using a moving time window of cumulative weighted averages (discarding noise spikes) to identify large absolute value residuals from a fitted model. The authors state that roughly 10-20% of previously reported activations in the neuroimaging literature are false positives. (This reader does not doubt this statement but it would be useful to learn how to produce

such estimates.) As pointed out in the previous paper by Drs. Lindquist, Zhang, Glover and Shepp in this issue, inaccuracies in estimates of onset delay and peak width can cause major deleterious effects on practical inferences and scientific interpretations. An important element in the authors' mismodeling detection kit is the assessment of size and shape parameters governing the assumed HRF. Freshly oxygenated blood is delayed by the transit time through the cerebral vasculature proportional to how far it has traveled from the site of flow regulation (Lee, Glover, and Meyer (1995)). In addition, the quantification and modeling of intravascular effects and the dependence of the BOLD signal on vessel size also continue to be important unresolved problems in fMRI research. The spatially localized size and shape parameters of the aforementioned Lange-Zeger HRF may improve model accuracy. The authors quantify bias and variance tradeoffs by fitting models with design matrices that include and exclude necessary covariates, their $X + \Gamma$ and X, respectively. It was unclear to this reader if they treat the case when X contains unnecessary covariates, and thus variance inflation, by specifying only that $\Gamma \neq 0$, unless some $-\Gamma$ performs the removal somehow; there appears to be an inconsistency in the role of Γ since it appears to be defined both as part of the larger "true" model and the incorrect, smaller model. The authors employ finite impulse response basis sets, as in the previous paper, and present useful simulated bias curves, power loss curves and spatial maps. It is difficult to understand what the authors mean by the "true onset time" in their actual fMRI data example purposely mismodeled. It may be of interest to note that in a brief section on maxima of Gaussian processes they mention Hotelling's volume-of-tubes formula, a result derived from a new branch of mathematics spawned by a practical scientific research problem and consistent with the editorial theme.

Martínez-Montes, Sánchez-Bornot and Valdés-Sosa offer a penalized version of multi-way factor analysis with constraints to obtain solutions to EEG regression problems. The authors argue that the high dimension and low signal-to-noise ratio (SNR) of brain science data require strong prior constraints in order to arrive at physiologically interpretable results. Their algorithm solves a trilinear system of optimization problems, each with ridge regression penalties. Starting with the solution to the unconstrained maximization problem followed by iterative estimation of penalty weights and approximate degrees of freedom by inspection of the logarithm of the generalized cross-validation criterion, they find an "optimal" (the authors' quotes) solution. Three types of sparseness constraints for EEG data with brief and infrequent signals are presented. They choose to make their solution depend strongly on their choice of "prior" distributions that are derived during the course of their iterations

and have some correspondence to existing knowledge of brain physiology. They demonstrate their method with simulations and with an example analysis of sparse EEG data.

Ombao, Shao, Rykhlevskaia, Fabiani and Gratton provide theory and method for nonparametric, asymptotically Gaussian estimation of spatiotemporal processes in the frequency domain. They demonstrate the utility of their approach with an example analysis of event-related optical signal (EROS) phase delay data collected by 160 detector pairs in bilateral medial-frontal and central-posterior gyri from a sole subject during a Stroop test of spatial-verbal task switching. The spatial resolution of brain EROS is about 5 mm and its temporal resolution is about 1 ms, the latter comparable to that of EEG. In 1935, Dr. John Stroop studied cognitive dissonance using an interference task, for instance, presenting the word *red* written in green (Stroop (1935)). His basic idea and its variations have since been employed throughout cognitive psychology. The authors claim that there have been no previous frequency domain approaches that analyze variation in spatially contiguous locations. Their results indicate expected left-dominant language lateralization and a possible role of a left central posterior gyrus when switching from a less challenging cognitive task to a more challenging one. Their paper is an important contribution to the theory and application of multivariate time series in brain science.

Purkayastha, Wager and Nichols propose a useful method for testing hypotheses regarding the codependence of fMRI brain activations arising from a bank of tasks administered to the same subject during a single experiment. The authors shift our attention away from "massively univariate" analyses of the mean function in spatiotemporal series to multivariate analyses of the variance-covariance function. They apply their proposal to an event-related fMRI study of working memory and reaction time in a 2 x 2 factorial design of attention switching tasks. Event-related fMRI designs sacrifice SNR to improve temporal resolution from about 2 seconds, the time it takes to collect a whole head, to the millisecond range by using fine-grained stimuli timings generated at random, by a gamma density for instance, followed by deconvolution. The authors suggest a classical two-stage approach to empirical Bayes model fitting by reducing individual data to regression summary statistics followed by between-subject aggregation. Their variance parameter estimate is maximum likelihood, appropriate also for restricted maximum likelihood (REML) estimation. These authors remind us that when counting degrees of freedom the sampling unit providing an independent source of information is the individual, not the timepoint,

brain voxel or region of interest. The authors mention two limitations of their proposal, its sensitivity to outliers and imperfect spatial normalization across subjects, both of which being addressed in related papers in this issue. Their central contribution is a straightforward adaptation of traditional methods for analyzing variance-covariance patterns arising from multiple brain locations to those arising from multiple conjoint tasks that addresses an important need in cognitive psychology and other disciplines.

Sánchez-Bornot, Martínez-Montes, Lage-Castellanos, Vega-Hernández and Valdés-Sosa contribute a second paper that applies a variation of the statistical methods proposed in their first paper to the study of neuronal connectivity. They develop and analyze symmetric and asymmetric connectivity matrices generated by interleaved fMRI and EEG data. The challenge here is again to find optimal solutions to constrained maximization problems for sparse data that contain small numbers of neuronal clusters. The nearly simultaneous recording of fMRI and EEG signals remains a challenging goal in functional brain imaging for the obvious reason that electrical and magnetic fields interact strongly with each other. Researchers attempt to obtain separable signals with minimum overlap by interleaving acquisition sequences for these two imaging modalities, exploiting their differences in temporal and spatial resolutions. The authors employ simulations and data from an fMRI-EEG study of resting state brain rhythms, another currently active research area in brain research. The authors present a many-many map with varying connection strengths between bilateral visual, somatosensory and insular cortices and thalamus. Their map is a fully connected, directed graph (except for the insignificant left insula-left somatosensory cortex edge). The authors ask the reader to compare their estimated connectivity network to a previous graph (not shown or described) that was obtained from the same data set by similar statistical machinery (Eichler (2005)). Doing so, it appears that the authors' graph shows many more connections between these cortical and subcortical brain regions.

Singh, Clowney, Okamoto, Cole and Dan add to their previous work on spatial normalization and false discovery rate in functional near-infrared spectroscopy (fNIRS) by comparing nonparametric and parametric hypothesis testing alternatives. fNIRS measures changes in the concentration of oxy- and deoxyhemoglobin, as does fMRI, as well as changes in the redox state of cytochrome-c-oxidase (Cyt-Ox). It is a type of optical imaging that employs a thin strip of sensors affixed to the subject's scalp, on the forehead without hair removal for instance. After a brief review of the basics of the t-, permutation and bootstrap tests, the authors use simulations and an example

fNIRS data set to investigate how family-wise error rates compare with one another. The number of input channels is also varied. The fNIRS example is taken from a word generation study in which nouns are generated after category naming. The authors conclude that the nonparametric alternatives they consider are preferable to parametric approaches in this context.

In their third paper in this issue, Vega-Hernández, Martínez-Montes, Sánchez-Bornot, Lage-Castellanos and Valdés-Sosa offer alternative regularized solutions to EEG inverse problems. EEG is sensitive to electromagnetic flux in gyri because they are generally parallel to the cortical surface, whereas MEG is suited for detecting activity at synapses of pyramidal neurons in sulci tangential to the surface. MEG appears to be less sensitive than EEG to the assumptions of conductivity models. In 1853, Dr. Hermann von Helmholtz saw that it is impossible to locate the internal sources of electromagnetic fields measured at the surface of the brain uniquely; the inverse problem is ill-posed and model assumptions are required. Regularized solutions to the inverse problem impose physiological, prior and penalty constraints in search of unique source localizations. It has also been shown that interleaved fMRI can provide useful constraints for EEG. As in their other contributions here, the authors provide an accessible review of previous relevant work, including Tikhonov regularization, spatiotemporal autogressive models to obtain smoother activity surfaces, non-convex penalties and combinations of penalties. They proceed to compare different members of the local likelihood estimation methods pioneered by Drs. Jerome Friedman, Trevor Hastie and Rob Tibshirani though simulations and a publicly-available example EEG data set. They find, in general, that approaches with non-convex penalties appear to provide more concentrated localizations than the popular and less regularized low-resolution electromagnetic tomography (LORETA) approach, yet demonstrations of validity are required.

Zhou and Wang provide us an excellent development and application of statistical theory that can reduce the number of time-consuming computations required to obtain exact permutation distributions in brain imaging. In simpler contexts, the *exact* solution is not necessarily better than an approximate one (Agresti and Coull (1998)). The authors approximate exact permutation distributions for univariate and multivariate linear and nonlinear test statistics by using the first four moments (when they exist) of a probability distribution proposed in 1895 by Dr. Karl Pearson in the mathematical theory of evolution for skew variation. The authors factor expressions for any moment of the permutation distribution into a permutation of test statistic coefficients and a

summation term over products of the data, reducing the order of the computation to the sample size or square of the sample size. They demonstrate that their approximations compare favorably with exact solutions via simulations and also in a cortical surface morphology example based on spherical harmonics, as in the Chung et al. paper in this issue, that compares 3D hippocampal surface shapes in a small-sample schizophrenia versus control study.

Zhu, Li, Tang, Bansal, Hao, Weissman and Peterson conduct an analysis of the effects of genetic variation and sex-age interactions on cortical thickness measurements gathered from structural MRI data contributed by n = 131 subjects sampled from N = 49 families of sizes ranging from 1 to 15. They employ a nonlinear spatial normalization method developed at Washington University, Saint Louis, and thus their cortical thickness measures after coregistration are likely to be less distorted than they could have been under a linear transformation, such as the publicly available and frequently used linear MNI stereotaxic method. They first define mixed-effects models with patterned variance-covariance matrices under a classical partition of total genetic variance into individual allele, within-locus and between-locus interactions. It is of interest to note that precursors of the compact mixed-effects models we employ today began with the statistical methods developed for very large-sample animal breeding experiments pioneered by Drs. Shayle Searle, Harold Henderson, David Harville and others. These methods include multilevel models, inversion formulas for large block-diagonal matrices, up- and down-dating formulas for regression diagnostics, and REML estimation. (Some of the principles and practice of the EM algorithm existed prior to the seminal paper by Drs. Art Dempster, Nan Laird and Don Rubin.) The very high dimension of brain imaging outcomes now calls for new, creative ways to combine what has been learned in population genetics with modern computer-intense inferential methods. This paper places wild bootstrap inference (Mammen (1993)) in competition with mixed-model based score tests derived by Newton-Raphson iteration and having asymptotic χ^2 distributions. Those readers interested in applications of the wild bootstrap in magnetic resonance diffusion tensor imaging (MR-DTI) may find the paper by Whitcher, Tuch, Wisco, Sorensen, and Wang (2008) useful. The authors use only the first two moments of their data and thus avoid a multivariate Gaussian assumption; it would have been informative to see results under that assumption and a distributional test. The authors provide log p-value maps of significant sex-age interactions on cortical thickness that have been corrected for testing multiplicity. Their tests for the effects of genetic variation did not yield any significant results after correction. The authors state that a larger sample size may be needed to detect genetic

effects on cortical thickness if they exist. The depth and breadth of the pedigree structure of a larger sample would also play a major role in improving the sensitivity of their method. The authors' contribution is an example of an important clinical application of classical and modern statistical procedures to the use of brain imaging in population genetic studies.

Concluding Remarks

All of the authors and *Statistica Sinica* should be commended for writing and publishing this collection of papers in this special Brain Science issue. There are important contributions here. Many statisticians interested in working in this vast area will learn some fundamental concepts and current findings in neuroscience and neuroscientists will now be more familiar with our methods that can help them design and conduct the best studies that are scientifically possible with us. There are valid institutional and personal reasons why statistical articles sometimes employ examples of brain data as seemingly an afterthought, without taking the time needed to more fully understand some of the underlying brain science that motivates and directs the study. When statisticians working the area are able to spend some time in the field — in MRI and PET control rooms, observing or participating in clinical brain imaging studies, designing and conducting their own studies, looking through the microscope, having peer-to-peer conversations with MR physicists, neurologists, biologists, molecular geneticists, asking questions — then not only will they make their own mistakes but they will also obtain a personal measure of the large gap between statistical theory and practice that exists in present day brain science. We will see that for statistical thinking to maintain and advance its unique and vital position in brain research this gap needs to be filled more effectively. Acceptance of statistical and imaging neuroscience discoveries by the larger scientific and medical community and application of the knowledge gained to the development of effective ways to improve people's lives depend critically on the quality of the research we do.

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