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THE MIND RESEARCH NETWORK—MENTAL ILLNESS AND NEUROSCIENCE DISCOVERY GRANT

Final Report
07/01/12–09/12/13

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Compiled by:
MRN Office of Research

PREPARED FOR THE UNITED STATES DEPARTMENT OF ENERGY / OFFICE OF BIOLOGICAL AND ENVIRONMENTAL RESEARCH PROGRAM

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OVERVIEW

The U.S. Department of Energy (DOE) originally awarded Grant No. DE-FG02-08ER64581 with funding in the amount of $11,478,000 to The Mind Research Network (MRN). This award was made in response to a competitively reviewed proposal submitted by the organization to continue its research in methods for improving the diagnosis and treatment of mental illness and brain disorders. The MRN proposal was initially approved for one year (04/01/2008 to 03/31/2009). Subsequent to award, an extension to the period of performance–to 09/30/2009–was requested and approved. Additional funding in the amount of $11,098,296 was awarded and the period of performance was extended to 09/28/2012. In September of 2012, a no cost extension was approved through 09/12/2013. The total value of the award was $22,576,296. This progress report covers the period 07/01/2012 to 09/12/2013.

As in past years, the scientific and technological programs of the MRN reflect DOE missions in basic science and associated instrumentation, computational modeling, and experimental techniques. MRN's technical goals - to develop and apply integrated, multi-modality functional imaging techniques - derive from a decade of DOE-supported research and technology development.

The period 2006 through 2009 represented significant growth in the organization, while activity in 2010 and 2011 leveled off and stabilized at the new "norm" for MRN. At 09/12/2013, MRN held 81 separate contracts and/or grants representing a total value of $31.1 M. Of these figures, 34 were "R01" grants, awarded by the National Institutes of Health. MRN employed 105 staff and 59 volunteers. MRN continues to occupy Pete and Nancy Domenici Hall (~33,000 square feet), on the medical school campus of the University of New Mexico (UNM).

MRN now enjoys status as a major biotech organization in the Albuquerque, N.M. region, through its creation of well-paying, high-tech jobs for the economy. The organization was recognized by *The New Mexico Business Weekly*'s *Book of Lists* as the number two biotechnology company in the state. As of November of 2011, Lovelace Research Respiratory Institute (LRRI) partnered with MRN. LRRI is a private, biomedical research organization dedicated to improving public health through scientific research. MRN became a subsidiary affiliate of the flagship company, LRRI. The joining of the two research institutions created new collaborative research opportunities for both organizations and offered new paths of funding for both LRRI and MRN. The combined organizations comprise the largest private biomedical company in New Mexico by more than $174 million in revenue, and are one of New Mexico's largest employers.

MRN investigators continued to excel in publishing, producing in 2012 a total of 200 peer-reviewed publications and many additional book chapters and conference abstracts.

During the period of performance, scientists at The Mind Research Network (MRN) continued their research into methods for improving the diagnosis and treatment of mental illness and other brain disorders. Recent research highlights include the following:

- The mobile research network has been expanded to include the deployment to a large animal non-human primate colony in New Mexico at the Lovelace Respiratory Research Institute to facilitate studies of animal models.
- Contract negotiations are currently underway with The Child Mind Institute in New York to provide imaging services.
- The 3T MRI will be used for our new Brain Safe Project, to study traumatic brain injury in competitive athletes.

- MRN continues to operate the MEG and MR scanners as service centers. Under a service center, all expenditures associated with operation of the activity must be recovered, including utilities, maintenance, etc.
- The child-friendly, high density EEG system has been fully integrated with the MEG system. This system does not require standard scalp preparation and children can be prepared for an EEG in <15 minutes compared to >60 minutes of traditional high-density EEG systems. This system is available to all investigators for use with children and adults. This provides additional support for the MEG/EEG core by facilitating multi-modal MEG/EEG studies. This system is now being used for both an adult study on schizophrenia and a study of prematurely born infants (3 & 6 months of age).

The MRN research program is organized as follows:

Areas of excellence:

- Psychosis
- Addiction
- Neuroinformatics
- Clinical Forensics

Areas of development:

- Neurodevelopment
- Traumatic Brain Injury
- Neurosystems for National Security

In addition to the research areas shown above, portions of the remaining DOE funding were used to fund small pilot projects. Progress reports for each of those projects are also included.

This progress report has been prepared to respond to all required performance reporting criteria for the projects advanced under DOE support. Given that the report encompasses multiple projects, selected information has been consolidated in appendices for ease of reading. All publications related to specific projects are included in the comprehensive publications list for 2012 (Appendix A). In addition, appendices include all grants awarded (Appendix B) and pending proposals (Appendix C), significant equipment purchases (Appendix D), and invention/patent applications (Appendix E). Human research performance metrics are provided to the DOE separately, in a comprehensive report submitted each October to the *Human Subjects Research Database* maintained by the Oak Ridge Institute for Science and Education.

During the period covered in this report actual expenditures were approximately $2 million. There have not been any significant changes in the schedule, key personnel, or consortium arrangements. No technology has been transferred. Our network of research collaborators now includes: Georgia State University, Hartford Hospital, Nathan Kline Institute, Rand Corporation, Rosalind Franklin University of Medicine and Science, University of California – San Francisco, University of Colorado – Boulder, University of Chicago, University of New Mexico, University of Texas at Dallas, University of Wisconsin, Yale University, and Washington University.

PSYCHOSIS (FORMERLY SCHIZOPHRENIA) RESEARCH

Since the organization's inception, psychosis, schizophrenia and other psychotic disorders have been a primary research focus for MRN and its partners. The Mind Clinical Imaging Consortium (MCIC) was a multi-institutional study of first episode and chronic schizophrenia patients, the goal of which was to identify neural markers for disease onset and progression through multi-modal brain imaging. Under this program, one of the world's largest, most comprehensive data sets incorporating anatomical and functional MRI, MEG, and immortalized cell lines for genetic data was established. This dataset produces numerous publications each year and continues to be mined for valuable information. MRN continues to build upon the founding consortium by adding new collaborations and expanded research methods.

MRN has made multiple important contributions to the field. For example, by combining expertise in psychotic disorders and neuroinformatics, a new diagnostic tool was developed to accurately classify patients with schizophrenia or bipolar disorder. These disorders often exhibit very similar initial symptoms and are therefore difficult to discriminate, resulting in an incorrect course of treatment in many cases. This finding may eventually provide clinicians with a method to accurately differentiate and diagnose these disorders earlier in the disease progression, thus resulting in the application of the most effective treatments sooner leading to a better long-term prognosis. Additional mechanisms developed include methods for identifying linked changes in large-scale genetic and functional brain imaging data. Using these tools, the relationships between multiple genetic markers and fMRI brain activation patterns in schizophrenia were identified. In studying the relationship between brain structure and function, ongoing research indicates that the relationship is different between schizophrenia patients and healthy controls. This suggests that there may be a fundamental difference in the brain organization of individuals with schizophrenia. Other MRN supported research in the field has found differences in the structural and functional organization of brain networks, as well as differences in gray and white matter, genetic abnormalities, attention, and the effects of smoking on blood flow.

MRN was selected by the National Institutes of Health (NIH) for a five-year, $11.6 million Institutional Development (IDeA) grant to study the neural mechanisms of schizophrenia. The IDeA grant supports the development of a Center for Biomedical Research Excellence (COBRE) with funding from the NIH National Center for Research Resources. At the end of the initial award, MRN was granted another five year COBRE Phase II award. The COBRE projects use multimodal imaging and analysis methods developed at MRN to study the alterations of brain networks that contribute to the etiology of schizophrenia, and may someday be used in the early diagnosis of schizophrenia or predict treatment outcome. In addition, the COBRE draws upon our neuroinformatics infrastructure including automated analysis, fusion of multimodal imaging data, and database tools. COBRE involves a close collaboration with UNM and other MRN partners.

We continue to make progress in studying brain networks in schizophrenia. Numerous papers have been published over the years, in addition to some interesting findings related to the interaction of brain networks and how these different in patients versus controls. We also continue to develop diagnostic tools for classification of patients and controls using brain imaging data. Recent work has focused upon combining brain imaging and genetics data along with advanced techniques based upon machine learning.

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Current funding:

2 grants for a total of $8,090,139.51, which represents 25% of research funding.

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Project Title: Transcranial Direct Current Stimulation on Brain Chemistry
Investigator: Vincent Clark, Ph.D.
Reporting Period: 7/1/12 through 9/12/13
Reporting Status: **FINAL**

This study was designed to identify the effects of transcranial direct current stimulation (tDCS) on brain chemistry. Subject's brain chemistry was tested using magnetic resonance spectroscopy (MRS) within left and right parietal cortex, then tDCS was performed over right parietal cortex, and MRS was performed again. It was found that tDCS increased the concentration of a combination of glutamate and glutamine and increased N-acetyl aspartate under the electrode, but not in the opposite hemisphere.

No new publications to report.

ADDICTION RESEARCH

MRN addiction research has continued to flourish over the past year. Collaborative efforts have allowed the researchers to combine, pharmacological, brain stimulation, neuroimaging and genetic approaches to conduct translational efforts in addictions research. These approaches include identifying genes that influence the progression of addiction and identifying the neurobiological substrates associated with alcohol use severity, both of which may eventually be used to guide treatment and prevention efforts. In addition, these efforts include direct attempts to translate neuroimaging findings by using brain stimulation to reduce hazardous alcohol use and attention bias modification to treat cocaine dependence.

MRN scientists published several translational papers in the area of addiction, including studies that examined the genetic basis of addiction, studies that examined neural substrates related to substance use, studies that evaluated the development of better methods for treating addiction, and those that examined substance use and related health risk behavior (risky sexual behavior) in adolescents. In addition to the prolific and high quality of the publications, this research group has been active in attending and presenting data collected at the MRN at several key conferences this year, including the Society for Behavioral Medicine, the Research Society on Alcoholism (RSA), the Organization for Human Brain Mapping (OHBM), the American Psychological Association (APA), and the American College of Neuropsychopharmacology (ACNP). Finally, the addictions research team has been quite successful in applying for and being awarded funding, with two continuing R01s and a new supplement to an existing R01 (Hutchison) awarded in 2013, an R21 (Mayer) awarded in 2012, and two new R21s (Claus) awarded in 2013. In addition, a contract was awarded from the FDA to LBERI to investigate the behavioral pharmacology of cigars, on which Dr. Claus is the senior scientist.

Current funding:
21 grants for a total of $7,724,981, which represents 24% of research funding.

Future goals for the addiction research area include the following:

- Submit six addiction grants across the age span (from youth through adults) to study the following:
  - Alcohol use and craving,
  - Health risk behavior including tobacco use, compulsive over-eating, and cannabis use,
  - Neural mechanisms of behavior change in alcohol dependence
  - Brain stimulation and cognitive retraining of addictive behaviors, and
  - Individual differences in the acute effects of alcohol on neural response
- Submit 15 manuscripts for publication.

Project Title: Intertemporal Choice and Contingency Learning Mechanisms in Binge Drinkers
Investigator: Eric Claus, Ph.D.
Reporting Period: 7/1/12 – 9/12/13
Reporting Status: **FINAL**

Summary/Abstract:

The goals of this study are to examine decision making and reward anticipation in heavy drinkers to determine 1) neural responses during anticipation and experience of taste rewards and punishments and 2) neural mechanisms that underlie decisions between immediately available alcohol and alcohol delivered after a delay. To accomplish these goals, 40 participants will be recruited who are either binge drinkers or social drinkers to compare brain activation during tasks that require decision to be made about alcohol. We expect that binge drinkers will show increased recruitment of brain regions involved in reward processing during the selection of immediately available alcohol rewards compared to social drinkers. In contrast, we expect to find reduced activation during the experience of unpleasant taste stimuli in binge drinkers compared to social drinkers. These results would further support claims that individuals at risk for developing alcohol dependence have disruptions to systems involved in assigning value to natural rewards, and that alcohol is able to obtain enhanced reward value that ultimately biases decisions toward alcohol use.

Aim 1: To investigate the neural responses during anticipation and experience of taste rewards and punishments in heavy drinkers
We hypothesize that during the anticipation of an alcohol reward, subjects will activate the ventral striatum and that greater problems with alcohol will show a *positive* correlation with ventral striatum activation. In addition, we expect that anticipation of negative outcomes will activate lateral orbitofrontal cortex (OFC) and insula, and that a *negative* relationship will emerge between activation in these areas and alcohol use severity.

Aim 2: To determine the neural mechanisms that underlie decisions between immediately available alcohol and alcohol delivered after a delay
We expect that selection of an immediately available reward such as alcohol will strongly activate ventral striatum and anterior cingulate cortex (ACC), whereas choosing to delay consumption will activate lateral OFC and dorsolateral prefrontal cortex (DLPFC). In addition, we expect that severity of alcohol use problems will be associated with the tendency to choose to consume alcohol immediately, and that activation of ventral striatal areas will be a key predictor of both impulsive choice and problematic drinking.

Progress since last progress report
Since the last progress report, an R21 application to NIH using pilot data from this project was funded. The project title is "Behavioral Regulation and Real-Time Reinforcement in Alcohol Dependence", and the project received $447,563 in total costs for a 2-year funding period.

In addition, an abstract/poster was submitted the annual Research Society on Alcoholism conference presenting the findings that address Aim 1 of the original research proposal. When comparing the anticipation of alcohol rewards to the anticipation of water, we found that participants showed enhanced response in ventral striatum as predicted, as well as anterior cingulate cortex and anterior insula. Comparison of the anticipation of negative outcomes to the anticipation of water outcomes showed similar patterns of response, consistent with our predictions.

NEUROINFORMATICS RESEARCH

In the past year, the neuroinformatics core is responsible for 61 peer-reviewed papers, 21 new grant submissions and over $7.5 million in NIH and NSF funding. We hosted a special issue on electronic data capture, in the Frontiers in Neuroinformatics Journal in which we published two papers on different aspects of our neuroinformatics capabilities. Approximately 30 more papers are in press, across data analysis methods, classification techniques, and applications in various biomedical domains.

MRN continues to develop and enhance its neuroinformatics software tools that enable investigators to manage their research data and projects. This permits MRN investigators to efficiently collect and analyze their data and selectively share data with others, leading to some of the largest, consistent fMRI samples available. The automated centralized analysis procedures for MRI data across all MRN studies provides a powerful tool for investigators to augment existing studies, serve as pilot data for novel data analyses or generate ideas for new projects. There have been considerable improvements in fMRI and diffusion imaging experiments by using the 32-channel coil and the multi-band processing sequences. Currently data analysis pipeline for these new data sets is being developed.

Data sharing methods have been under development to make the neuroimaging and other datasets available to the research community, for broader exposure and scientific benefit. A data catalog has been developed to allow users to see summaries of what data are available. The ability to select, anonymize, and package data for re-use has been developed, and is being wrapped into a querying tool for the research community to have access to the datasets without compromising subject confidentiality.

MEG auto-archiving is in place and we have continued to implement the automated MEG analysis during this year. The neuroinformatics core also focuses on translating new software tools into other research areas. Success in this area is evidenced by the number of journal articles published and funded grant proposals. For example, the analysis methods have been applied to schizophrenia, psychopathy, neurodevelopment, and addiction.

Current funding:
21 grants for a total of $5,180,249, which represents 16% of research funding.

Future goals for the Neuroinformatics area of research include:

- Continue to develop and extend tools for multimodal data and classification, supporting the research efforts refining the dysfunctions in psychosis, autism, addictions, post-traumatic stress disorder and traumatic brain injury.
- Continue to expand upon the real-time quality assurance and quality control procedures across all data acquisition and analysis within MRN.
- Submit multiple manuscripts disseminating novel algorithms, methods, informatics approaches, and applications, building upon the algorithm developments for combining different imaging modalities and different genetic data types.
- Roll-out the public query and data delivery system, while continuing to improve upon the real-time data exploration and reporting tools.
- Augment the neuroinformatics tools with flexible analysis techniques to enable rapid data selection and large-scale data mining.
- Develop new methods for integrating imaging, behavioral, and large-scale genetic data.
- Expand the neuroinformatics center to incorporate semantically meaningful data representations, to integrate with other neuroimaging centers and facilitate the translation of research results across animal and human neuroscience.

Project Title: MRI methods for measuring lung perfusion in smokers
Investigator: Arvind Caprihan, Ph.D.
Reporting Period: 7/1/12 – 9/30/13
Reporting Status: **FINAL**

Abstract: A method for measuring perfusion weighted images is proposed based on correlation between the MRI signal in the aorta and the lung. This method lets you calculate a delay image between the blood flow signal in the aorta and in the lung, which can potentially be a useful measure of pulmonary vasculature compliance in a diseased population. We compare results for a free-breathing RF spoiled turbo-flash sequence (TFL), a partial breath-hold TFL sequence, and a perfusion weighted image calculated as a difference of diastole and systole images for a HASTE sequence. The correlation method can also be implemented in the Fourier domain and is related the Fourier decomposition (FD) method proposed earlier by Bauman et al. [1].

Methods: The experiments on healthy subjects with IRB approval were done on a Siemens 3T Tim Trio scanner with the TFL sequence. The voxel size was 3.3x3.3 mm with a slice thickness of 14 mm, and TR/TE = 180/0.83ms. The data was obtained under free-breathing and partial breath-hold conditions. Partial breath-hold consisted of the subject holding the breath under expiration state as long as possible but being free to breath as needed. The total acquisition time was 60s. Data was also collected with an ECG gated HASTE sequence. All the images are registered to a reference image using the Siemens Lung registration program (fMRLung) described in Bauman et al. [1]. The relative

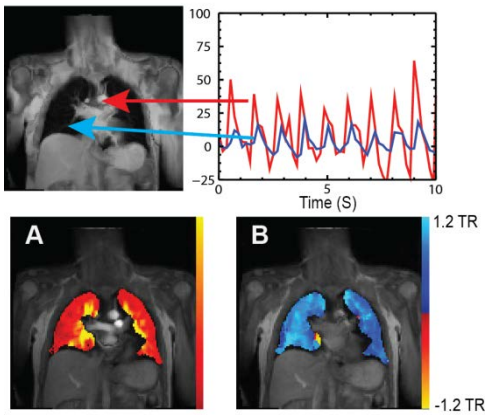

Figure 1. The signal in the lung and in the aorta is shown at the top. A) Relative perfusion image and B) the Delay image.

perfusion

$$RP = \max_{delay} \int A(t - delay)B(t)dt \Big/ \int A(t - delay)^2 dt$$

is the maximum value of the normalized inner product between the signal in the aorta $A(t)$ and the signal in the lung $B(t)$, after removing the respective means. The delay and the relative perfusion at resolutions below than sampling-interval (TR) is calculated by fitting a parabola around the integral value of the delay with maximum correlation.

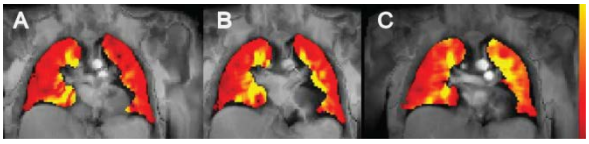

Figure 2. Perfusion weighted images: A) Free-breathing, B) Partial breath-hold, and C) HASTE difference image

Results: A comparison of the perfusion weighted images for the three methods is shown in Figure 2. There is no ground truth here to judge the accuracy of the respective perfusion weighted images. We used correlation between the aortic signal to the lung signal as a measure of goodness. 65% of voxels in the lung with partial breath-hold had higher correlations as compared to free breathing.

Discussion: At the current echo-time of TE = 0.83 ms for the TFL sequence, the HASTE images showed greater signal in the lung parenchyma and measured perfusion closer to lung walls. The partial breath-hold method gave better results than the free-breathing method in the sense of higher correlation between the lung and the aorta signal. This was to be expected because with partial breath-hold we have longer

date sets collected for almost the same lung position, thus improving lung registration results. The HASTE method requires ECG gating and breath-hold for short multiple periods of 15s. In the future we will have to understand the effect of different pleural pressures in the free breathing and partial breath-hold condition on pulmonary perfusion to correctly interpret these images.

Conclusion: Correlations between the signal in the lung and a reference signal allows perfusion weighted image and a delay image to be obtained. The sensitivity of these methods to monitor lung perfusion changes in diseased populations needs to be evaluated. The results of the TFL sequence will improve with shorter echo times. The delay image can only be calculated if the aorta is within the slice, while the relative perfusion image can be calculated for all slices, provided one slice includes the aorta.

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Stephen JM, Kodituwakku PW, Kodituwakku EL, Romero L, Peters AM, Sharadamma NM, **Caprihan** A, Coffman BA. Delays in Auditory Processing Identified in Preschool Children with FASD. Alcohol Clin Exp Res. 2012 Mar 28.

Hanlon FM, Houck JM, Klimaj SD, **Caprihan** A, Mayer AR, Weisend MP, Bustillo JR,Hamilton DA, Tesche CD. Frontotemporal anatomical connectivity and working-relational memory performance predict everyday functioning in schizophrenia. Psychophysiology. 2012 Aug

Ling, J., Merideth, F., **Caprihan**, A., Pena, A., Teshiba, T., Mayer, A.R., 2012. Head injury or head motion? Assessment and quantification of motion artifacts in diffusion tensor imaging studies. Hum Brain Mapp 33, 50-62.

Monnig, M.A., **Caprihan**, A., Yeo, R.A., Gasparovic, C., Ruhl, D.A., Lysne, P., Bogenschutz, M.P., Hutchison, K.E., Thoma, R.J., 2013. Diffusion tensor imaging of white matter networks in individuals with current and remitted alcohol use disorders and comorbid conditions. Psychol Addict Behav 27, 455-465.

Bessette, K.L., Nave, A.M., **Caprihan**, A., Stevens, M.C., 2013. White matter abnormalities in adolescents with major depressive disorder. Brain Imaging Behav.

Calhoun, V.D., Potluru, V.K., Phlypo, R., Silva, R.F., Pearlmutter, B.A., **Caprihan**, A., Plis, S.M., Adali, T., 2013a. Correction: Independent Component Analysis for Brain fMRI Does Indeed Select for Maximal Independence. PLoS One 8.

Calhoun, V.D., Potluru, V.K., Phlypo, R., Silva, R.F., Pearlmutter, B.A., **Caprihan**, A., Plis, S.M., Adali, T., 2013b. Independent component analysis for brain FMRI does indeed select for maximal independence. PLoS One 8, e73309.

Duncan, A.F., **Caprihan**, A., Montague, E.Q., Lowe, J., Schrader, R., Phillips, J.P., 2013. Regional Cerebral Blood Flow in Children From 3 to 5 Months of Age. AJNR Am J Neuroradiol.

Sanjuan, P.M., Thoma, R., Claus, E.D., Mays, N., **Caprihan**, A., 2013. Reduced white matter integrity in the cingulum and anterior corona radiata in posttraumatic stress disorder in male combat veterans: A diffusion tensor imaging study. Psychiatry Res 214, 260-268.

White, T., Ehrlich, S., Ho, B.C., Manoach, D.S., **Caprihan**, A., Schulz, S.C., Andreasen, N.C., Gollub, R.L., Calhoun, V.D., Magnotta, V.A., 2013. Spatial characteristics of white matter abnormalities in schizophrenia. Schizophr Bull 39, 1077-1086.

Aine, C.J., Sanfratello, L., Adair, J.C., Knoefel, J.E., Qualls, C., Lundy, S.L., **Caprihan**, A., Stone, D., Stephen, J.M., 2014. Characterization of a normal control group: Are they healthy? Neuroimage 84, 796-809.

Damaraju, E., **Caprihan**, A., Lowe, J.R., Allen, E.A., Calhoun, V.D., Phillips, J.P., 2014. Functional connectivity in the developing brain: A longitudinal study from 4 to 9months of age. Neuroimage 84, 169-180.

Haney-Caron, E., **Caprihan**, A., Stevens, M.C., 2014. DTI-measured white matter abnormalities in adolescents with Conduct Disorder. J Psychiatr Res 48, 111-120.

Funded Grants

1R01AG029495 (PI: Aine) 09/15/2008 - 08/31/2013
NIH/National Institute on Aging
Imaging the Development of Memory Strategies in Aging
This project attempts to: 1) demonstrate the development of memory strategies across adulthood as maturational changes in white matter tracts occur and 2) differentiate between healthy successful aging versus normal aging, or aging accompanied by disease processes such as hypertension and type 2 diabetes. Multimodal imaging measures (DTI, MEG, morphometrics) will help delineate the neural circuits that are compromised in working spatial and verbal memory circuits.
Role: Develop and analyze diffusion tensor imaging data to study aging

Delle Foundation Donation (PI: Caprihan) 02/13/2009 – 12/31/2013
Private Donation
Development and Neuroanatomy in Young Children: A Longitudinal Analysis
The goal of this project is to establish normal pattern of regional brain development in infants and toddlers and to understand the relationship between neuroimaging, basic environmental factors and developmental skill acquisition, focusing on early working memory.
Role: Principal Investigator

R01MH065304 (PI: Canive) 1/1/2010 – 12/31/2013
NIH
Schizophrenia Gating Deficit Mechanisms: Extending the Circuit
Instruct and supervise technicians in data collection, oversee the data collection specific to DTI and to perform the necessary DTI analyses.
Role: Principal Investigator on Subaward

R01HD059856 (PI: Ohls) 4/6/2010 - 2/29/2014
NIH
Brain Imaging and Developmental Follow-Up of Infants with Erythropoietin
Dr. Caprihan is responsible for all aspects of MRI done at MRN. He will be responsible for analysis of MRI data and the multivariate analysis to combine data from different modalities. He will also write papers for dissemination of the information.
Role: Principal Investigator on Subaward

1 P20 RR021938-01 (PI: Calhoun) 10/01/2008 - 06/30/2013
Neural mechanisms of schizophrenia: Use of Multiple Tools to Examine Dysfunctions in Neural Integration (COBRE)
This project examines functional and anatomical connectivity in schizophrenia using multimodal neuroimaging analyses.
Role: Co-Investigator

2R01 NS052305-06A1 (PI: Rosenberg) 09/01/2012 – 8/31/2017
NIH
Biomarkers for White Matter Injury in Mixed and Vascular Cognitive Impairment
Dr. Arvind Caprihan will assist with automating existing analysis methods for spectroscopy and permeability measurement. In addition, diffusion tensor imaging and cerebral blood flow measurements will be done and related to permeability in subjects with vascular cognitive impairment. MRN will provide a software engineer to assist Dr. Caprihan,. MRN will also provide access to its Siemens 3T Trio MRI.
Role: Co-Investigator

FORENSICS AND SOCIAL COGNITION RESEARCH

MRN research in forensic populations experienced another impressive year of growth. The mobile imaging laboratory was used in local prisons and in four collaborative sites in Wisconsin studying adult men and women with antisocial and addiction issues. To date, data has been collected from over 1700 inmates in over 2500 imaging sessions, making this the largest brain imaging data set ever collected from forensic populations. Over the course of the funding period, ~53 papers published, thereby expanding the literature on this research area of excellence. The manuscripts were published in top tier journals, including the *Archives of General Psychology* and *Journal of Abnormal Psychology*. Key results include our finding of structural brain abnormalities in paralimbic regions in individuals diagnosed as psychopathic. Also Shane and colleagues reported that adult cocaine abusers show capacity to voluntarily reduce neural response within brain regions underlying cocaine craving. The latter findings have direct implications for how cocaine dependence may be treated. Data collected is also being used to support the submission of several new NIH grant applications, including several multi-year protocols focused on improving diagnostic and treatment opportunities for substance abusers and violent/sexual offenders.

The Mobile MRI Research Network received two large NIH sub-awards from the University of Chicago (PI Jean Decety) and Rosalind Franklin University (PI David Kosson). These sub-awards represent the initial success of the concept to deploy the MRN mobile MRI around the country as a national resource to access populations of individuals who would otherwise not be accessible to brain imaging studies. The data generated from these projects is currently being written up and several manuscripts that are in press are listed here. Future studies are planned where the mobile MRI will be deployed to military bases to study Post-Traumatic Stress Disorder and traumatic brain injury.

Current funding:
5 grants for a total of $5,815,819, which represents 18% of research funding.

Future goals for the clinical forensics research area include the following:

- Submit renewals for existing NIH grants.
- Acquire new NIH grants (grants pending in adult morality, sexual offenders, substance abuse).
- Conduct genetic studies in forensic populations to help develop novel treatment approaches.

Publications (2011-2013):

1. Swanson, N., Eichele, T., Pearlson, G.D., Kiehl, K.A. & Calhoun, V.D. (2011). Lateral differences in the default mode network in healthy controls and schizophrenia patients. *Human Brain Mapping*, 32, 654-64.

2. Harenski, C.L. & Kiehl, K.A. (2011). Emotion and morality in psychopathology. *Emotion Review, 3, 299-301.*

3. Kiehl, K.A., & Hoffman, M.B. (2011). The criminal psychopath: History, neuroscience and economics. *Jurimetrics: The Journal of Law, Science, and Technology, Summer 2011, 355-397.*

4. Cope, L.M., Schaich Borg, J., Harenski, C.L., Sinnott-Armstrong, W., Lieberman, D. Nyalakanti, P.K., Calhoun, V.D., & Kiehl, K.A. (2010). Hemispheric asymmetries during processing of immoral stimuli. *Frontiers in Evolutionary Neuroscience*, 2, 1-14.

5. Claus, E.D., Kiehl, K.A., & Hutchison, K.E. (2011). Determinants of impulsive choice: Neural mechanisms and relationship with alcohol use problems. *Alcoholism: Clinical and Experimental Research, 35:* 1209-1219. PMCID: PMC3158325

6. E. Allen, E., Erhardt, E., Damaraju, E., Gruner, W., Segall, J., Silva, R., Havlicek, M., Rachakonda, S., Fries, J., Kalyanam, R., Michael, A., Turner, J., Eichele, T., Adelsheim, S., Bryan, A., Bustillo, J., Clark, V., Feldstein, S., Filbey, F., Ford, C., Hutchison, K., Jung, R., Kiehl, K.A., Kodituwakku, P., Komesu, Y., Mayer, A., Pearlson, G.D., Phillips, J., Sadek, J., Stevens, M., Teuscher, U., Thoma, R.J., & Calhoun, V.D. (in press). A baseline for the multivariate comparison of resting state networks (2011). *Frontiers in Systems Neuroscience, 5* (Article 2), 1-23.

7. Schaich Borg, J., Sinnott-Armstrong, W., Calhoun, V.D. & Kiehl, K.A. (2011). Neural basis of moral verdict and moral deliberation. *Social Neuroscience, 6 (4),* 398-413.

8. Aharoni, E., Antonenko, O, & Kiehl, K.A. (2011). Disparities in the moral values of adult criminal offenders: The role of psychopathy. *Journal of Personality Disorders, 45,* 322–327.

9. Aharoni, E., Sinnott-Armstrong, W., & Kiehl, K.A. (2011). Can psychopathic offenders discern moral wrongs? A new look at the Moral/Conventional distinction. *Journal of Abnormal Psychology* (epub advanced online edition)

10. Shannon, B.J., Raichle, M.E., Snyder, A.Z., Fair, D.A., Mills, K.L., Zhang, D., Bache, K., Calhoun, V.D., Nigg, J.T., Nagel, B.J., Stevens, A.A. & Kiehl, K.A. (2011). Premotor functional connectivity predicts impulsivity in juvenile offenders. *Proceedings of the National Academy of Science (PNAS), 1-5 (early edition).*

11. Allen, E., Liu, J., Kiehl, K.A., Gelernter, J., Pearlson, G.D., Perrone-Bizzozerod, N.I., & Calhoun, V.D. (2011). Components of cross-frequency modulation in healthy and disease. *Frontiers in System Neuroscience, 5* (Article 59), 1-16.

12. Edwards, B., Calhoun, V.D., & Kiehl, K.A. (2012). Joint ICA of ERP and fMRI during error-monitoring. *Neuroimage, 59,* 1896–1903.

13. Yu, Q., Sui, J., Rachakonda, S., He, H., Gruner, W., Pearlson, G.D., Kiehl, K.A., & Calhoun, V.D. (2011). Altered topological properties of functional network connectivity in schizophrenia during resting state: A small-world brain network study. *PLoS ONE*, 6 (9), 1-12.

14. Shoemaker, J.M., Holdsworth, M.T., Aine, C., Calhoun, V.D., de La Garza, R., Feldstein Ewing, S.W., Hayek, R., Mayer, A.R., Kiehl, K.A., Petree, L.E., Sanjuan, P., Scott, A., Stephen, J., & Phillips, J.P. (2011). A practical approach to incidental findings in neuroimaging research. *Neurology*, 77, 2123-2127.

15. Harenski, C.L., Harenski, K.A., Shane, M.S., & Kiehl, K.A. (2012). Neural development of mentalizing in moral judgment from adolescence to adulthood. *Developmental Cognitive Neuroscience,* 2, 162–173.

16. Harenski, C. L., Thornton, D. M., Harenski, K. A., Decety, J., & Kiehl, K. A. (2012). Increased fronto-temporal activation during pain observation in sexual sadism: Preliminary findings. *Archives of General Psychiatry*, 69, 283-292.

17. Motzkin, J., Newman, J.P., Kiehl, K.A., & Koenigs, M. (2011). Reduced prefrontal connectivity in psychopathy. *Journal of Neuroscience*, 31(48), 17348-17357.

18. Calhoun, V.D., Sui, J., Kiehl, K.A., Turner, J., Allen, E., & Pearlson, G.D. (2012). Exploring the psychosis connectome: Default mode regions serve as hub to other intrinsic networks in schizophrenia and bipolar disorder. *Frontiers in Neuropsychiatric Imaging and Stimulation*, 1 (Article 75), 1-13.

19. Khullar, S., Michael, A.M., Cahill, N.D., Kiehl, K.A., Pearlson, G., Baum, S.A., & Calhoun, V.D. (2011). ICA-fNORM: Spatial normalization of fMRI data using intrinsic group-ICA. *Frontiers in Systems Neuroscience*, 5 (Article 93), 1-18.

20. Aharoni, E., Sinnott-Armstrong, W., & Kiehl, K.A. (2012). Can psychopathic offenders discern moral wrongs? A new look at the Moral/Conventional distinction. Journal of Abnormal Psychology, 121 (2), 484-497. Ermer, E., Cope, L.M., Nyalakanti, P.K., Calhoun, V.D., & Kiehl, K.A. (2012). Aberrant paralimbic gray matter in criminal psychopathy. Journal of Abnormal Psychology, 121 (3), 649-658.

21. Anderson, N.E. & Kiehl, K.A. (2012). The psychopath magnetized: Insights from brain imaging. Trends in Cognitive Science (TICS), 16, 52-60.

22. Ermer, E. Kahn, R., Salovey, P. & Kiehl, K.A. (2012). Emotional intelligence in incarcerated men with psychopathic traits. Journal of Personality and Social Psychology, 103 (1), 194-204.

23. Yu, Q., Plis, S.M., Erhardt, E.B., Allen, E.A., Kiehl, K.A., Pearlson, G.D., & Calhoun, V.D. (2012). Modular organization of functional network connectivity in healthy controls and patients with schizophrenia during the resting state. Frontiers in Systems Neuroscience, 5, (103), 1-16.

24. Fink, B.C., Tant, A., Tremba, K., & Kiehl, K.A. (2012). Assessment of psychopathic traits in a youth forensic sample: A methodological comparison. Journal of Abnormal Child Psychology, 40 (6), 971-986.

25. Ly, M, Kirk, G.R., Newman, J.P., Kiehl, K.A., & Koenigs, M. (2012). Cortical thinning in psychopathy. American Journal of Psychiatry, 169 (7), 684-687.

26. Baskin-Sommers, A.R., Curtin, J.J, Larson, C.L., Stout, D, Kiehl, K.A. & Newman, J.P. (2012). Characterizing the anomalous cognition-emotion interactions in externalizing. Biological Psychology, 91 (1), 48-58.

27. Du, W., Li, H., Calhoun, V.D., Ma, S., Eichele, T., Kiehl, K.A., Pearlson, G.D., & Adali, T. (2012). High classification accuracy for schizophrenia with rest and task fMRI data. Frontiers in Human Neuroscience, 6, 145, 1-12.

28. Juarez, M., Kiehl, K.A., & Calhoun, V.D. (2012). Intrinsic limbic and paralimbic networks are associated with criminal psychopathy. Human Brain Mapping

29. Arbabshirani, M. R., Havlicek, M., Kiehl, K.A., Pearlson, G.D., & Calhoun, V.D. (in press) Functional network connectivity during rest and task conditions: A comparative study. Human Brain Mapping

30. Clark, V.P., Beatty, G., Anderson, R.E., Kodituwakku, P., Phillips, J., Lane, T.D.R., Kiehl, K.A, Calhoun, V.D. (in press). Reduced fMRI activity predicts relapse in patients recovering from stimulant dependence. Human Brain Mapping

31. Decety, J., Skelly, L.R., & Kiehl, K.A. (2013). Brain response to empathy-eliciting scenarios in incarcerated psychopaths. Archives of General Psychiatry, 70, 638-645.

32. Ermer, E. Cope, L.M., Nyalakanti, P.K., Calhoun, V.D., & Kiehl, K.A. (2013). Aberrant paralimbic gray matter in incarcerated male adolescents with psychopathic traits. Journal of the American Academy of Child and Adolescent Psychiatry, 52, 94-103.

33. Aharoni, E. & Kiehl, K.A. (in press). Evading justice: Quantifying criminal success in incarcerated psychopathic offenders. Criminal Justice and Behavior

34. Sui, J., He, H., Pearlson, G.D., Adali, T., Kiehl, K.A., Yu, Q., & Calhoun, V.D. (in press). Three-Way (N-way) fusion of brain imaging data based on mCCA+jICA and its application to discriminating schizophrenia. Neuroimage

35. Cope, L.M., Shane, M.S., Segall, J.M., Nyalakanti, P.K., Stevens, M.S., Pearlson, G.D., Calhoun, V.D., & Kiehl, K.A. (2012). Examining the effect of psychopathic traits on gray matter volume in a community substance abuse sample. Psychiatry Research: Neuroimaging, 204, 91-100.

36. Yu, Q., Sui, J., Liu, J., Plis, S.M., Kiehl, K.A., Pearlson, G.D., & Calhoun, V.D. (in press). Disrupted correlation between low frequency power and connectivity strength of resting state brain networks in schizophrenia. Schizophrenia Research

37. Christodoulou, A.G., Kiehl, K.A., Feldstein Ewing, S.W., Bryan, A.D., & Calhoun, V.D. (in press). A quality control method for detecting and suppressing uncorrected residual motion in fMRI studies. Magnetic Resonance Imaging

38. Aharoni, E., Vincent, G., Harenski, C., Calhoun, V.D., Sinnott-Armstrong, W., Gazzaniga, M.S., & Kiehl, K.A. (2013). Neuroprediction of future re-arrest. Proceedings of the National Academy of Science (PNAS), 110 (15), 6223-6228.

39. Saks, M.J., Schweitzer, N.J., Aharoni, E., & Kiehl, K.A. (in press). The impact of neuroimages in the sentencing phase of capital trials. Journal of Empirical Legal Studies

40. Schaich Borg, J., Kahn, R.E., Sinnott-Armstrong, W., Kurzban, R., Robinson, P.H., & Kiehl, K.A. (in press). Subcomponents of psychopathy have opposing contributions to punishment judgments. Journal of Personality and Social Psychology

41. Motzkin, J.C., Baskin-Sommers, A., Curtin, J., Newman, J.P., Kiehl, K.A. & Koenigs, M. (in press). Neural correlates of substance abuse: Reduced functional connectivity between areas underlying reward and cognitive control. Social, Cognitive, and Affective Neuroscience (SCAN).

42. Larson, C.L., Baskin-Sommers, A.R., Stout, D.M., Balderston, N.L., Schultz, D.H., Curtin, J.J., Kiehl, K.A., & Newman, J.P. (in press). The interplay of attention and emotion: Top-down attention modulates amygdala activation in psychopathy. Cognitive, Affective, & Behavioral Neuroscience

43. Steele, V., Aharoni, E., Munro, G.E., Calhoun, V.D., Nyalakanti, P., Stevens, M.S., Pearlson, G.D., & Kiehl, K.A. (in press). A large scale (n=102) functional neuroimaging study of response inhibition and error-processing. Behavioral Brain Research

44. Kiehl, K.A. & Lushing, J. (2013). Psychopathy. Scholarpedia. A peer-reviewed encyclopedia. www.scholarpedia.org/article/Psychopathy

45. Arbabshirani, M., Kiehl, K.A., Pearlson, G.D., & Calhoun, V.D. (in press). Classification of schizophrenia patients based on resting-state functional network connectivity. Frontiers in Brain Imaging Methods.

46. Decety, J., Chen, C., Harenski, C.L., & Kiehl, K.A. (in press). An fMRI study of affective perspective taking in individuals with psychopathy: Imagining another in pain does not evoke empathy. Frontiers in Human Neuroscience

47. Fryer, S.L., Woods, S.W., Kiehl, K.A., Calhoun, V.D., Pearlson, G.P., Roach, B.J., Ford, J.M., Srihari, V.H., McGlashan, T.H. & Mathalon, D.H. (in press). Deficient suppression of default mode regions during working memory in individuals with early psychosis and at clinical high-risk for psychosis. Frontiers in Schizophrenia

48. Steele, V.R., Fink, B.C., Mauer, J.M., Arabshirani, M.R., Wilber, C.H., Jaffe, A.J., Sidz, A.,Pearlson, G.D., Stevens, M.C., Calhoun, V.D., Clark, V.P., & Kiehl, K.A. (in press). Brain potentials predict completion of substance abuse treatment. Biological Psychiatry

49. Cope, L.M., Ermer, E., Nyalakanti, P.K., Calhoun, V.D., & Kiehl, K.A. (in press). Paralimbic gray matter reductions in incarcerated adolescent females with psychopathic traits. Journal of Abnormal Child Psychology

50. Yu, Q., Sui, J., Kiehl, K.A., Pearlson, G.D., & Calhoun, V.D. (in press). State-related functional integration and functional segregation brain networks in schizophrenia. Schizophrenia Research

51. Castro, E., Gomez-Verdejo, V., Martinez-Ramon, M., Kiehl, K.A. & Calhoun, V.D. (in press). A multiple kernel learning approach to perform classification of groups from complex-valued fMRI data analysis: Application to schizophrenia. Neuroimage

52. Decety, L., Skelly, L. R., Yoder, K. J., & Kiehl, K.A. (in press). Neural processing of dynamic facial expressions of emotion in psychopaths. Social Neuroscience

Presentations:

1. Kiehl, K.A. (February, 2012). *The criminal psychopath magnetized: Implications of brain imaging for psychology, medicine, law and policy.* Neuroscience and Public Policy Program, University of Wisconsin-Madison http://npp.wisc.edu/. Madison, WI. Invited speaker.

2. Kiehl, K.A. (April, 2012). *The neuroscience of the criminal psychopath: Any implications for law?* Boston Society of Neurology and Psychiatry, Harvard Medical School. Boston, MA. Invited Keynote Speaker.

3. Kiehl, K.A. (April, 2012). *The criminal psychopath magnetized: Implications of brain imaging for psychology, medicine, law and policy*. Duke University Law School. Invited speaker.

4. Kiehl, K.A. (April, 2012). *The Legal Implications of Criminal Psychopathy.* Federal judicial education seminar, National Workshops for U.S. Magistrate Judges, Organized by the National Federal Judicial Center in Washington, D.C., Miami, FL. Invited speaker.

5. Kiehl, K.A. (July, 2012). *The Legal Implications of Criminal Psychopathy.* Federal judicial education seminar, National Workshops for U.S. Magistrate Judges, Organized by the National Federal Judicial Center in Washington, D.C., Denver, CO. Invited speaker.

6. Kiehl, K.A. (August, 2012). *The Psychopath.* Invited paper, Google/Nature/O'Reily Sci Foo Conference, Google Campus, Mountain View, CA.

7. Kiehl, K.A. (September, 2012). *The usual suspects magnetized: When law and neuroscience collide.* PAL lecture series, Department of Psychology, University of New Mexico, Albuquerque, NM.

8. Kiehl, K.A. (October, 2012). *The criminal psychopath magnetized: Insights from brain imaging.* Grand Rounds presentation to the Department of Psychiatry, Duke University, Durham, NC. Invited speaker.

9. Kiehl, K.A. (October, 2012). *The criminal psychopath magnetized: Insights from brain imaging.* Grand Rounds presentation to psychiatric staff at Central Mental Hospital, Duke University/University of North Carolina residents program. Invited speaker

10. Kiehl, K.A. (October, 2012). *Roundtable discussion on law and neuroscience*. Seminar on future tense, The New America Foundation, Washington, DC. Invited speaker.

11. Kiehl, K.A. (February, 2013). *The cognitive neuroscience of criminal psychopaths*. South Carolina Psychiatric Association 2013 Annual Conference. Charleston, SC. Invited speaker.

12. Kiehl, K.A. (March, 2013). *The science of psychopaths: Assessment, recidivism, neuroscience, and treatment.* Forensic Mental Health Association of California (FMHAC). Monterrey, CA. Invited Keynote speaker.

13. Kiehl, K.A., (May, 2013). *Psychopaths and the Law: Assessment, Recidivism, and Neuroscience*. Nevada Federal District Conference for Federal Judges, Las Vegas, NV. Invited Keynote speaker.

14. Kiehl, K.A., (May, 2013). *The Usual Suspects Magnetized: When Law and Neuroscience Collide*. Alaska Bar Convention. Juneau, AK. Invited Keynote speaker.

15. Kiehl, K.A. (May, 2013). *Psychopaths and the Law: Assessment, Recidivism and Treatment.* Alaska Bar Convention. Juneau, AK. Invited keynote speaker.

16. Kiehl, K.A. (May, 2013). *The Usual Suspects Magnetized: When Law and Neuroscience Collide.* New Mexico Bar Association. Judicial Education Seminar. Albuquerque, NM. Invited lecture by Judge Ronald Kennedy, New Mexico Court of Appeals.

17. Kiehl, K.A., (June, 2013). *The Usual Suspects Magnetized: When Law and Neuroscience Collide*. Santa Barbara Judicial Meeting, Santa Barbara, CA. Invited speaker.

18. Kiehl, K.A. (June, 2013). *The Usual Suspects Magnetized: When Law and Neuroscience Collide.* New Mexico Judicial Conclave. Albuquerque, NM. Invited Lecture.

19. Kiehl, K.A. (July, 2013). *Neuroscience and Crime*. Summer Institute in Cognitive Science, Lake Tahoe, CA. Invited speaker.

20. Kiehl, K.A. (November, 2013). Title TBD. New York University Child Study Center Grand Rounds. Invited Speaker.

Neurodevelopment Research

An emerging research area at MRN is developmental neuroscience. In 2011, a growing list of neurodevelopment papers were published, including: understanding the moderators of alcohol and drug self-report in adolescents, results identifying differences in brain development in children born prematurely and results identifying timing differences in sensory processing in young children and adolescents diagnosed with fetal alcohol spectrum disorder. Currently, MRN scientists are characterizing normal development from birth to 3 years of age using MRI, identifying atypical brain development in children diagnosed with fetal alcohol spectrum disorders, and identifying markers of atypical brain development in children diagnosed with an autism spectrum disorder to better tailor interventions to improve function in these children. This research effort is now funded by multiple NIH R01 and R21 grants. A new R01 was awarded to understand the impact of prenatal alcohol exposure on brain development in infants at 6 and 20 months of age.

Current funding:
10 grants for a total of $3,217,089, which represents 10% of research funding.

Future goals for the neurodevelopment area of research include:

- Apply methods to determine sensitivity and specificity of brain measures in the diagnosis of neurodevelopmental disorders.
- Submit grants to identify early markers for autism, continue work to evaluate and tailor autism treatments, identify early markers and evaluate treatment options for fetal alcohol spectrum disorders, characterize the effects of erythropoietin in premature infants, and study executive function in preterm infants.

Representative Publications

1. Funke ME, Moore K, Orrison WW Jr, Lewine JD. The role of magnetoencephalography in “nonlesional” epilepsy. Epilepsia 2011 52(Suppl 4):10-14.
2. Phillips JP, Montague EQ, Aragon M, Lowe JR, Schrader RM, Ohls RK, Caprihan A. Prematurity affects cortical maturation in early childhood. Pediatr Neurol. 2011 45(4):213-9.
3. Burgess RC, Funke ME, Bowyer SM, Lewine JD, Kirsch HE, Bagic AI, American Clinical Magnetoencephalography Society Clinical Practice Guideline 2: presurgical functional brain mapping using magnetic evoked fields. J Clin Neurophysiol 2011, 28(4):355-61.
4. Lowe JR, Maclean PC, Caprihan A, Ohls RK, Qualls C, Vanmeters J, Phillips JP. Comparison of cerebral volume in children aged 18-22 and 36-47 months born preterm and term. J Child Neurol 2012 27(2):172-7.
5. Coffman BA, Kodituwakku P, Kodituwakku EL, Romero L, Sharadamma NM, Stone D, Stephen JM. Primary visual response (M100) delays in adolescents with FASD as measured with MEG. Hum Brain Mapp 2013 34(11):2852-62.
6. Stephen JM, Kodituwakku PW, Kodituwakku EL, Romero L, Peters AM, Sharadamma NM, Caprihan A, Coffman BA. Delays in auditory processing identified in preschool children with FASD. Alcohol Clin Exp Res 2012 36(10):1720-1727.
7. Damaraju E, Caprihan A, Lowe JR, Allen EA, Calhoun VD, Phillips JP. Functional connectivity in the developing brain: A longitudinal study from 4 to 9 months of age. Neuroimage 2014. 84:169-180.
8. Stephen JM, Coffman BA, Stone D, Kodituwakku PW. Differences in MEG gamma oscillatory power during performance of a prosaccade task, Frontiers Hum Neurosci. In print.
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TRAUMATIC BRAIN INJURY RESEARCH

Mild traumatic brain injury (mTBI) represents a natural union of MRN's interests in attention, advanced neuroimaging and clinical care. Although there has been much debate about long-term cognitive outcome following mTBI (Dikmen et al., 2009), a recent meta-analysis suggests a moderate effect size (d = .54) for executive, working memory and attention dysfunction during the semi-acute injury phase (Belanger et al., 2005). Laboratory measures suggest that attentional disengagement and selective attention are particularly affected (Drew et al., 2007; Halterman et al., 2006), providing a natural bridge for our in these fields. Second, routine clinical imaging scans (MRI and CT) are usually negative (Belanger et al., 2007; Bigler, 2008; Iverson, 2005), suggesting that these techniques are not sensitive to the pathophysiological changes commonly reported in animal injury models. As a result, alternative neuroimaging techniques are well-positioned to provide unique information about putative "silent lesions" and their impact on cognition functioning.

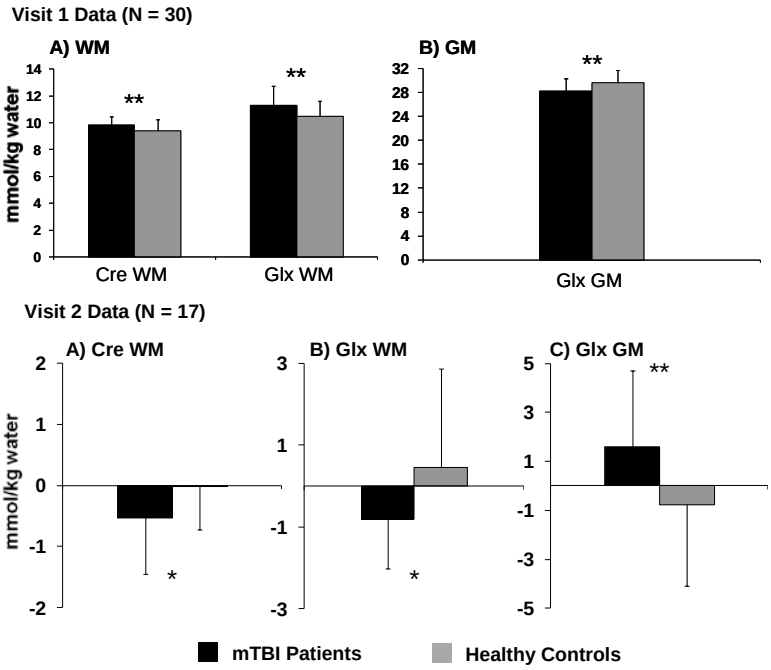

Figure 1: Magnetic spectroscopy data for both Visit 1 (top panel) and Visit 2 (bottom panel) in white (WM) and grey matter (GM) for patients (black bars) and controls (grey bar). Values are displayed for creatine (Cre) and glutamate/glutamine (Glx) with single (trend) or double (significant) asterisks denoting significance. Evidence of recovery was present for all metabolites during visit 2.

To this end, published data from MRN provides preliminary evidence of tissue-specific dysfunction and self-reported neuropsychiatric disturbances. This includes increased fractional anisotropy in white matter, likely secondary to cytotoxic edema, secondary inflammatory processes and potential structural alterations in neurofilaments and myelin (Mayer et al., 2010; Ling et al., 2011). White matter creatine and the combined glutamate/glutamine peak (Glx) are also increased (Figure 1), possibly indicative of increased energetics for cell repair (Gasparovic et al., 2009; Yeo et al., 2011). Grey matter is characterized by reduced Glx, potentially representing an adaptive response to avoid excitotoxicity (Gasparovic et al., 2009; Yeo et al., 2011). A tight coupling exists between the release of glutamate into the synaptic cleft, the cycling of glutamate and glutamine between neurons and astrocytes, and the hemodynamic response (Hyder et al., 2006; Mangia et al., 2009; Schummers et al., 2008). Therefore, it is no surprise that mTBI was also associated with hypoactivation of the frontoparietal reorienting network during spatial orienting (Mayer et al., 2009), hypoactivation within the dMFC and lateral PFC during multisensory selective attention (Mayer et al., manuscript in preparation), and behavioral deficits. The balance of intrinsic neuronal fluctuations also appears to be affected by injury (Figure 2), with reduced connectivity in the DMN and increased connectivity in frontoparietal attention networks (Mayer et al., 2011). Given that approximately 80% of the brain's energy budget is devoted to the cycling of glutamate and glutamine (Hyder et al., 2006; Shulman et al., 2004) and maintaining intrinsic neuronal activity

(Raichle and Mintun, 2006; Fox and Raichle, 2007), these functions may be particularly susceptible to diffuse injury following mTBI.

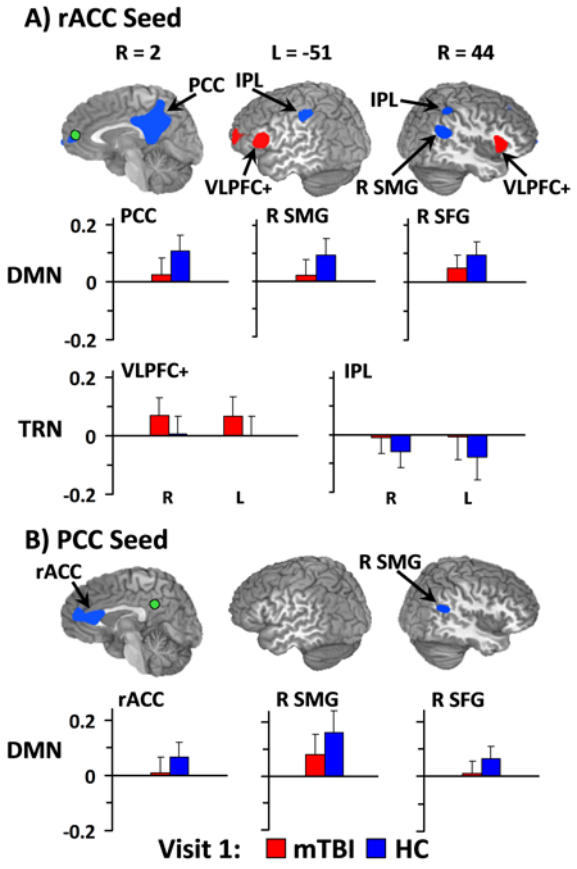

Figure 2: Panels A and B indicate decreased functional connectivity within the default mode network (DMN) based on seeds (green circles) in the rostral anterior (rACC; Panel A) and posterior (PCC; Panel B) cingulate gyrus. In addition, increased connectivity was observed between the rACC and the bilateral ventrolateral prefrontal cortex for patients (red) relative to controls (blue).

Thus, our current working hypothesis is that a tissue-specific pattern of injury characterizes semi-acute injury, and that these underlying neuronal changes contribute to attentional dysfunction. A key goal of our future work is to determine which changes are most deleterious to cognition. Are orienting and selective attention deficits following mTBI the result of decreased neuronal/metabolic/hemodynamic grey matter response or secondary to a disconnection between frontoparietal sites? Or are cognitive deficits/increased errors following mTBI the result of an imbalance between primary cortical networks mediating internal mentations (DMN) and attention to external events?

Mild TBI also presents an ideal "natural experiment" for examining both the initial consequences of the lesion and the substrate for cognitive recovery (usually 3-6 months post-injury). Results from our lab and others suggest a partial recovery in white matter (Arfanakis et al., 2002; Mayer et al., 2010), with a more robust recovery (Figure 1) of biochemical markers (Vagnozzi et al., 2010; Yeo et al., 2011). We also observed that biochemical recovery is impacted by general cognitive status (Yeo et al., 2011), representing an intriguing possibility about the role of cognitive reserve in mTBI. Finally, reports of persistent hemodynamic abnormalities in clinically asymptomatic mTBI patients (Mayer et al., 2011; McAllister et al., 2006) may explain why a second, temporally proximal mTBI results in greater cognitive deficits than a single injury of comparable severity (Vagnozzi et al., 2008; Wall et al., 2006; Vagnozzi et al., 2005).

Over the past three years, we received 3 NIH awards (R24, R21 and a challenge grant) for our mTBI work. We have amassed a unique multimodal imaging dataset on 55 well-characterized (full neuropsychological and clinical battery) semi-acutely injured mTBI patients and 55 well-matched healthy controls (data collection complete in March 2011), publishing several papers on our initial FMRI, 1H-MRS and DTI findings from our first cohort of patients (samples varied between 16 to 30 patients). The longitudinal aspect of data collection concludes in the fall of 2011, coincidental with the conclusion of our NIH funding. However, much work remains to be done. Replication is a cornerstone of science, and our most immediate goal (1-2 years) is to determine the reproducibility of our initial neuroimaging findings in our second independent cohort (25 patients and controls). MEG data was also collected on the second cohort using identical cognitive (evoked) and resting state (intrinsic) tasks, providing an unparalleled dataset for examining the dynamic relationship between electrophysiological and hemodynamic activity. Finally, a basic multisensory task was employed to ensure that widespread

hypoactivation during cognitive tasks was not due to differences in basic properties of the hemodynamic response.

Two more long-term goals (3-5 years) is to conduct longitudinal imaging studies on the relatively small percentage of patients with "complicated" mTBI and pediatric patients. Patients with complicated mTBI have visible focal lesions on CT scans and are more likely to have chronic neuropsychiatric symptoms/poor outcome following injury (Borgaro et al., 2003; Lee et al., 2008; Kashluba et al., 2008; Lange et al., 2009). Current theories (Bigler, 2010; Smits et al., 2008) suggest the focal lesions cause residual cognitive deficits. While intuitive, support for this theory has been mixed (Hughes et al., 2004; Lee et al., 2008; Smits et al., 2008). An alternative theory supported by our work is that poor cognitive outcomes are the result of diffuse injuries in otherwise healthy appearing tissue. More recently, we have also conducted a preliminary study with 16 pediatric mTBI patients and matched controls. Two publications from this work are pending, and we have also submitted a R01 to NIH.

Current funding:
2 grants for a total of $180,498, which represents 1% of research funding

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MRN CORES
Introduction

The MRN operates a number of core resources that offer access to advanced technologies and specialized equipment as a shared, or pooled, resource for the organization's research activities, investigators, and their sponsors. These state-of-the-art facilities and equipment facilitate the MRN investigator's ability to conduct leading-edge research. They provide support for programs within the organization and, as time permits, to external users as well. Funding from the DOE has enabled MRN to build this inventory of capability towards the goal of establishing a world class neuroimaging facility in New Mexico.

The extended network of institutions within which MRN collaborates, similarly, enjoys state-of-the-art neuroimaging equipment, including some pieces of hardware such as high-field MRI's and a neonatal MEG that are unique in the world. Selected instruments, for example, certain MRIs and the adult MEG systems, are calibrated across the sites so that results can be shared among the participants. This calibration effort was lead by MRN over a period of several years through support from DOE. The importance of this calibration is significant, allowing for the pooling of data, improving the statistical depth of studies, facilitating access to large amounts of research data, and overall leveraging the impact of the original funding in a substantial and positive way.

Complementing the hardware, MRN has a variety of unique software applications for both anatomical and functional MR imaging, including high-resolution Diffusion Tensor Imaging (DTI) pulse sequences and analysis software and MRI-MEG integration software. The entire enterprise is supported and enhanced by a collective neuroinformatics capability lead and maintained by MRN.

MRN's shared resources are organized into the following cores:

- Magnetic Resonance Technology Development Core
- Mobile Imaging Technology Core
- Magnetoencephalography and Electroencephalography Technology Development Core
- Image Analysis Technology Development Core
- Neurogenetics Technology Development Core
- Information Technology Core

Each core is lead by a senior MRN researcher, who is responsible for core operations, maintenance of equipment, provision of technical expertise to users, and who serves as a focal point for inter-core initiatives.

Historically, support to operate the core infrastructure has been drawn from the organization's DOE awards. As part of larger efforts for MRN to become self sustaining, much of core operations transitioned to a service center basis effective 01/01/2009. The remaining ones are planned to convert in coming periods. Service center operations are a standard approach for many organizations to account for shared resources or services. MRN's service centers have been structured in compliance with all federal regulations.

Project Title: Magnetic Resonance Technology Development Core
Investigator: Vince D. Calhoun, Ph.D.
Reporting Period: 7/1/2012–6/30/2013
Reporting Status: **FINAL**

Abstract:
The Magnetic Resonance Core provides access to state-of-the-art magnetic resonance imaging equipment for MRN investigators and the UNM community. In addition, the team coordinates with the partner sites in advancing important technological issues involved in the use of imaging information as a diagnostic tool.

The MR Core provides access to the Siemens 3T Trio with Total Imaging Matrix (TIM) Application Suite: The Trio 32-channel system represents state of the art in MRI hardware. It is capable of BOLD EPI, diffusion tensor imaging, perfusion and diffusion imaging, and spectroscopy. With 32 usable receiver channels as standard, the system allows for the use of current phased array coils (from 4 to 16) to improve sensitivity and speed of acquisition and is ready for future coil designs with more than 16 elements. This system is interfaced to an MR-compatible patient monitoring unit featuring pulsed oximetry, heart rate monitor, O_2, CO_2, NO, and halothane measurement, blood pressure monitor and EKG (OmniTrak, InVivo Research, Inc. Orlando, FL).

Accomplishments:
MR Core Service Center: MRN continues to operate the MR scanner as a service center. Under a service center, all expenditures associated with operation of the activity must be recovered, including utilities, maintenance, etc. These costs are accumulated for a specified period of time and rates for access to the resource developed on a basis that distributes the total outlays equitably to all prospective users. In other words, service centers are structured to neither make nor lose revenue over time; the objective is to only cover expenses. Activity is reviewed periodically, and the rate is re-calibrated to true up income against the required target. If an established rate has been too high, over-collecting income against expenses, it will be reduced for the next period to compensate for the excess. Conversely, if the rate has been too low, it will be increased to adjust for the income shortfall.

MRN has a current billing rate of $410/scan-hour. Billing is to the nearest one-half hour. Scan time is ordered as a pre-paid reservation entitling users to a "reserved scan slot" on the system's schedule. The slot is to be used within the following 30 days. Users will be billed for the amount of time they pre-purchase. This model places management of and financial responsibility for subject participation on the using investigator (and/or their staff). Rates are re-evaluated every six months.

Automated analysis: We continue to extend the capabilities of the automated analysis pipeline and have processed over three thousand datasets, each of which includes multiple modalities including fMRI, DTI, sMRI, MRS, and EEG. The following summarizes the capabilities of the automated analysis pipeline:

- Automated Analysis (AA) tracks daily scan collection, performs first level analysis of all new data sets from multiple modalities, and provides an analysis summary for each scan. Study investigators know within a few hours of data collection what the subject's head movement and behavioral performance was, which can be critical in certain clinical studies.
- The automation team continuously monitors daily automation reports, identifies analysis issues and resolves open issues on a timely manner.
- AA identifies and investigates integrity issues with the archive pipeline and database issues.
- AA provides support to archive the acquired SVS and CSI spectroscopy data in MRN data hierarchy; AA also helps with archiving MRSI files that do not conform to the MRN naming conventions.
- AA supports automated analysis of SVS and CSI spectroscopy data using LC Model and applying in-house developed partial volume correction.
- AA provides support to analyze data from multiple sites, including MRN's own mobile scanner.

The data is managed by a neuroinformatics platform call the Collaborative Informatics and Neuroimaging Suite (COINS). COINS currently manages 493 studies with 332,752 clinical assessments and 31,148 MRI and MEG scan sessions collected from 21,823 participants at the Mind Research Network, Nathan Kline Institute, University of Colorado – Boulder, Olin Neuropsychiatry Research Center, and other sites. It has grown into a long term sustainable project through the initial DOE investment and maintains and external collaborative based in addition to funding from several NIH grants and multiple pending grants.

Project Title: Mobile Imaging Technology Development Core
Investigator: Kent Kiehl, Ph. D.
Reporting Period: 7/1/2012–6/30/2013
Project Status: **FINAL**

Abstract: The Mobile Imaging core is dedicated to the use of state-of-the-art brain imaging techniques to delineate the neurocognitive architecture underlying some of society's most enigmatic and costly mental health disorders. These disorders include alcohol and substance abuse, and criminal psychopathy (i.e., psychopathic personality). These latter mental health disorders are commonly associated with severe and repetitive criminal behavior that may lead to incarceration. The MRN Mobile Imaging system is the first of its kind to be deployed to such facilities to study these populations in large numbers. The goal of the MRN Mobile Imaging Program is to develop a better understanding of the neurobiology of psychopathy and related mental health disorders so that effective treatments for these conditions can be developed.

The MI Core supports a Siemens' 1.5T Avanto Magnetic Resonance Imaging system and a 72-channel high-resolution EEG/ERP Biosemi system (Figure 1). The Avanto is the most advanced 1.5T system in the Siemens product line. The Avanto is a ultra-short 150cm (4'11'') long, whole body superconductive 1.5T magnet with 5th generation active shielding (AS) technology with counter coils, External Interference Shielding (E.I.S.) and excellent homogeneity (based on 24 plane plot, 50 cm DSV type. 0.8 ppm). The system comes equipped with a 12-element Matrix head coil capable of ultra-fast parallel acquisition in either 4-channel (CP Mode), 8-channel (Dual Mode) or 12-channel (Triple Mode) settings. The SQ-engine Gradient System with AudioComfort was selected. The SQ-engine gradients have maximum amplitude of 45 mT/m for the longitudinal direction and 40 mT/m for horizontal and vertical direction. The gradient slew rate is 200 T/m/s with a minimal rise time of 200 μs (from 0-40 mT/m amplitude). AudioComfort is an acoustic noise buffer that leads to a 30dB (A) attenuation of gradient noise compared to other conventional systems that leads to a reduction of 97% in sound pressure. This latter sound reduction is of great benefit to functional imaging studies. The MR system comes completely integrated into a trailer, which also houses an EEG/ERP data collection system for brain potential studies.

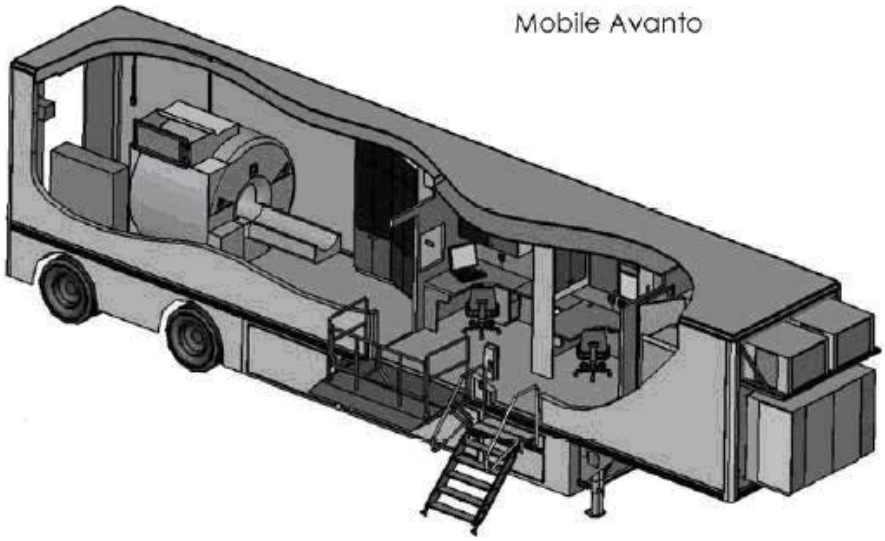

Figure 1: Representation of the mobile imaging laboratory (provided by Medical Coaches, Inc.).

The Mobile Imaging System is supported by a combination of grants. The Mobile project would not have been possible without DOE support. The MI System is open to use by all DOE and non-DOE (i.e., federally funded) activities.

Accomplishments:

Over the course of the funding period, we have collected brain imaging data on 2000 male and female inmates, which represents the largest brain imaging dataset from incarcerated populations in the world. The data that was collected has been written up and submitted to top-tier journals and we are in the process of writing up the remaining datasets for submission. The collected datasets are also being used to support independent R01 and K award applications by our postdoctoral fellows/junior PIs (i.e. Carla Harenski, Nathaniel Anderson, Vaughn Steele).

The mobile system as delivered to the MRN on 21 February 2007. During the subsequent six weeks following delivery, custom auditory and visual presentation capabilities for functional magnetic resonance imaging were installed. The mobile trailer was custom designed with a special projector housing, multiple waveguides for passing fiber optic response devices from the control room to the MR room, and the control room was split into two rooms–one for MR data collection and the other for EEG data collection. The team interfaced with the Siemen's MR console to pass all the raw imaging data to an offline computer for processing. The MI system was ready for pilot data collection by 15 March 2007, and was deployed to New Mexico prisons in May 2007. The mobile MRI commenced data collection at the New Mexico Women's Correctional Facility in September 2008. The PI's NIMH l collects data from the female inmates, which represents the first brain imaging studies of female inmates. From July 2010 to November 2010 the mobile was deployed to 2 new sites in the state of Wisconsin: Sand Ridge Secure Treatment Center and Fox Lake Correctional Institution. From July 2011-September 2011, the mobile MRI returned to the two Wisconsin Correctional Facilities to complete longitudinal assessments of previous participants.

This research has been working on data collection for the PI's NIMH funded project's "Neurocognitive assessment of 'Callous' Conduct Disordered youth" (1 R01 MH071896-01) and the "Cognitive Neuroscience of Female Psychopathy" (R01 MH085010-01A1) and the NIDA funded projects "Action Monitoring, Action Observation and Dopamine Genes as Predictors of Substance Abuse" (1R01DA026964-01A1), "Neurocognitive changes associated with behavioral treatment in cocaine abusers" (R01 DA020870-01) and "Socio-moral processing in psychopathy and substance abuse" (R01 DA026505-01A1).

In addition in 2011 the MRN received two substantial subawards from NIMH grants to Dr. Jean Decety and Dr. David Kosson to deploy the mobile MRI to collect data for their respective awards. Total contract value is well over one million per subaward. These collaborations are still maintained.

Quality control: The Siemen's Avanto is the most advanced 1.5T MRI system that is currently available. The mobile system has been custom designed for cognitive neuroscience research. Previously, one of the major limitations in studying the neurocognitive systems implicated in psychopathy is access to technologically advanced equipment necessary to conduct brain imaging research. Imaging systems, especially ones capable of high-speed imaging for functional brain research, are virtually unheard of in prison settings. To our knowledge, there are no mobile imaging systems dedicated to the study of incarcerated populations in North America. This opportunity thus represents a unique and novel means to examine psychopathy and related substance abuse disorders in these samples. The MRN Mobile imaging system is the first of its kind to perform state-of-the-art multimodal imaging in such populations. With respect to quality control, all of the raw imaging data will be processed by the MRN Image Analysis Core and subjected to the same quality control measures as the other MRI scanners in the extensive MRN

network (i.e., MGH, Minnesota, and the MRN 3T scanner). It is estimated that the MI system can collect approximately 150 MRI sessions/month, which translates to an effective per scan cost of about $350/session, well below the typical MRI rate of $450-$600/session.

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26. Steele, V., Aharoni, E., Munro, G.E., Calhoun, V.D., Nyalakanti, P., Stevens, M.S., Pearlson, G.D., & Kiehl, K.A. (in press). A large scale (n=102) functional neuroimaging study of response inhibition and error-processing. Behavioral Brain Research

27. Kiehl, K.A. & Lushing, J. (2013). Psychopathy. Scholarpedia. A peer-reviewed encyclopedia. www.scholarpedia.org/article/Psychopathy

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29. Decety, J., Chen, C., Harenski, C.L., & Kiehl, K.A. (in press). An fMRI study of affective perspective taking in individuals with psychopathy: Imagining another in pain does not evoke empathy. Frontiers in Human Neuroscience

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32. Cope, L.M., Ermer, E., Nyalakanti, P.K., Calhoun, V.D., & Kiehl, K.A. (in press). Paralimbic gray matter reductions in incarcerated adolescent females with psychopathic traits. Journal of Abnormal Child Psychology

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34. Castro, E., Gomez-Verdejo, V., Martinez-Ramon, M., Kiehl, K.A. & Calhoun, V.D. (in press). A multiple kernel learning approach to perform classification of groups from complex-valued fMRI data analysis: Application to schizophrenia. Neuroimage

35. Decety, L., Skelly, L. R., Yoder, K. J., & Kiehl, K.A. (in press). Neural processing of dynamic facial expressions of emotion in psychopaths. Social Neuroscience

Presentations:

1. Kiehl, K.A. (February, 2012). *The criminal psychopath magnetized: Implications of brain imaging for psychology, medicine, law and policy.* Neuroscience and Public Policy Program, University of Wisconsin-Madison http://npp.wisc.edu/. Madison, WI. Invited speaker.

2. Kiehl, K.A. (April, 2012). *The neuroscience of the criminal psychopath: Any implications for law?* Boston Society of Neurology and Psychiatry, Harvard Medical School. Boston, MA. Invited Keynote Speaker.

3. Kiehl, K.A. (April, 2012). *The criminal psychopath magnetized: Implications of brain imaging for psychology, medicine, law and policy.* Duke University Law School. Invited speaker.

4. Kiehl, K.A. (April, 2012). *The Legal Implications of Criminal Psychopathy*. Federal judicial education seminar, National Workshops for U.S. Magistrate Judges, Organized by the National Federal Judicial Center in Washington, D.C., Miami, FL. Invited speaker.

5. Kiehl, K.A. (July, 2012). *The Legal Implications of Criminal Psychopathy.* Federal judicial education seminar, National Workshops for U.S. Magistrate Judges, Organized by the National Federal Judicial Center in Washington, D.C., Denver, CO. Invited speaker.

6. Kiehl, K.A. (August, 2012). *The Psychopath.* Invited paper, Google/Nature/O'Reily Sci Foo Conference, Google Campus, Mountain View, CA.

7. Kiehl, K.A. (September, 2012). *The usual suspects magnetized: When law and neuroscience collide.* PAL lecture series, Department of Psychology, University of New Mexico, Albuquerque, NM.

8. Kiehl, K.A. (October, 2012). *The criminal psychopath magnetized: Insights from brain imaging.* Grand Rounds presentation to the Department of Psychiatry, Duke University, Durham, NC. Invited speaker.

9. Kiehl, K.A. (October, 2012). *The criminal psychopath magnetized: Insights from brain imaging.* Grand Rounds presentation to psychiatric staff at Central Mental Hospital, Duke University/University of North Carolina residents program. Invited speaker

10. Kiehl, K.A. (October, 2012). *Roundtable discussion on law and neuroscience*. Seminar on future tense, The New America Foundation, Washington, DC. Invited speaker.

11. Kiehl, K.A. (February, 2013). *The cognitive neuroscience of criminal psychopaths*. South Carolina Psychiatric Association 2013 Annual Conference. Charleston, SC. Invited speaker.

12. Kiehl, K.A. (March, 2013). *The science of psychopaths: Assessment, recidivism, neuroscience, and treatment.* Forensic Mental Health Association of California (FMHAC). Monterrey, CA. Invited Keynote speaker.

13. Kiehl, K.A., (May, 2013). *Psychopaths and the Law: Assessment, Recidivism, and Neuroscience*. Nevada Federal District Conference for Federal Judges, Las Vegas, NV. Invited Keynote speaker.

14. Kiehl, K.A., (May, 2013). *The Usual Suspects Magnetized: When Law and Neuroscience Collide*. Alaska Bar Convention. Juneau, AK. Invited Keynote speaker.

15. Kiehl, K.A. (May, 2013). *Psychopaths and the Law: Assessment, Recidivism and Treatment.* Alaska Bar Convention. Juneau, AK. Invited keynote speaker.

16. Kiehl, K.A. (May, 2013). *The Usual Suspects Magnetized: When Law and Neuroscience Collide.* New Mexico Bar Association. Judicial Education Seminar. Albuquerque, NM. Invited lecture by Judge Ronald Kennedy, New Mexico Court of Appeals.

17. Kiehl, K.A., (June, 2013). *The Usual Suspects Magnetized: When Law and Neuroscience Collide*. Santa Barbara Judicial Meeting, Santa Barbara, CA. Invited speaker.

18. Kiehl, K.A. (June, 2013). *The Usual Suspects Magnetized: When Law and Neuroscience Collide.* New Mexico Judicial Conclave. Albuquerque, NM. Invited Lecture.

19. Kiehl, K.A. (July, 2013). *Neuroscience and Crime*. Summer Institute in Cognitive Science, Lake Tahoe, CA. Invited speaker.

20. Kiehl, K.A. (November, 2013). Title TBD. New York University Child Study Center Grand Rounds. Invited Speaker.

Project Title: Expanding the MRN Mobile Research Network
Investigator: Kent Kiehl, Ph.D.
Reporting Period: 7/1/2012–6/30/2013
Report Status: **FINAL**

This research project was designed to expand the MRN Mobile Research Network. MRN maintains a one-of-a-kind research dedicated mobile imaging system that permits access to difficult to reach populations for research studies. Examples include Native American populations residing on pueblos, war fighters deployed at military bases for studies of traumatic brain injury, retirement communities for studies of aging, dementia and animal colonies for the study of disease and mental health disorders.

Accomplishments:
The MI system was ready for pilot data collection by 15 March 2007, and was deployed to New Mexico prisons in May 2007. The mobile MRI commenced data collection at the New Mexico Women's Correctional Facility in September 2008. From July 2010 to November 2010 the mobile was deployed to 2 new sites in the state of Wisconsin: Sand Ridge Secure Treatment Center and Fox Lake Correctional Institution. Mobile research was further expanded in WI to include OshKosh Correctional Facility and Fox Lake Correctional Facility. The mobile MRI returned to the Wisconsin Correctional Facilities to complete longitudinal assessments of previous participants. Additionally, the mobile research network has been expanded to include:

- Deployment to a large animal non-human primate colony in New Mexico at the Lovelace Respiratory Research Institute to facilitate studies of animal models.
- Contract negotiations are currently underway with The Child Mind Institute in New York to provide imaging services.
- The mobile unit will also be used for our new Brain Safe Project, to study traumatic brain injury.

Publications

- We are currently working on a manuscript about incidental findings from radiology scans compiled from the mobile unit. We anticipate this publication to be out at the beginning of next year.

Project Title: Magnetoencephalography and Electroencephalography Technology Core
Investigator: Julia M. Stephen, Ph.D.
Reporting Period: 7/1/2012–6/30/2013
Report Status: **FINAL**

Abstract: Magnetoencephalography (MEG) is a non-invasive functional neuroimaging technique that records the magnetic fields generated by the brain. When used in combination with magnetic resonance imaging (MRI), the locations and time courses of activity in the brain can be specified on a spatial scale of millimeters and a temporal scale of milliseconds. As a functional imaging modality, MEG is a highly specialized technique conducted at approximately 100 sites worldwide. MEG has an advantage in spatial resolution over electroencephalography (EEG), and 100-1000 times greater temporal resolution than functional MRI (fMRI), positron emission tomography (PET), or single photon emission computed tomography (SPECT). The unique information provided by MEG provides novel contributions to basic research, clinical research, and clinical diagnostic applications. The MEG instrument operates at roughly 50% capacity during standard working hours in support of internal and external research. The MEG program at MRN is critical to the performance of multiple externally funded grants.

The MEG/EEG Program also provides support to EEG users of the BioSemi high density EEG system. These include Dr. Kiehl's ongoing projects using the EEG in conjunction with his fMRI studies, Dr. Stephen's EEG data collection in conjunction with her multi-modal Schizophrenia COBRE project. In addition, Dr. Lewine, a recent MRN recruit will continue his Autism research using both MEG and separate EEG studies.

The MEG/EEG core holds quarterly meetings to keep the MEG/EEG users informed of developments. These meetings are organized and run by the MEG/EEG Program personnel. Intermediate updates are provided via email. The PIs and their staff are advised of changes to MEG/EEG Program policies and procedures, and input from the MEG users is solicited in an effort to improve the service of the MEG/EEG Program.

Accomplishments and goals:
There are ~8 externally funded projects being run on the MEG scanner with 5 MRN investigators and 5 external investigators as the principal investigators on these projects. The MEG core transitioned to a service center on January 1, 2010 and has been self-sustaining since that time. The MEG center provides auto transfer of the data, and auto logging of all datasets into the COINS database. This helps to protect against data loss for the investigators as well as automatic data acquisition tracking through the COINS database. The second step, preprocessing auto analysis of the data, is now implemented. The auto-analysis pipeline is implemented for new studies and is continuing to be modified to accommodate all MEG studies.

The clinical MEG program is continuing to grow under the management of Dr. Jeffrey Lewine and Dr. Bruce Fisch, the Director of the Comprehensive Epilepsy Program at UNMHSC. The MEG technicians are fully trained for MEG clinical patients and the current rate of clinical cases is ~4-5/month with additional increases expected with patient availability. Dr. Lewine also brings expertise in Autism Spectrum Disorders, epilepsy, traumatic brain injury and post-traumatic stress disorder and is using MEG to better understand these disorders in conjunction with other MRN investigators. In addition, MEG is being used as a resource for attorneys in cases of Traumatic Brain Injury. Dr. Lewine is providing expert testimony in these cases.

In addition, the child-friendly, high density EEG system (EGI 128-channel hydrocell – ARRA Supplement funding – PI J. Stephen) has been fully integrated with the MEG system. This system does not require standard scalp preparation (scrubbing) of traditional EEG systems and children can be prepared for an EEG in <15 minutes compared to >60 minutes of traditional high-density EEG systems. This system is available to all investigators for use with children and adults. This provides additional

support for the MEG/EEG core by facilitating multi-modal MEG/EEG studies. This system is now being used for both an adult study on schizophrenia and a study of prematurely born infants (3 & 6 months of age).

The EEG data auto-transfer has also now been implemented to facilitate EEG data tracking through the COINS database. The BioSemi EEG system continues to be maintained and allows MRN PIs and external PIs to use the EEG system at minimal cost.

The goals for the next period are to continue to 1. Support the current MEG/EEG funded investigators. The MRN MEG/EEG Core supports one of the largest research MEG programs in existence, providing support for investigations across the age spectrum (from infants to elderly) as well as supporting research projects addressing a number of challenging clinical populations (e.g. clinical epilepsy program, autism, schizophrenia). We will continue to work directly with investigators to obtain optimal data from these individuals. 2. Provide support to MEG/EEG investigators developing new projects and provide MEG/EEG expertise to recruit new investigators to the field to ensure high quality data is obtained for pilot projects and grant applications; 3. Fully implement the MEG auto-analysis pipeline to facilitate data analysis for current and future MEG users. This approach allows even novice users to receive a preliminary analysis of their data for grant submission and to summarize pilot data results

Products produced, technology transfer activities accomplished, technologies or techniques developed:

The MEG website has been updated and re-organized to facilitate use by both novice and expert MEG users. Standard QA measurements of the MEG system and stimulus equipment is now performed on a weekly/monthly basis. The MEG technicians have been trained in basic data analysis to allow investigators without MEG expertise to contract MEG analysis time for preliminary analysis of pilot studies. This service will help facilitate recruitment of new PIs to MEG.

All MEG users are now required to take an online safety training course prior to working in the MEG facility. This training course helps to ensure that the investigator teams are well-prepared for MEG data collection to ensure good quality data collection occurs for all studies as well as maintaining the MEG equipment.

Project Title: Image Analysis
Investigator: Vincent D. Calhoun, Ph.D.
Reporting Period: 7/1/2012–6/30/2013
Report Status: **FINAL**

Abstract: The Image Analysis Core provides algorithm development and infrastructure for *automated* and *large-scale* processing of the many different data types collected as part of MRN. This includes various quality assurance measures in order to evaluate the reliability of the data. The team routinely collects multimodal data, which includes functional MRI, structural MRI, EEG, MEG, diffusion tensor imaging, spectroscopy, neuropsychological test scores, and diagnostic information. To take maximum advantage of the data collected at multiple sites, including the FIRST program and the MCIC program, in addition to the multiple studies conducted locally at MRN, these data need to be processed to utilize the available information optimally. The IA Core implements a "pipeline" approach for each modality, using the best processing scheme currently available.

Toolboxes:
Several statistical analysis toolboxes have been developed and/or improved to assist researchers with commonly used data analysis. These toolboxes can be found at http://icatb.sourceforge.net and http://mialab.mrn.org/software/. Over 8000 unique downloads have been recorded. A brief summary of the toolboxes follows:

Group ICA of fMRI Toolbox (GIFT) and EEG ICA Toolbox (EEGIFT):
GIFT and EEGIFT are Matlab toolboxes that implement multiple algorithms for independent component analysis (ICA) of group (and single subject) functional magnetic resonance imaging data. ICA is a blind-source separator method, which allows one to divide the overall brain activations into components (sources) that are most distinct from each other. This helps associate particular region(s) of the brain with particular activations. We incorporate new features constantly. For example, we recently added the capability to estimated dynamic connectivity states from fMRI data using these tools (implementing a method we published this year in Cerebral Cortex).

Fusion ICA Toolbox (FIT):
FIT is a Matlab toolbox that implements data fusion approach using independent component analysis. It is used to examine the shared information between the features (SPM contrast image, EEG data). In the past year it has been substantially updated and expanded upon to include the analyses of genetic data in connection with imaging data. The parallel ICA techniques applied to imaging and genetics data can identify potential multi-genetic influences on brain structure and

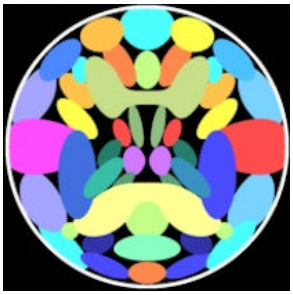
function. We have added multiple new functions to the tools including our joint ICA + mCCA (joint independent component analysis + multiset canonical correlation analysis) method for identifying modality common and modality unique disease biomarkers from multimodal imaging data.

Functional Connectivity Toolbox (FNC):
FNC is a Matlab toolbox that finds and displays temporal relations amongst components, which can help determine causal relations in the brain. We have added multiple new functions including a Granger method. In addition, we implemented additional FNC functionality within the GIFT toolbox mentioned above.

Group Inter-participant Correlation (GIPC):
GIPC is a Matlab toolbox that can compare spatial activation similarities among subjects in a study group, and also compare group spatial activations among different study groups.

Laterality User Interface:
LUI is a Matlab toolbox that generates the lateral difference maps of brain images. We have just submitted a new paper which uses a high model order ICA analysis to identify lateralized networks which are showing age and gender differences.

Simulation Toolbox (SimTB):
SimTB is a Matlab toolbox designed for flexible generation of fMRI datasets under a model of spatiotemporal separability, to facilitate the testing of a variety of analytic methods.



Publications:
A total of 122 new journal publications from the Image Analysis Lab have been published during 2012 and 2013.

Project Title: Multimodal Data and Classification Techniques
Investigator: Vincent D. Calhoun, Ph.D.
Reporting Period: 7/1/2012–6/30/2013
Report Status: **FINAL**

The Research project has been specifically developing multimodal data and classification techniques, and evaluating their use in datasets from clinical populations. The different genotypic data types provided by the Neurogenetics Core include millions of data points from genome-wide scans (GWS), or more quantitative measures of copy number variations (CNVs) or methylation measurements, which require careful consideration and modification to the techniques.

Accomplishments: We have developed novel methods for working with GWS data in the context of imaging genetics, applying it to sensorimotor studies and attentional studies to determine genetic influences on disease dysfunction. This has resulted in dozens of publications during 2012-2013. Our multivariate algorithms have been evaluated in schizophrenia, borderline personality disorder, criminal psychopathy, and bipolar disorder, resulting in another sixteen papers so far this year. We have also published multiple review papers on these methods. We recently received a $13 million phase II COBRE which includes a project specifically focused on imaging genetics methods including GWS, CNVs, and methylation data in schizophrenia and bipolar disorder.

Project Title: Information Technology Core
Investigator: Rachel Blea
Reporting Period: 7/1/2012–6/30/2013
Report Status: **FINAL**

Abstract
The Information Technology (IT) Department supports MRN Investigators and their partners with a secure and reliable computing environment for their research as well as all administrative functions (Payroll, Accounting, HR, and Grant Administration). IT services ensure systems and applications operate effectively, provide appropriate confidentially, integrity, and network availability. Access into the Data Centers is managed through a computerized system under a controlled proximity card reader with a picture ID. Contractors, visitors or vendors are required to be escorted while in the data center.

Data Storage
MRN's computing infrastructure consists of ~744TB Isilon Network Attached Storage (NAS) system that consolidates all research data to facilitate easy access and retrieval. The Isilon storage system is capable of scaling into multiple Petabyte range as data storage demands rapidly increase. The network infrastructure is based on Cisco switches and uses 10 Gigabit Ethernet connections for core connectivity, critical systems, storage, and to a high availability data center that houses core services as well as multiprocessor compute servers.

Computing Environment/Applications
Scientific end users are able to access the MRN resources using a single sign on environment that enables sharing of data across the Windows, Linux and Macintosh platforms. The data center houses several large shared memory systems ~20 cores & 128GB RAM on average. Additionally there are currently over 30 image analysis and neuroinformatic applications installed and administered uniformly across all workstations. Primary data analysis packages are MATLAB, SPM, GIFT/ICA, AFNI, FSL and FreeSurfer. FreeSurfer primarily runs on MRN's 48 processor core Univa Grid Engine clusters.

With the addition of the Dell R910 server, the computational resources of this server provide an addition 40 cores of processing resources as well as 512Gb of memory. This server provides additional resources for the image analysis and neuroinformatics applications such as MATLAB and other resource intensive applications.

The data center is backed by an 80 KW N+3 UPS Uninterruptible Power Supply. The UPS is integral to providing stability to the data center and network infrastructure. The replacement of the aging batteries for the UPS helps guarantee the un-interruption of service to the users or loss of data or process that could be cause by a power failure or surge in electrical power. By maintaining and keeping these batteries serviced and replaced ensures the capabilities of the data center's 80KW UPS power supply. This along with the backup generator is key, to providing emergency power for the servers and network infrastructure.

A diesel generator for emergency power protects the data center and the cooling system. The data centers infrastructure, power and cooling systems are monitored 24/7.

Network
All desktop workstations communicate with MRN's data center and network attached storage via dual redundant fiber links. MRN is connected to the Internet via gigabit fiber to a 100 megabit per second link on the University of New Mexico's campus. A Virtual Private Network allows researchers and collaborators to access MRN computing resources remotely through an encrypted link. Our VPN utilizes Cisco System's Clean Access Manager to protect MRN's network by only allowing fully patched systems

with updated anti-virus scanners onto the network. MRN's internal network is also Cisco based and follows best practices for fault tolerance employing a full mesh topology between the core and edge networks.

The addition of the Brocade 360 and VDX 6720 switches will increase and update the capacities of the Fiber Channel and 10Gb fiber switches used to connect the Isilon storage arrays into the network. These switches allow for redundant and dual layer infrastructure between the servers and the storage to provide redundancy and failover capabilities.

Acquisition/Storage
Data acquisition computers across all modalities (1.5T Mobile, 3T, MEG, EEG) have standardized stimulus delivery systems i.e. pupilometry, audio, video and time coding. The mobile data acquisition system includes a group of centrally managed workstations used for psychological assessment, digital video and document imaging in forensic populations.

MRN's storage and backup infrastructure must be dynamic and expandable, fault tolerant and highly available to meet the needs of the organization. With these goals in mind, MRN IT has deployed a seven node, 744 TB EMC Isilon high availability filer. Storage is accessible via a NAS topologies over a meshed Cisco based fiber-channel fabric and IP network. Research data is stored in a self-documenting directory hierarchy (both raw and processed).

Backup
Disaster preparedness (backup and recovery) is a major role of the IT infrastructure. The backup schedule consists of daily snapshots, monthly, and annual archival, as well as mail server archive. A "snapshot" backup of data is taken three times during the day and once at night. The nightly snapshots, which include study volumes and home directories, are retained for seven days. A FalconStor Virtual Tape Library (VTL) solution capable of backing up ~390TB compressed will take full archival backups approximately every two months and then export them to tape via eight streaming tape drives in an Overland Neo 8000 robotic tape library to be removed to our off-site disaster recovery facility.

Virtualization plays a key role in providing business continuity in the event of a disaster. MRN has a cluster of VMware servers at the ready to continue processing our day-to-day administrative and operations tasks.

Appendix A

Publications:

53. A. G. Christodoulou, T. E. Bauer, K. A. Kiehl, S. Feldstein Ewing, A. D. Bryan, and V. D. Calhoun, "A Quality Control Method for Detecting and Suppressing Uncorrected Residual Motion in fMRI Studies," Magnetic Resonance Imaging, in press.

54. Aharoni, E. & Kiehl, K.A. (in press). Evading justice: Quantifying criminal success in incarcerated psychopathic offenders. *Criminal Justice and Behavior*

55. Aharoni, E., Antonenko, O, & Kiehl, K.A. (2011). Disparities in the moral values of adult criminal offenders: The role of psychopathy. *Journal of Personality Disorders*, *45*, 322–327.

56. Aharoni, E., Sinnott-Armstrong, W., & Kiehl, K.A. (2011). Can psychopathic offenders discern moral wrongs? A new look at the Moral/Conventional distinction. *Journal of Abnormal Psychology* (epub advanced online edition)

57. Aharoni, E., Sinnott-Armstrong, W., & Kiehl, K.A. (2012). Can psychopathic offenders discern moral wrongs? A new look at the Moral/Conventional distinction. Journal of Abnormal Psychology, 121 (2), 484-497. Ermer, E., Cope, L.M., Nyalakanti, P.K., Calhoun, V.D., & Kiehl, K.A. (2012). Aberrant paralimbic gray matter in criminal psychopathy. *Journal of Abnormal Psychology*, 121 (3), 649-658.

58. Aharoni, E., Vincent, G., Harenski, C., Calhoun, V.D., Sinnott-Armstrong, W., Gazzaniga, M.S., & Kiehl, K.A. (2013). Neuroprediction of future re-arrest. *Proceedings of the National Academy of Science* (PNAS), 110 (15), 6223-6228.

59. Aine, C.J., Sanfratello, L., Adair, J.C., Knoefel, J.E., Qualls, C., Lundy, S.L., Caprihan, A., Stone, D., Stephen, J.M., 2014. Characterization of a normal control group: Are they healthy? *Neuroimage* 84, 796-809.

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36. Kiehl, K.A. (*April*, 2012). *The neuroscience of the criminal psychopath: Any implications for law? Boston* Society of Neurology and Psychiatry, Harvard Medical School. Boston, MA. Invited Keynote Speaker.

37. Kiehl, K.A. (April, 2012). *The criminal psychopath magnetized: Implications of brain imaging for psychology, medicine, law and policy*. Duke University Law School. Invited speaker.

38. Kiehl, K.A. (April, 2012). *The Legal Implications of Criminal Psychopathy.* Federal judicial education seminar, National Workshops for U.S. Magistrate Judges, Organized by the National Federal Judicial Center in Washington, D.C., Miami, FL. Invited speaker.

39. Kiehl, K.A. (July, 2012). *The Legal Implications of Criminal Psychopathy.* Federal judicial education seminar, National Workshops for U.S. Magistrate Judges, Organized by the National Federal Judicial Center in Washington, D.C., Denver, CO. Invited speaker.

40. Kiehl, K.A. (August, 2012). *The Psychopath.* Invited paper, Google/Nature/O'Reily Sci Foo Conference, Google Campus, Mountain View, CA.

41. Kiehl, K.A. (September, 2012). *The usual suspects magnetized: When law and neuroscience collide.* PAL lecture series, Department of Psychology, University of New Mexico, Albuquerque, NM.

42. Kiehl, K.A. (October, 2012). *The criminal psychopath magnetized: Insights from brain imaging.* Grand Rounds presentation to the Department of Psychiatry, Duke University, Durham, NC. Invited speaker.

43. Kiehl, K.A. (October, 2012). *The criminal psychopath magnetized: Insights from brain imaging.* Grand *Rounds* presentation to psychiatric staff at Central Mental Hospital, Duke *University/University of North Carolina residents program. Invited speaker*

44. *Kiehl, K.*A. (*October*, 2012). *Roundtable discussion on law and neuroscience*. Seminar on future tense, The New America Foundation, Washington, DC. Invited speaker.

45. Kiehl, K.A. (*February*, 2013). *The cognitive neuroscience of criminal psychopaths*. South Carolina Psychiatric Association 2013 Annual Conference. Charleston, SC. Invited speaker.

46. Kiehl, K.A. (March, 2013). *The science of psychopaths: Assessment, recidivism, neuroscience, and treatment. Forensic* Mental Health Association of California (FMHAC). Monterrey, CA. Invited Keynote speaker.

47. Kiehl, K.A., (May, 2013). *Psychopaths and the Law: Assessment, Recidivism, and Neuroscience*. Nevada *Federal* District Conference for Federal Judges, Las Vegas, NV. Invited Keynote speaker.

48. Kiehl, K.A., (May, *2013*). *The Usual Suspects Magnetized: When Law and Neuroscience Collide*. Alaska *Bar* Convention. Juneau, AK. Invited Keynote speaker.

49. Kiehl, K.A. (May, 2013). *Psychopaths and the Law: Assessment, Recidivism and Treatment.* Alaska Bar *Convention*. *Juneau*, AK. Invited keynote speaker.

50. Kiehl, K.A. (May, *2013*). *The Usual Suspects Magnetized: When Law and Neuroscience Collide.* New *Mexico* Bar Association. Judicial Education Seminar. Albuquerque, NM. Invited lecture by Judge Ronald Kennedy, New Mexico Court of Appeals.

51. Kiehl, K.A., (June, 2013). *The Usual Suspects Magnetized: When Law and Neuroscience Collide*. Santa Barbara Judicial Meeting, Santa Barbara, CA. Invited speaker.

52. Kiehl, K.A. (June, 2013). *The Usual Suspects Magnetized: When Law and Neuroscience Collide.* New Mexico *Judicial* Conclave. Albuquerque, NM. Invited Lecture.

53. Kiehl, K.A. (July, 2013). *Neuroscience and Crime*. Summer Institute in Cognitive Science, Lake Tahoe, CA. *Invited* speaker.

54. Kiehl, K.A. (*November*, 2013). Title TBD. New York University Child Study Center Grand Rounds. Invited Speaker.

55. Lane T, Plis S, Clark VP, Anderson B, Oyen D. ayesian Analysis of Neural-Behavioal Interaction in Mental Illness. *Collaborative Research in Computational Neuroscience* (2008).

56. Lauriello J, Bustillo J, Schulz SC, Andreasen N, Gollub R, Ho BC, Clark V, Bockholt J, Lim KO. Overview of the MIND Imaging Consortium. *International Congress on Schizophrenia Research* (2007).

57. Lim KO, Bockholt J, Magnotta V, Gollub RL, Andreasen N, White T, Schulz C. White matter abnormalities in first episode and chronic schizophrenia using diffusion tensor imaging in the MIND Clinical Imaging Consortium Study. *International Congress on Schizophrenia Research* (2007).

58. Liu J, Xu L, Caprihan A, and Calhoun VD. Extracting Principle Components For Discriminant Analysis of fMRI Images. *IEEE International Conference on Acoustics, Speech, and Signal Processing* (2008).

59. Machado GR, Clark VP, Gollub RL, Lauriello J, Magnotta V, White T, Calhoun VD, Probing schizophrenia with a sensorimotor task: large-scale (n=273) independent component analysis of first episode and chronic schizophrenia patients. *Society for Neuroscience* (2007).

60. Michael A, Baum S, Calhoun VD, Caprihan A. Correlations of Diffusion Tensor Imaging Values and Symptom Scores in Patients with Schizophrenia. *Engineering in Medicine and Biology Conference* (2008).

61. Michael A, Calhoun VD, Baum S, Andreasen NC. A Method to Classify Schizophrenia using Inter-Task Spatial Correlations of Functional Brain Images. *Engineering in Medicine and Biology Conference* (2008).

62. Michael A, Fries J, Baum S, Ho BC, Andreasen NC, Calhoun VD. A Method to Analyze Correlations between Multiple Brain Imaging Tasks to Characterize Schizophrenia. *IEEE Southwest Symposium on Image Analysis and Interpretation* (2008).

63. Michael AM, King MD, Ehrlich S, Pearlson GD, White T, Holt D, Andreasen NC, Sakoglu U, Ho BC, Schulz SC, Calhoun VD. A Method to Identify Brain Clusters with Different Structure-Function Correlation between Two Groups. *Organization for Human Brain Mapping*. (2011)

64. Michael, AM, King, MD, Calhoun, VD. A Method to Explore and Reduce Gray Matter–Function Whole Brain Correlations: Differences in Schizophrenia. *Neural Computation II, Los Alamos National Labs* (2011).

65. Michael, AM, King, MD, Calhoun, VD. Gray Matter Concentration and Functional Activation for a Working Memory Task Shows Inverse Correlation in Schizophrenia. *International Congress on Schizophrenia Research* (2011).

66. Morrow EM, Wallace S, Pacheco J, Bockholt J, White T, Ho B, Kuperberg G, Magnotta V, Lim KO, Seidman L, Goff D, Andreasen N, Schulz C, Fischl B, Gollub RL. Structural brain study across lifetime of schizophrenia using computer automated quantification of subcortical volumes in the MIND multisite study. *International Congress on Schizophrenia Research* (2007).

67. Nichols, B. N., J. A. Turner, L. T. Detwiler, J. L. Mejino, D. L. Rubin and J. F. Brinkley (2011). Integration of Semantically Annotated Neuroimaging Data via Chained Queries. INCF 2011. Boston, MA.

68. Olson S, White T, Vuchetich J, Lim KO, Ho BC, Lauriello J, Andreasen NC, Magnotta VA, Bockholt JH , Calhoun VD, Gollub RL, Schulz SC. Fractional Anisotropy and Movement Disorder in Schizophrenia. *International Congress on Schizophrenia Research.* (2009)

69. Potluru V, Calhoun VD. Group Learning using NMF Variants. *IEEE International Symposium on Circuits and Systems* (2008).

70. Potluru V, Plis SM, Calhoun VD. Multiplicative updates for non-negative kernel SVM. *Association for the Advancement of Artificial Intelligence* (2008).

71. Potluru V, Plis SM, Calhoun VD. Sparse shift-invariant NMF. IEEE Southwest Symposium on Image Analysis and Interpretation (2008).

72. Roffmann J, Gollub RL, Manoach DS, Calhoun V. Interactive effects of MTHFS C677T and COMT Val158Met on executive function and prefrontal activation in schizophrenia. *SIRS* (2007).

73. Schulz SC, Georgopoulos A, Gollub RL, Andreasen NC, Ho BC, Lauriello J, Calhoun VD. Linear Discriminate Analysis Applied to a Multicenter First Episode Schizophrenia Sample. *Winter Workshop on Schizophrenia* (2008).

74. Scully M, Anderson B, Lane T, Bockholt HJ, Burge J, Clark VP, Gollub RL, Lauriello J, Schulz SC, Calhoun VD, et al. A Dynamic Bayesian Network Analysis of Functional Network Difference During the Oddball Task, Related To General Intelligence Proc. *Society for Neuroscience* (2007).

75. Silva R, Calhoun VD. Identification of Brain Image Biomarkers by Optimized Selection of Multimodal Datasets. *International Society for Magnetic Resonance in Medicine* (2008).

76. Silva RF, Calhoun VD. Identification of Brain Imaging Biomarkers by Optimized Selection of Multimodal Independent Components. *IEEE Southwest Symposium on Image Analysis and Interpretation* (2008).

77. Stefan Ehrlich MD,1,2,3 Randy L. Gollub MD, PhD,1,2 Doug N. Greve PhD, 1 Anastasia Yendiki, PhD,1 Dara S. Manoach PhD,1,2 Beng-Choon Ho MD,4 Tonya White MD,5 S. Charles Schulz MD, 5 Daphne J. Holt MD, PhD1,2 Association between negative symptoms in schizophrenia and poor striatal function. *Organization for Human Brain Mapping* (2010)

78. Stefan Ehrlich MD,1,2,3 Stefan Brauns1,3, Anastasia Yendiki, PhD,1 Beng-Choon Ho MD,4 Vince Calhoun PhD,5,6 S. Charles Schulz MD,7 Randy L. Gollub MD, PhD,1,2 Scott R. Sponheim, PhD 8,7 Associations of cortical thickness and cognition in patients with schizophrenia and healthy controls *International Congress on Schizophrenia Research*. (2011)

79. Sui J, Calhoun VD. A Method for Group Difference Enhancement by Constraining Mixing Coefficients of ICA Framework. *International Society for Magnetic Resonance in Medicine* (2008).

80. Sui J, Liu J, Wu L, Michael A, Xu L, Adali T, Calhoun VD. A Constrained Coefficient ICA Algorithm For Group Difference Enhancement. *IEEE International Conference on Acoustics, Speech, and Signal Processing* (2008).

81. Turner, J. A., J. L. Mejino, L. T. Detwiler, M. Martone, J. Brinkley and D. L. Rubin (2011). Extension and Application of RadLex to Annotation of Neuroimaging Data. Radiological Society of North America (RSNA), Chicago, IL.

82. Turner, J. A., M. King, A. Belger, V. D. Calhoun, S. Ehrlich, J. G. Csernansky, S. G. Potkin, R. Gollub, D. H. Mathalon, J. M. Segall, R. Kikinis, J. M. Ford, F. Macciardi, M. Morgan, K. O. Lim, D. S. O'Leary, A. W. Toga, T. Van Erp, L. Wan and C. G. Wible (2011). Heritability and genetics of source based morphometry in schizophrenia. *International Congress on Schizophrenia Research. Colorado Springs, CO*.

83. Van Erp T, Chiang MC, Sun D, Hardt MCE, Bockholt JH, Turner JA, Calhoun VD, Johnson HJ, Greve DN, Williams S, O'Leary D, Lauriello J, Wible CG, Lim KO, Mueller BA, Brown GG, Voyvodic J, McCarthy G, Mathalon D, Ford JM, Potkin SG, Cannon TD, Thompson PM, Toga AW. 3D Pattern of Brain Abnormalities in Chronic Schizophrenia Visualized Using Tensor-Based Morphometry: a Multi-Site Structural Imaging Study. *Organization for Human Brain Mapping* (2008).

84. Van Erp T, Segall JB, Turner J, Greve DN, Toga AW, Wible CG, Lim K, Mueller B, Lauriello J, O'Leary DS, et al. Voxel-Based Morphometric analysis of a multi-site study on schizophrenia. Society for Neuroscience (2007).

85. Wallace S, Gollub RL, Norman K, Vangel G, Manoach V, Lim KO, Lauriello J, Andreasen N, Kunkel L. Diagnostic utility of neurological exam abnormalities in schizophrenia. *Society for Neuroscience*. (2007).

86. White T, et al. Cigarette Smoking Disrupts White Matter Integrity in Patients with Schizophrenia. *Organization for Human Brain Mapping* (2009).

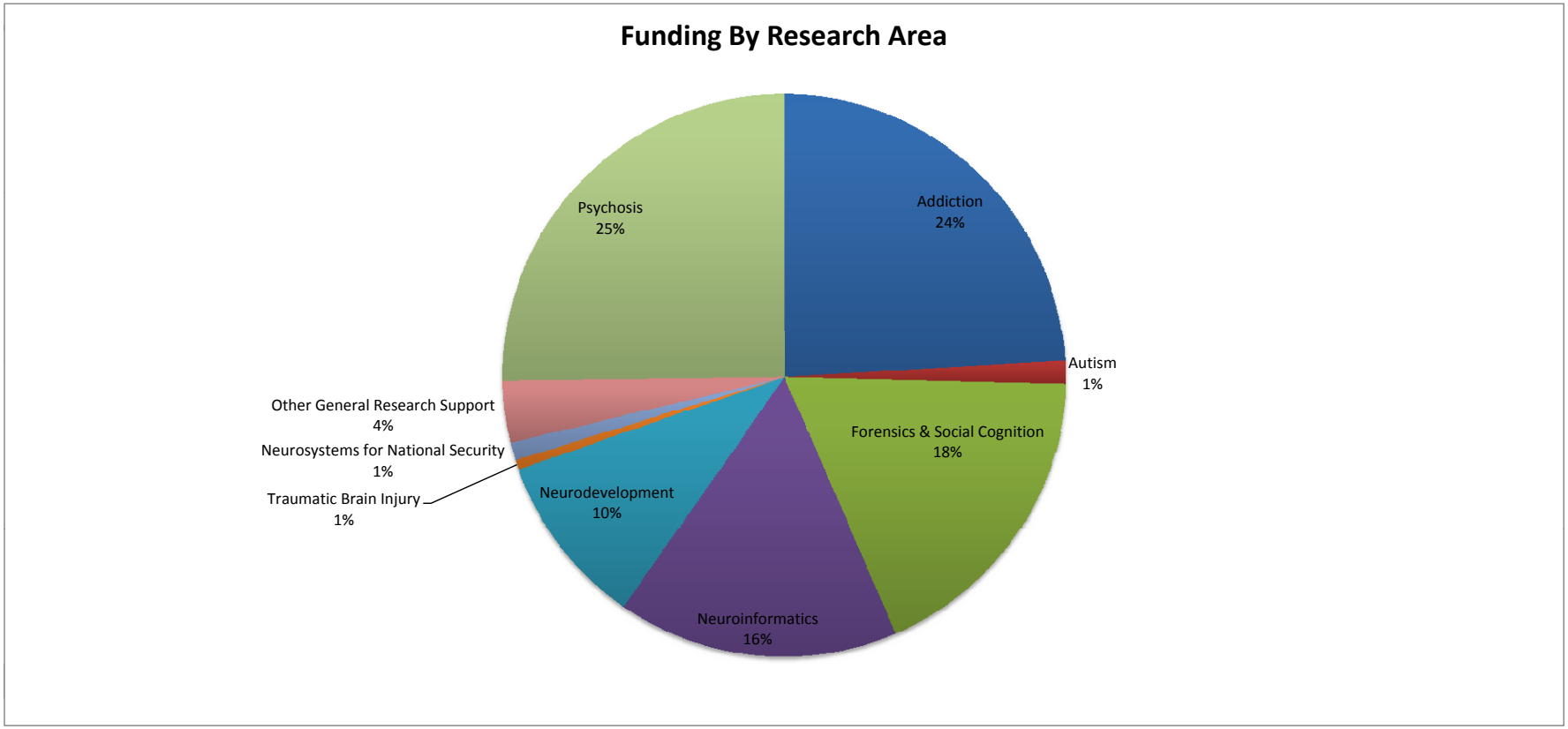
87. White T, Magnotta V, Bockholt HJ, Williams S, Pierson R, Johnson H, Wallace S, Gollub RL, Calhoun VD, Lim K. Frontal and age-related white matter abnormalities in schizophrenia: a multi-site diffusion tensor imaging study. *Winter Workshop on Schizophrenia* (2008).

88. White T, Magnotta V, Bockholt HJ, Williams S, Pierson R, Johnson H, Wallace S, Gollub RL, Calhoun VD, Lim K. White Matter Abnormalities in Schizophrenia: A Multi-site diffusion tensor imaging study. Oral presentation, *Winter Workshop on Schizophrenia and Bipolar Disorder* (2008).

89. Wu L, Calhoun VD. An Approach for Fusion between EEG and fMRI Data. *International Society for Magnetic Resonance in Medicine* (2008).

Appendix B
Awards by Research Area as of 9/12/13

Area of Research	Total Funded in FY13	%	Total Active Projects in FY13
Addiction	7,724,981.32	24%	21
Autism	421,994.00	1%	4
Forensics & Social Cognition	5,815,819.00	18%	5
Neuroinformatics	5,180,249.19	16%	21
Neurodevelopment	3,217,089.22	10%	10
Traumatic Brain Injury	180,498.00	1%	2
Neurosystems for National Security	322,675.00	1%	1
Other General Research Support	1,150,404.00	4%	7
Psychosis	8,090,139.51	25%	10
Total	32,103,849.24	100%	81



APPENDIX C
Pending Proposals as of 9/12/2013

Res/Area	PI	Title	Government Client	MRN Client	Duration	Total Anticipated Value	Date Proposal Submitted
Addiction	Bryan, Angela	Change Talk on risky sexual behavior	NIH	UNM	2 yrs	$ 42,580.20	08/30/12
Addiction	Claus, Eric	mechnism of action between alcohol and partner violence	NIH	University of New Mexico	2 yrs	$ 118,038.00	10/08/12
Addiction	Claus, Eric	Reglatory Science (P50) - Center for Translating Research to Regulate Emerging Tobacco	NIH	University of Kentucky	5 yrs	$ 57,703.00	11/02/12
Addiction	Claus, Eric	functional brain markers of substance	NIH		4 yrs	$ 779,250.00	02/05/13
Addiction	Claus, Eric	Change in Alcohol Dependence: A Longitudinal fMRI	NIH		5 yrs	$ 3,793,140.00	03/05/13
Addiction	Claus, Eric	Retraining to Augment Pharmacotherapy for	NIH		2 yrs	$ 493,404.00	06/17/13
Addiction	Hutchison, Kent	Sequelae of Alcohol Abuse: Role of	NIH	University of Colorado	3 yrs	$ 298,337.00	11/04/11
Addiction	Hutchison, Kent	Naltrexone for Individuals of Asian (PQA-5) DNA	NIH	UCLA	3 yrs	$ 104,000.00	11/02/12
Addiction	Hutchison, Kent	Methylation and cancer prevention: duration and intensity exercise	NIH	University of Colorado	4 yrs	$ 350,039.00	11/26/12
Forensics	Calhoun, Vincent	Functional anatomy of genetic variation of serotonin transporter in PTSD (Sub to Bearer)	NIH	UNM	2 yrs	$ 104,454.00	03/07/12

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Res/Area	PI	Title	Government Client	MRN Client	Duration	Total Anticipated Value	Date Proposal Submitted
Forensics	Kiehl, Kent	The Forensic, Imaging, Risk Assessment and Ethics (FIRE) COBRE	NIH		5 yrs	$ 12,830,849.00	02/15/13
Forensics	Kiehl, Kent	CMI - Construction Services Mobile MRI Sites	CMI		1 yr	$ 60,000.00	11/20/13
Forensics	Shane, Matthew	Neuromodulation of ACC Response to Error as Neuroscience-Based Treatment for ADHD	NIH		5 yrs	$ 1,509,535.00	12/27/12
Forensics	Kiehl, Kent	CMI - Professional Services Mobile MRI Sites	CMI		1 yr	$ 808,475.00	11/20/13
Neuro Informatics	Calhoun, Vincent	A community of brain imaging data: a collaborative neuroinformatics blueprint	NIH		4 yrs	$ 1,739,200.00	03/22/13
Neuro Informatics	Calhoun, Vincent	Characterizing Spatiotemporal Change in Functional Connectivity Networks	NIH		5 yrs	$ 3,803,093.00	03/19/13
Neuro Informatics	Calhoun, Vincent	Integration of fMRI imaging, SNPs and methylation data	NIH	Tulane University	4 yrs	$ 630,446.00	03/13/13

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Res/Area	PI	Title	Government Client	MRN Client	Duration	Total Anticipated Value	Date Proposal Submitted
Neuro Informatics	Calhoun, Vincent	Neural Architecture of Emotion Regulation, Adolescent Development and Depression	NIH	Hartford Hospital	5 yrs	$ 110,380.00	03/18/13
Neuro Informatics	Caprihan, Arvind	Mechanisms Underlying Increased Anisotropic Diffusion Following Mild Traumatic Brain Injury (Sub to Mayer)	NIH	LBERI	2 yrs	$ 213,000.00	02/13/12
Neuro Informatics	Calhoun, Vincent	BIGDATA: Mid-Scale Project: ESCE: DA: Data-Intensive Predictive Analytics of MRI-derived Brain Graphs for Clinical Psychiatry (Sub to Burns)	NSF	Johns Hopkins University	3 yrs	$ 192,435.00	06/07/12
Neuro Informatics	Calhoun, Vincent	Biomarker for Cognitive Impairment in Chronic Schizophrenia (Sub to Pettigrew)	NIH	PHFR, Inc.	3 yrs	$ 365,769.00	03/08/12
Neuro Informatics	Calhoun, Vincent	Integrated analysis of brain imaging and genetic data with sparse models	NIH	Tulane University	5 yrs	$ 708,458.00	10/11/12

APPENDIX C
Pending Proposals as of 9/12/2013

Res/Area	PI	Title	Government Client	MRN Client	Duration	Total Anticipated Value	Date Proposal Submitted
Neuro Informatics	Calhoun, Vincent	CRCNS: Collaborative Research: Integration of multi-modal imgaging and genetics datas with sparse models	NSF		4 yrs	$ 652,798.00	11/09/12
Neuro Informatics	Calhoun, Vincent	US-French Collaboration: Flexible models for capturing connectivity dynamics to differentiate schizophrenia and bipolar disease	NSF		4 yrs	$ 763,103.00	11/09/12
Neuro Informatics	Calhoun, Vincent	The Preprocessed Connectomes Project_An Open Science Data Analysis Inititative	NIH	Nathan S. Kline Institute for Psychiatric Research	4 yrs	$ 175,000.00	05/29/13
Neuro Informatics	Calhoun, Vincent	Neural network changes over the lifespan after brain injury	NIH	Pennsylvania State	6 yrs	$ 334,349.00	05/29/13
Neuro Informatics	Calhoun, Vincent	Data Sharing of New and Existing Neuroimaging Data with the IIDEAA Consortium (NIH Supplement)	NIH	University of Texas Dallas	3 yrs	$ 80,942.00	05/29/13
Neuro Informatics	Calhoun, Vincent	The UNM-CHLA Conte Center on the Developing Mind (P50)	NIH	UNM	5 yrs	$ 1,922,015.00	05/29/13

APPENDIX C
Pending Proposals as of 9/12/2013

Res/Area	PI	Title	Government Client	MRN Client	Duration	Total Anticipated Value	Date Proposal Submitted
Neuro Informatics	Calhoun, Vincent	Linking Local Gamma Activity and Network Connectivity: A Pharmaco-MEG/fMRI Approach	NIH	University of Nebraska Medical Center	5 yrs	$ 842,434.00	07/16/13
Neuro Informatics	Caprihan, Arvind	Brain and Development after Prenatal Opiate Exposure	NIH	UNM HSC	2 yrs	$ 368,513.00	02/04/13
Neuro Informatics	Caprihan, Arvind	Anesthesiology, Brain and Development Study (ABCD Study)	NIH	UNM	5 yrs	$ 1,673,503.00	06/05/13
Neuro Informatics	Liu, Jingyu	A Multidimensional approach for Understanding Cognitive Control Deficits in Psychopathology (Sub to Mayer)	NIH	LBERI	5 yrs	$ 963,903.00	02/02/12
Neuro Informatics	Liu, Jingyu	Integrated analysis of genetic effects on SUDs manifested in brain	NIH		3 yrs	$ 1,023,000.00	06/04/12
Neuro Informatics	Liu, Jingyu	The Epigenetic Link Between Immune System Dysregulation and Schizophrenic Symptoms	NIH		2 yrs	$ 493,553.00	06/17/13

APPENDIX C
Pending Proposals as of 9/12/2013

Res/Area	PI	Title	Government Client	MRN Client	Duration	Total Anticipated Value	Date Proposal Submitted
Neuro Informatics	Liu, Jingyu	Alcohol Use Disorders: Indentifying intrinsic brain networks and associated genetic networks	NIH		2 yrs	$ 479,500.00	06/17/13
Neuro Informatics	Liu, Jingyu	Genetic Networks Influencing Gray Matter Changes in Childhood and Adult ADHD	NIMH		2 yrs	$ 406,275.00	07/16/13
NSNS	Clark, Vincent	Brain Activity During Family Interaction Among Drug Abusing Teens	NIH	Oregon Research Institute	1 yr	$ 105,819.00	10/11/12
Other General Research	Calhoun, Vincent	Collaborative Proposal: A New Class of Complex-Valued Data Analysis Tools Balancing Flexibility and Robustness	NSF		3 yrs	$ 249,897.00	01/23/12
Other General Research	Calhoun, Vincent	Small: Collaborative Research: Sparse representation of multi-subject and multi-modal data for integrative study of fMRI imaging, genetics and IQ (sub to Wang)	NSF	Tulane University	3 yrs	$ 198,919.00	12/14/12

APPENDIX C
Pending Proposals as of 9/12/2013

Res/Area	PI	Title	Government Client	MRN Client	Duration	Total Anticipated Value	Date Proposal Submitted
Other General Research	Calhoun, Vincent	Neural Circuitry Associated with Disinhibition and Adolescent Substance Use	NIH	University of Iowa	1 yr	$ 110,380.00	01/23/13
Other General Research	Calhoun, Vincent	Longitundinal Neuroimaging Biomarkers of Concussion and Alzheimer's Disease	NIH	University of Iowa	3 yrs	$ 549,043.00	01/28/13
Other General Research	Weisend, Michael	Transcranial direct current stimulation effects on white matter tracts in the brain	NIH		2 yrs	$ 468,877.00	02/19/13
Psychosis	Calhoun, Vincent	COINSTAC: Decentralized and Scalable Analysis of Loosely Coupled Data	NIH		5 yrs	$ 4,139,196.00	07/26/13
Psychosis	Mayer, Andrew	A Multidimensional Approach for Understanding Cognitive Control Deficits in Psychopathology	NIMH		4 yrs	$ 2,528,405.00	07/01/13
Psychosis	Turner, Jessica	The Dana Foundation: Brain and Immuno-imaging Program	NIH	UNM	3 yrs	$ 92,443.00	06/11/12
Psychosis	Turner, Jessica	Functional Neurodynamics of Active Auditory Hallucinations	NIH	UNM	5 yrs	$ 1,583,251.00	10/19/12

APPENDIX C
Pending Proposals as of 9/12/2013

Res/Area	PI	Title	Government Client	MRN Client	Duration	Total Anticipated Value	Date Proposal Submitted
Psychosis	Turner, Jessica	CRCNS Data Sharing: Extending The Mind NeuroInformatics framework to enable dynamic sharing of brain imaging, genetics, and assessment data	NSF		4 yrs	$ 1,090,920.00	11/05/12
TBI	Mayer, Andrew	NIH - Promoting and Measuring Changes in Neuroplasticity Following Traumatic Brain Injury	US Army		3 yrs	$ 2,679,829.00	05/30/13

APPENDIX D
FIXED ASSET SUMMARY

Contractor Name	The Mind Research Network
Contract Number	DE- FGO2-08ER64581
Period of Performance	04/01/08 - 09/28/2012
Current as of: DATE, MONTH, YEAR	11 Dec 2013

Type of GFP	Quantity	Brief description of GFP (including model number, factory label)	In Service Date	Purchase Price Charged to DOE
Scientific Equipment	1	Dell PowerEdge R910 Server, S/N# 86Q29Y1 , Tag# A4552	9/12/2013	$28,511.96
Scientific Equipment	1	Brocade VDX 6720 Switch, S/N# BCRALJ2521J0Y2, Tag# A4535	8/9/2013	$6,595.16
Scientific Equipment	1	Brocade VDX 6720 Switch, S/N# BCRALJ2521J0Z0, Tag# A4536	8/9/2013	$6,595.16
Scientific Equipment	1	Brocade 360 24P Switch, S/N# ALJ2527J0D9, Tag# A4537	8/9/2013	$6,543.00
Scientific Equipment	1	Brocade 360 24P switch, S/N# ALJ2527J0EH, Tag# A4538	8/9/2013	$6,543.00

APPENDIX E

Patents and Inventions:

No new patents to report at this time.