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Scientific Accomplishments for ARL Brain Structure-Function Couplings Research on Large-Scale Brain Networks from FY11–FY13 (DSI Final Report)

by Jean M. Vettel, P. Justin McKee, Amy Dagro, Manny Vindiola, Alfred Yu, Kaleb McDowell, and Piotr Franaszczuk

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14. ABSTRACT

The origin of individual differences in behavior is at the core of human science research. Many disciplines have relied on behavior alone, but the field of neuroscience capitalizes on continual advancements in brain imaging methodologies, computational approaches, and modeling techniques to better understand and predict the interaction between the brain and behavior. Leveraging recent innovations in structural imaging and computational modeling, our research program on brain structure-function couplings combines experimental and modeling research to study large-scale brain networks. Our program has three intertwined research areas: neurophysiological data collection and analysis to examine empirical relationships among structure, function, and behavior that capture individual differences; neurophysiological modeling to identify theoretical relationships between structural network topologies and functional activity patterns; and biomechanical modeling to simulate how blast and blunt impact loading conditions transfer to estimated tissue cell death and associated damage to structural connectivity. This report reviews our scientific accomplishments from FY11–FY13 with references to associated publications.

15. SUBJECT TERMS

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Executive Summary

The origin of individual differences in behavior is at the core of human science research. Every individual has a unique set of talents and skills, and these individual differences manifest in the speed and accuracy of behavioral responses across tasks, the strategies employed to solve problems, and the reactions to challenging experiences, to name just a few. Researchers have attempted to explain these differences in human capabilities for centuries. Many disciplines have relied on behavior alone, but the field of neuroscience capitalizes on continual advancements in brain imaging methodologies, computational approaches, and modeling techniques to better understand and predict the interaction between the brain and behavior. By studying neural processing mechanisms in the brain, neuroscientists hope to unravel how the brain enables the mind.

The brain consists of both gray matter, primarily neuronal cell bodies and glial cells, and white matter, myelinated axons that transmit electrochemical signals between gray matter regions. The gray matter is heterogeneous, and different brain regions consist of a wide variety of neuronal cell types with different physical shapes and structural connections. Decades of research has focused on understanding the functional role of these segregated brain areas; however, many leading neuroscientists have argued that piecemeal efforts to explain brain regions will not lead to a full understanding about how the brain works. The field needs a shift to experimental paradigms and novel tools that enable broad, multidisciplinary approaches to examine the integrated activity of the brain's circuitry across large-scale networks. Such a shift is occurring in part through recent advancements in neuroimaging methodologies and computational modeling approaches. These advancements have spawned several international, multi-million dollar efforts (e.g., President Obama's Brain Research through Advancing Innovative Neurotechnologies (B.R.A.I.N.) initiative, the European Human Brain Project), where big data efforts are being pursued, rather than small-scale laboratory studies. These new approaches are poised to revolutionize our understanding of when variability in structural connectivity and/or dynamic functional networks can predict differences in task performance.

Consistent with the aim to embrace multidisciplinary approaches and examine large-scale integrated brain activity, our U.S. Army Research Laboratory (ARL) research program on brain structure-function couplings (BSFC) combines experimental and modeling research to study large-scale brain networks, where studied regions of brain tissue are a cubic millimeter or more in volume (Vettel, Dagro, et al., 2012; Vettel et al., 2013). Our program has three intertwined research areas: neurophysiological data collection and analysis to examine empirical relationships among structure, function, and behavior that capture individual differences; neurophysiological modeling to identify theoretical relationships between structural network topologies and functional activity patterns; and biomechanical modeling to simulate how blast

and blunt impact loading conditions transfer to estimated tissue cell death and associated damage to structural connectivity.

Accomplishments in our neurophysiological data collection and analysis research area cover three experimental topic domains: a comparative examination of the reproducibility of innovative structural imaging methods and identification of promising structural connectivity metrics to capture individual differences (Vettel et al., 2010); comparison and improvement of functional analysis methods that enable the study of dynamic task networks in real-world environments (Gordon et al., 2013; Lau et al., 2012; McDowell et al., 2010; Snyder et al., 2013; Vettel et al., 2012); and design of novel structure-function-behavior datasets across a set of task domains to explore analytic methods that can identify predictive connectivity relationships with variability in task performance (Kantner et al., submitted; Vettel et al., submitted). Accomplishments in our neurophysiological modeling research are tightly integrated with our experimental research, and highlighted results inform our understanding about the reliability and interpretability of the functional connectivity measures and their use on experimental data (Gordon et al., 2013; Snyder et al., 2013; Vindiola et al., in press). Accomplishments in our biomechanical modeling area include a finite element model of brain tissue informed by experimentally-collected, structural imaging data, and a set of blast and blunt impact simulations to investigate how tissue damage may manifest in structural network changes (Kraft & Dagro, 2011; Kraft et al., 2012; McKee et al., 2013).

Our BSFC research program is aligned with ARL's broader translational neuroscience approach by embracing translational research themes (e.g., studying the brain in real-world environments) and targeting transition goals (e.g., enhancing neuroimaging devices for use in operational contexts and improving Soldier protection systems). We specifically aimed to develop new approaches to quantify individual differences and recover time-evolving functional networks that can enhance algorithms needed for neurotechnologies designed for use in real-world contexts. We also aimed to improve material models of the brain for use in simulations that can improve the design of protection equipment to minimize neural injury. We believe this translational focus enhances the probability that the fundamental structure-function-behavior relationships uncovered in this basic research program will have application for both healthy and clinical populations, including individual differences that arise from experience and training or differences that arise from injury and rehabilitation. This focus allows the research to address several of the Army challenges highlighted in the Army's Ready and Resilient campaign.

Over the past three years, our results have been accepted for publication and presentation at international research conferences, including Society for Neuroscience, Cognitive Neuroscience Society, Psychonomic Society, Institute of Electrical and Electronics Engineers (IEEE) Neural Engineering, and Army Science Conference. We have four publications in peer-reviewed journals, with two more under review, five peer-reviewed conference proceedings, four published tech reports, nine manuscripts in preparation, and ten conference presentations.

1. Introduction

The brain consists of roughly 86 billion neurons, plus another 84 billion non-neuronal support cells (Azevedo et al., 2009). These functional units are constantly active and forming complicated and dynamic networks that function to meet two diverse requirements: localized roles for processing specific types of information and global roles for integrated activity across disparate brain regions (Friston, 1994; Sporns, Tononi, & Edelman, 2000). Neuroscientists have traditionally relied on neuroimaging technologies that only sample brain activity from a few neurons in localized regions or coarse brain activity from large patches of cortex, and these imaging tools fostered a focus in the 20th century on understanding segregated areas of the brain and local specialization of neuronal populations (Alivisatos et al., 2012). However, many leading neuroscientists have argued that piecemeal efforts to explain brain regions will not lead to understanding about how the brain works, and the field needs a shift to experimental paradigms and novel tools that enable broad, multidisciplinary approaches to examine the integrated activity of the brain's circuitry across large-scale networks (Alivisatos et al., 2012; Friston, 1994; Sporns, Chialvo, Kaiser, & Hilgetag, 2004).

Several recent technology innovations have enabled brain science to move beyond traditional, reductionist approaches and examine the role of brain networks in guiding behavior. First, revolutionary advances in computing power for computational brain imaging occurred from increased availability of massively parallel, thousand-core supercomputers, and initiatives like Henry Markram's Blue Brain project (Markram, 2006) arose with an impressive aim to reverse-engineer the mammalian brain, where the fidelity of each simulated neuron was estimated to require the equivalent of a laptop computer. Second, improvements in neuroimaging technologies have enabled unprecedented resolution of *in-vivo* imaging of the brain's white matter fiber structure, providing a novel capability to study the "wiring" between brain regions. These two innovations, among a few others, have incited many large-scale, multi-million dollar international research efforts, such as President Obama's B.R.A.I.N. Initiative, the Human Connectome Project, the European Human Brain Project, and the Allen Institute for Brain Science. These technological advances have provided increasing evidence that spatially distributed brain areas are actively engaged in coordinated communication during many behaviors (Behrmann & Plaut, 2013; Blinowska, Kaminski, Brzezicka, & Kaminski, 2013; Ioannides et al., 2012; Philiastides & Sajda, 2006; Sakkalis, 2011; Supp et al., 2005; Sun et al., 2009), and even when the individual is at rest (Greicius, Krasnow, Reiss, & Menon, 2003; Raichle et al., 2001).

Our research interest in studying couplings among brain structure, function, and behavior was largely influenced by the rise of network science within neuroscience (Bullmore & Sporns, 2009). In particular, work by (Honey et al., 2009) used converging information from multiple

imaging modalities to show that white matter pathways guide and constrain the ways in which brain regions communicate during a quiescent resting state, but they also found that brain regions are often functionally connected in the absence of direct or measurable structural connections. This result indicates that purely structural information had limited predictive power for resting state brain activity; instead, they found that indirect functional connections, rather than structural connections, account for a large proportion of the resting brain network activity.

Many questions remain about whether the same pattern holds true for task-dependent functional networks: can variability in structural connections be used to predict variability in brain regions activated during a cognitive task; does the amount of functional variability accounted for by structure vary greatly based on specifics of the task; how stable are structural measurements over time, or conversely, are cutting-edge structural imaging techniques sensitive to changes induced by learning, experience, injury, and rehabilitation? Our research examines when variability in structural connectivity, either due to natural variability between healthy individuals or traumatic insult, can be used to predict differences in the brain's functional connectivity for task-dependent networks (Vettel et al., 2013;Vettel, Dagro, et al., 2012).

Within that context, the scope of our research program is further refined by our alignment with a scientific vision for translational neuroscience. A typical neuroscience experiment is conducted in a quiet, barren room where stimuli are presented in isolation on a single computer monitor, and participants are asked to minimize both body movements and eye blinks in order to minimize artifacts in the physiological measurements. While this environment is designed for studying specific cognitive processes, without confounds of concurrent tasks or excessive noise overriding the physiological signal of interest, the laboratory may limit our understanding about how tasks are performed in the real-world, where our bodies and eyes move freely and we are often faced with multiple, concurrent tasks (Vettel, Lance, et al., 2012). A central scientific question is whether brain function is the same in traditional neuroscience experiments, where participants execute simplified tasks with simplified stimuli within artificial environments, as it is in real-world, operational settings, with concurrent tasks, perceptually-rich stimuli, and real-world stress, fatigue, amongst other states (Gramann et al., 2011; Hasson, Malach, & Heeger, 2010; Kingstone, Smilek, Ristic, Friesen, & Eastwood, 2003; Kingstone, Smilek, & Eastwood, 2008; Oie & McDowell, 2011; Shackman, Maxwell, McMenamin, Greischar, & Davidson, 2011). As one example, Hasson and colleagues (Hasson et al., 2010) review differences in neural responses to naturalistic stimuli compared to simple, artificial stimuli, and they cite evidence about changes in the precision of neural spike train activity, the statistical properties of the response, and predictive power of the functional model itself. They also emphasize that some complex behaviors can only be studied in natural contexts since many common tasks require cognitive processes that unfold over time, such as reading books, watching movies, and engaging in social events.

This need to move research into more complex, time-evolving task environments echoes a sentiment in a recent White House report on critical research themes for understanding causes

and effects of human activity to secure the welfare of citizens and implement effective policies ("NRC Report: Social, Behavioral, and Economic Research in the Federal Context," 2009). The report argues that questions about the origin of individual behavior are at the core of human science research, and it identifies understanding the structure and function of the brain as a foundational research theme. The brain underlies thoughts, feelings, and actions, but we have limited knowledge about how these abilities arise from the complex interactions among the mind, brain, and external environment. Thus, to improve our understanding of the brain in real-world contexts, we have to develop the experimental paradigms and analysis tools to decode neural patterns while participants are moving freely and interacting in natural ways (e.g., see McDowell et al., 2013). The NRC report cites a need for neuroscience research to influence clinical assessments and treatments, educational practices, and accuracy of eyewitness testimony; however, there are significant hurdles for development of neurotechnologies to improve learning, performance, or treatment, especially given the known differences in the anatomical structure and functional activity patterns between individuals. Our approach focuses on how to use information about the brain to characterize brain function in real-world contexts and design algorithms to improve system design and optimize human-system performance.

Consequently, our research program examines innovative methodologies for recovering time-evolving functional networks from neuroimaging data, in addition to understanding structural constraints on function and behavior. Our current research on functional networks includes both functional magnetic resonance imaging (fMRI) data that tracks changes in blood flow as a proxy measure of brain activity and electroencephalography (EEG) data that records electrical activity on the scalp that reflects the underlying synaptic activity summed across thousands of neurons. The former requires participants to lie still on their backs in an MRI scanner, and the evolution of the hemodynamic response takes 8–12 s with sampling every 1–3 s. This approach may provide insights into structure-function relationships, but it has limited utility for studying unconstrained behavior in real-world situations. EEG, on the other hand, is a mobile neuroimaging technology that samples ongoing brain activity every few milliseconds, providing temporal dynamics closer to the time scale of behavioral actions. Although EEG has limited spatial resolution of interacting neural sources, this trade-off does not impede our aim to understand how information about the brain may be used to design neurotechnology systems that improve human-system performance. Our research program emphasizes enhancing functional connectivity methods for EEG research on Army-relevant tasks in real-world settings, which we argue is critical for supporting translational neuroscience experiments where brain networks underlying dynamic behaviors are studied with realistic tasking. These improved methodologies allow us to pivot from a laboratory-based understanding of the brain to more sophisticated models of the brain-behavior relationships within real-world environments.

In sum, our research leverages advances in multi-scale modeling and multimodal imaging analysis to develop integrative, predictive models of network structure, brain function, and task performance. We focus on understanding how the brain functions in real-world environments

and the identification of predictive relationships among structural and functional connectivity measures and variability in task performance. Our scientific research focuses on understanding real-world, task-relevant brain states, and ongoing and future ARL research with our academic and industry partners will advance the state of the art in using connectivity metrics to predict differences in cognitive performance. The current, targeted transition of this basic research program is to understand how fundamental BSFC relationships can improve algorithms for neurotechnologies designed for real-world settings, as well as improve the design of Soldier protection technologies to minimize neural injury.

2. Technical Approach

Our technical approach combines experimental and modeling research to study brain networks across multiple spatial and temporal scales, but our three intertwined research areas all target an understanding of large-scale brain networks, where studied regions of brain tissue are a millimeter or more in size. Our focus on large-scale networks is dictated by the available, non-invasive neuroimaging techniques for studying human behavior in unconstrained, real-world environments. In order to link variability in structure and function to task performance, all three research areas examine structural connections and brain activity at the level of large-scale networks. Specifically, we focus on variability in connectivity, both between individuals and within individuals over time, and examine its ability to predict and shape outcomes relevant to task performance. This focus enhances the probability that the fundamental structure-function-behavior relationships uncovered in this basic research program will have application for both healthy and clinical populations, including individual differences that arise from experience and training, or differences that arise from injury and rehabilitation.

An overview of our three research areas is shown in figure 1, with a short description of our scientific focus for each. The purple boxes indicate that the research area examines both structure and function, while the blue box indicates an emphasis on purely structural changes that link to function through its connections to other research areas. The two black boxes capture research domains needed to enable structure-function-behavior experimentation. The following sections for each area will first describe the rationale for the research and then provide the analytic framework and terminology definitions for the area's technical accomplishments, which are described in their corresponding Results section.
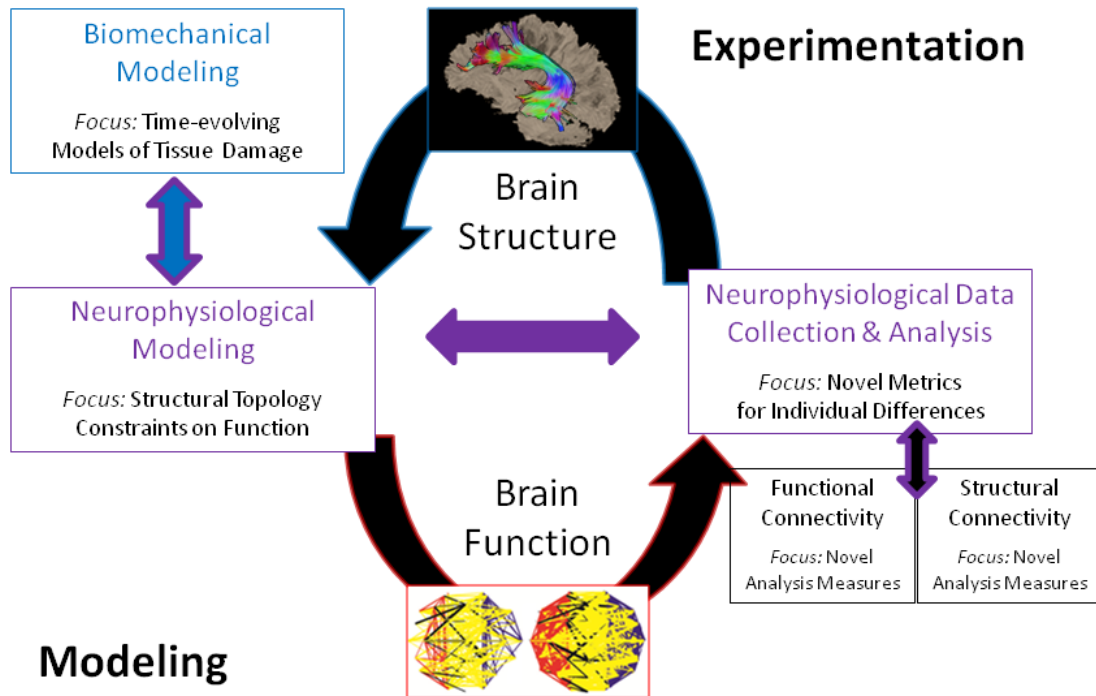
Figure 1. Each of the three main research areas is shown in a purple or blue box with arrows to indicate interactions with one another. Purple indicates that the research area examines both structure and function, while the blue box indicates an emphasis on purely structural changes that link to function through its connections to other research areas. The two black boxes capture research domains needed to enable structure-function-behavior experimentation. Each box concisely describes the scientific focus that advances the state of the art in the field and addresses the scientific vision of our laboratory.

2.1 Neurophysiological Data Collection and Analysis

Our experimental research largely focuses on three intertwined domains: structural connectivity, functional connectivity, and predictive relationships among structure, function, and behavior. Our current research portfolio relies on two neuroimaging technologies: *Magnetic resonance imaging* (MRI) and *Electroencephalography* (EEG). The first can provide both structural and functional brain data, while the second provides only functional data.

MRI provides information about the tissue composition of millimeter-scale elements in the brain, known as voxels. Our structural MRI datasets include two image types. The magnetization-prepared rapid gradient-echo (MPRAGE) scan captures the gyri and sulci (folds) of gray matter brain regions, and these anatomical landmarks are used to delineate brain regions through segmentation algorithms or subject matter expert delineations. A diffusion weighted imaging (DWI) scan captures the directional diffusion of water within a voxel, and reconstruction algorithms are used to estimate the pathways of the white matter fiber tracts, since water diffuses in the same direction as the local fiber tract(s). This process of reconstructing fiber streamlines estimates the structural connections between brain regions, and it is known as tractography. Additionally, functional MRI (fMRI) data provide information about the blood flow that has

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been linked to functional brain activity at a slightly greater spatial scale, typically 2 to 3 millimeter cubic voxels.

All of our projects with MRI datasets must be collected in conjunction with academic partners since no MRI scanner is located at ARL. The expense and logistical overhead of the scanner seems best suited for our academic partners, and we currently have jointly designed experiments and ongoing analyses with the Institute for Collaborative Biotechnologies (ICB) at the University of California, Santa Barbara, Carnegie Mellon University (collaborator originally affiliated with University of Pittsburgh), and the Institute for Soldier Nanotechnologies (ISN) at the Massachusetts Institute for Technology. We are also able to leverage structure-function MRI datasets collected by partners in the Cognition and Neuroergonomics Collaborative Technology Alliance (CaN CTA), including Columbia University, the University of Michigan, Ann Arbor, and the University of California, San Diego.

Electroencephalography (EEG) records the synchronous electrical activity of centimeter-scale populations of neurons after propagation to the scalp via volume conduction through the skull and other tissues surrounding the brain. Many of our EEG datasets are collected at ARL to capitalize on our local expertise in novel EEG imaging and analysis techniques (Lawhern, Hairston, McDowell, Westerfield, & Robbins, 2012; Marathe, Ries, & McDowell, 2013, in press; McDowell et al., 2013), and our unique access to operational test protocols, environments, and military personnel (Davis, Smyth, & McDowell, 2010; Davis, Animashaun, Schoenherr, & McDowell, 2008; Lance et al., 2011; McDowell, Nunez, Hutchins, & Metcalfe, 2008; Vettel, Lance, et al., 2012). These datasets facilitate our study of functional brain networks that underlie dynamic behaviors with realistic tasking; however, when our experimental questions require structural and functional information from the same individual, we have adopted two approaches.

The first approach is to support EEG data collection in our collaborating academic laboratories, including several datasets with simultaneous EEG and fMRI dataset collection. These simultaneous datasets facilitate functional network analyses across neuroimaging methodologies to examine differential understanding about task-dependent functional network dynamics from a method with high spatial and low temporal resolution (fMRI) and a method with low spatial and high temporal resolution (EEG). Likewise, these two functional imaging methods provide different technical approaches to link functional activity with variability found in structural networks: fMRI and DWI have similar spatial resolution in millimeter-sized voxels, while EEG captures spatially dispersed signals on the scalp that require source localization algorithms to estimate their accordance with DWI spatial locations. Ongoing research examines sensitivity to structure-function-behavior relationships across these neuroimaging methodologies.

The second approach relies on 15 ARL volunteers who flew to academic partners to be scanned, providing critical structural data that can be paired with additional functional and behavioral datasets that can be collected at ARL and/or partner sites. Using local volunteers enables efficient expansion to Army-relevant task domains as emerging needs change, but with long-

term personnel as volunteers, we can also investigate the stability of structure-function-behavior relationships over time. The robustness of predictive relationships is critical for the transition of this basic research to Army applications, including individual-specific neurotechnologies to improve performance. While 15 subjects is a relatively small sample size, this will be adapted as needed based on emerging scientific questions and available resources.

Across our research program, we focus on large-scale networks across and rely on a formalism from network theory to facilitate the integration of results across experimentation and modeling where networks simply consist of nodes (brain regions) connected by edge weights (e.g., connectivity relationships).

2.1.1 Structural Connectivity

Our research on structural networks has focused on the acquisition and reconstruction of the MRI imaging data itself. As discussed earlier, technological advancements in structural imaging enabled new approaches three years ago, and as expected, the field continues to make rapid advancements in both the DWI scanning protocols and the algorithms to reconstruct the white matter fiber tracts from the imaging data (Yeh & Tseng, 2013; Yeh, Wedeen, & Tseng, 2011). Most of our research over the past three years has focused on comparing imaging methods and examining the reproducibility of structural networks. This work provides the foundation to develop structural metrics of individual differences that can be examined for their predictive relationship with variability in functional networks and behavioral performance.

In figure 2, the analysis pipeline to generate a structural network is depicted in the left panel. Individual subjects lie in an MRI scanner while the MPRAGE and DWI structural scans are acquired. From the MPRAGE scan, segmentation algorithms or subject matter experts delineate the 3D brain volume into brain regions of needed spatial resolution for the experimental question. Data from the DWI scan is used in reconstruction algorithms to estimate the streamlines that provide structural connections between brain regions.

In a structural network, the gray matter regions are the nodes and the streamline connections, representing reconstructed white matter tracts, determine the edge weights.
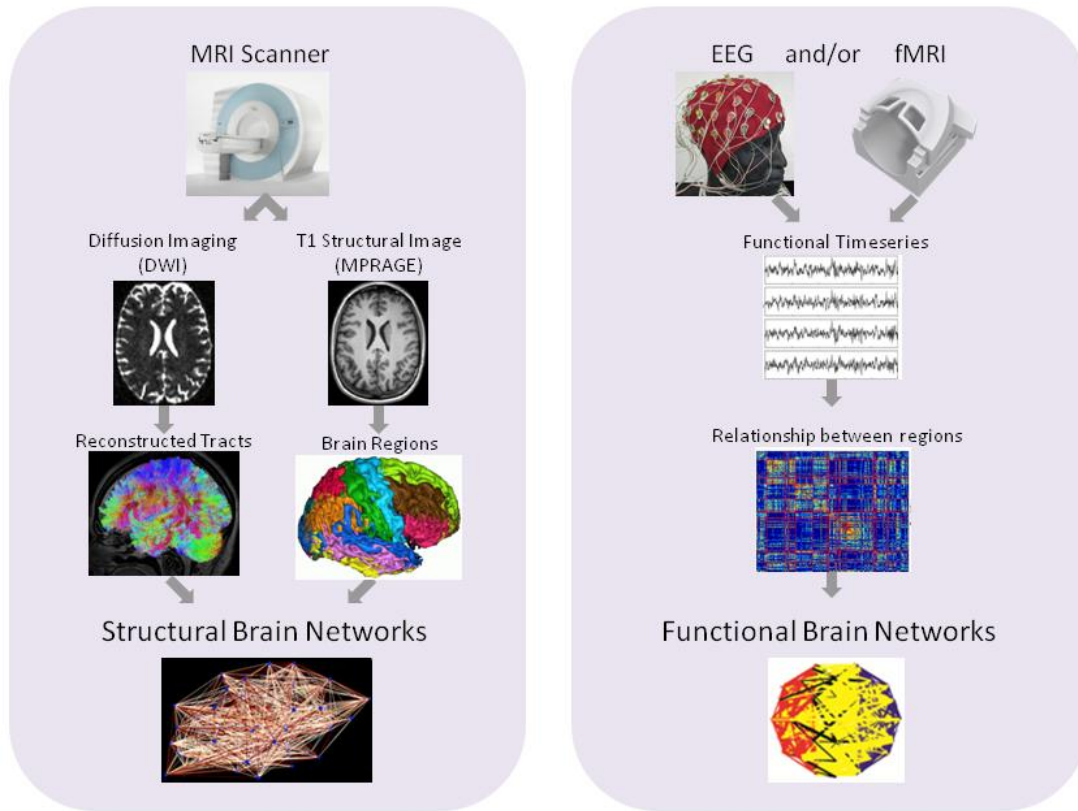
Figure 2. The neuroimaging methodologies and processing pipeline used to generate structural brain networks from diffusion-weighted imaging data from an MRI scanner and functional brain networks from either EEG or fMRI data.

2.1.2 Functional Connectivity

Although our long-term research portfolio will likely require a multi-modality collection of functional neuroimaging methods, our initial research focus has been on implementing, comparing, and evaluating functional connectivity measures for a single modality, EEG. The advantage of EEG for conducting translational neuroscience research is well-described elsewhere (Gramann et al., 2011; Lance, Kerick, Ries, Oie, & McDowell, 2012; McDowell et al., 2013), but one of the central benefits of EEG over other current functional neuroimaging technologies is its applicability for studying unconstrained behavior in real-world situations. Current experimental protocols sample brain activity every few milliseconds, a timeframe that is well-aligned with the timescale of behavior. Thus, EEG enables the study of functional networks that underlie task performance in the type of mobile, operational environments where we target the transition of our basic research for both the Army and the international neuroscience community.

However, the mobility advantage of EEG is paired with a substantial technical challenge: separating the underlying brain signals from volume-conducted noise on the scalp arising from muscle activity, body movements, and external electrical sources. This challenge is further increased based on our desired emphasis to recover *dynamic brain networks* from the recorded

electrical activity on the scalp; EEG relies on volume conduction of the synaptic brain activity through the scalp, where the same brain signal contributes to the signal recorded at multiple EEG electrodes. Therefore, our research needs require innovative methodologies that can distinguish complex interdependencies that exist between disparate brain regions from volume conduction effects of sources unrelated to the task-dependent brain activity of interest. Most of our research in the past three years has focused on implementing and comparing cutting-edge methods to parse volume-conducted signals from underlying brain signals in EEG network analysis. This work provides the foundation to develop functional metrics of individual differences that can be examined for their predictive relationship with variability in structural networks and behavioral performance.

In figure 2, the analysis pipeline to generate a functional network is depicted in the right panel. For functional networks, an individual subject is either outfitted with a high-density EEG cap with 64 to 256 electrodes on their scalp, or they lie in an MRI scanner with a head coil surrounding their brain. Functional network connectivity arises from neural circuits that are dynamically formed from coordinated activity of neurons communicating by sending electrical signals between brain regions (EEG) or from the blood flow between regions that reflects recently activated brain regions (fMRI). Both neuroimaging methodologies sample the time-evolving nature of these dynamic, short-lived functional networks while the subject performs cognitive tasks, and then functional connectivity measures are calculated to determine statistical relationships among the recorded brain signals. This analysis estimates a time-evolving functional network that captures dynamic changes among the sampled brain regions, and these changes can be linked to differences in task performance (Wymbs, Bassett, Mucha, Porter, & Grafton, 2012), mental state (such as changing levels of fatigue or stress), or mental disease state (He, Yang, Wilke, & Yuan, 2011).

In a functional network, the gray matter regions are the nodes, and the statistically significant signal pairs identified by the connectivity measure(s) determine the edge weights.

2.1.3 Structure, Function, and Behavior Research

The structural and functional connectivity research emphasizes the development of methods to quantify networks as a means to identify metrics of individual differences; however, these metrics are merely the building blocks for research on brain structure-function couplings. That is, structural and functional network metrics are measures of differences among individuals that enable research to examine whether predictive statistical relationships exist among structure, function, and behavior for real-world task domains. Thus, network metrics are the foundation needed for our future work to examine these predictive relationships for Army-relevant tasks. During the last three years, our work has focused on identifying task domains for investigating brain structure-function relationships, securing funds to collect these datasets with our academic partners who have the research MRI scanners needed for structural imaging, designing collaborative experimental protocols, conducting joint data analysis, and leveraging existing

structure-function-behavior datasets to examine technical approaches to investigate relationships among these three classes of individual difference metrics.

2.2 Neurophysiological Modeling

Our neurophysiological modeling research examines the relationships between structural network topologies and the resulting functional network properties. As discussed earlier, advancements in parallel computing have enabled radical new approaches for computational models of the brain. Our research interests were largely inspired by promising advancements in the multi-million-dollar Blue Brain Project, which began in 2005 in conjunction with one of IBM's famous supercomputers, the BlueGene/L. The project aims to reverse engineer the mammalian brain. Using a mixture of automated, robotic experiments, thousands of experiments provided data to reconstruct the brain neuron by neuron, where the fidelity of each simulated neuron was estimated to require the equivalent of a laptop computer. The landmark success in 2007 was a biologically valid model that replicates the activity of a rat's cortical column, and the project envisions the existing models of neurons and microcircuits as the basic building blocks for larger-scale models leading towards a complete, virtual model of the human brain (Markram, 2006).

Our effort, however, is not focused on modeling the entire brain across all scales. Instead, we target biologically inspired models that simulate large-scale brain networks that can be directly tied to the experimental results from our neuroimaging work (see Results 3.1) and the simulated networks from our biomechanical modeling research (see Results 3.3). Our dynamic models of interacting functional brain nodes are configured based on a structurally defined network topology in order to uncover theoretical relationships between structure and function. The models use structural imaging data to parameterize the connections between the simulated nodes, and the functional oscillations of the nodes are matched to experimental results or chosen theoretically. The structural network data can come from research on healthy individuals or patients, or it can be simulated output from the biomechanical modeling of structural network damage estimated from a blast or blunt force simulation.

In the last three years, we have implemented two neurophysiological models at complementary spatial scales. Our neural mass models abstract and simulate the oscillatory activity of individual cortical columns at each node, while our single neuron-level model simulates thousands of biophysical models of inhibitory and excitatory neurons connected into a network with oscillatory activity at each node. Although these two projects capture different spatial scales, they both aim to uncover theoretical relationships between structural connectivity and the resulting functional connectivity at the level of large-scale networks. In each case, we built our expertise about the models by generating small, 2–4-node networks to test functional connectivity methods when the underlying connectivity of the network is known. This demonstrates another way that the modeling research can influence experimental research by

improving our understanding about the reliability and interpretability of the functional connectivity measures.

In figure 3, the pipeline to implement a neurophysiological model is depicted in the left panel. A simplified network is defined with unidirectional or bidirectional connections among the desired number of nodes. Spatial relationships can be represented using experimentally-derived delays in the underlying equations that control signal propagation between node pairs. Each node is parameterized to oscillate at the desired frequency range(s), and the simulation produces simulated neural activity in the network. Following the same procedure as the experimental research, functional connectivity measures are then calculated on the time series between the node pairs to determine statistical relationships among the simulated brain signals. This model reveals dependencies among the structural topology and the resulting functional network, and it can also refine our understanding about the reliability and interpretability of the functional connectivity measures when underlying connectivity is known.
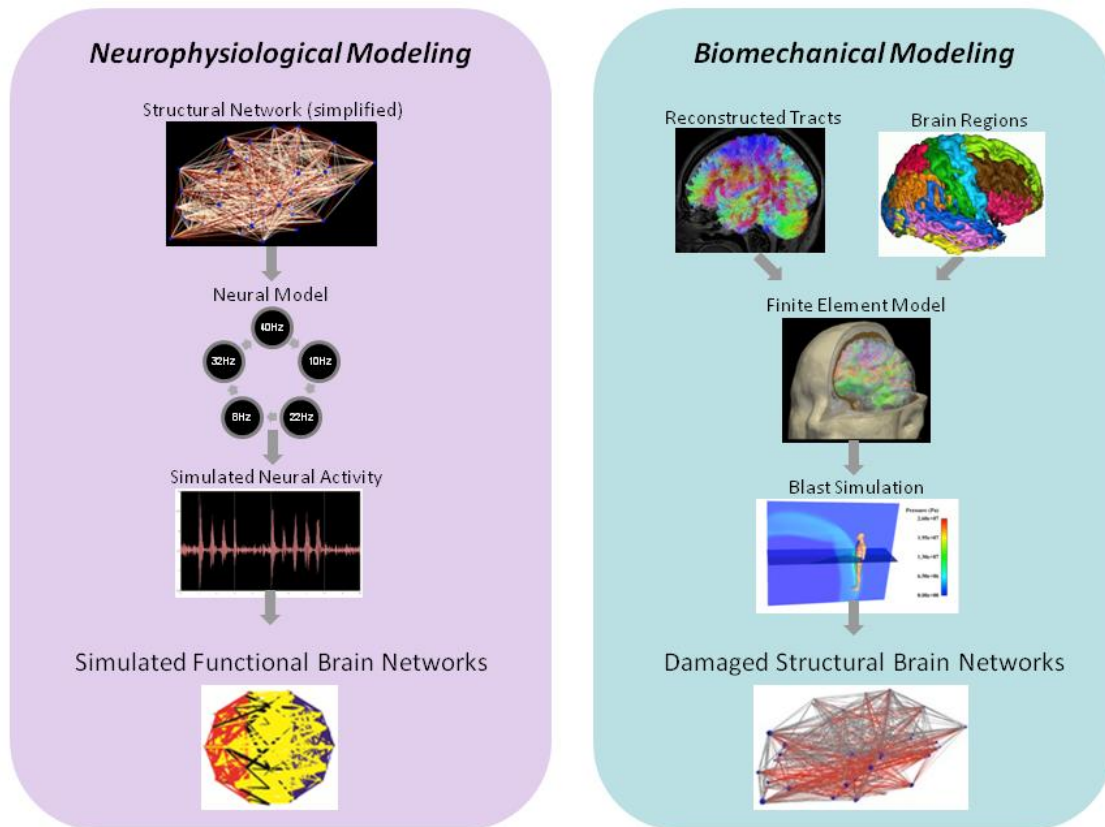
Figure 3. The modeling approaches rely on structural connectivity data to establish the underlying network. The neurophysiological research simulates oscillatory brain activity in a simplified network to investigate relationships between structural network topologies and functional activity patterns, while in the biomechanical research, blast simulations are used to estimate damage to the structural network.

2.3   Biomechanical Modeling

Our biomechanical modeling research aims to improve our understanding of how mechanical loading to the head propagates to degraded structural connectivity between brain regions. The assessment, delineation, and treatment of traumatic brain injury (TBI) are critically needed across civilian and military populations. TBI occurs when an external force impacts the head and causes a loss of consciousness, amnesia, and/or alterations in normal brain function. The Centers for Disease Control and Prevention report that, on average, approximately 1.7 million people sustain a TBI annually (Faul, Xu, Wald, & Coronado, 2010). Blast-related TBI is of particular interest due to its prevalence in recent military conflicts (Gupta & Przekwas, 2013). An ongoing challenge has been to identify the neural mechanisms underlying brain injury.

Diffuse axonal injury is believed to be a classic signature of TBI neural damage (Gupta & Przekwas, 2013), and it is characterized by widespread structural lesions in white matter fiber tracts (the axons of neurons) that connect brain regions and allow neurons to communicate with one another (Taber, Warden, & Hurley, 2006). In severe TBI, shearing and deformation forces can immediately injure axons (Le & Gean, 2009), leading to measurable decrements in performance on cognitive tasks (Kraus et al., 2007; Kumar et al., 2009; J. Y. Wang et al., 2008; Xu, Rasmussen, Lagopoulos, & Håberg, 2007). These forces may also trigger a cascade of brain injury mechanisms, which can degrade the structural fiber tract connections between brain regions over the course of hours, days, and even months (Smith, Meaney, & Shull, 2003). Degraded structural connectivity has been linked to many disease states, including schizophrenia and Alzheimer's (Bassett et al., 2008; He, Chen, Gong, & Evans, 2009), and it may underlie the cognitive deficits characteristic of mild, moderate, and severe cases of TBI (Vettel, Bassett, Kraft, & Grafton, 2010).

In the biomechanical modeling effort, we use finite element modeling (FEM) and empirically-derived formulas to relate how simulated blast or blunt impact forces transfer to cellular death in neural tissue. FEM provides the capability to directly model the forces experienced by discrete elements within the brain. The availability of high-performance computing resources allows us to probe these forces at spatial scales matching our neuroimaging efforts. Ongoing efforts link the resulting cellular damage estimates to hypothesized changes in the structural connectivity between brain regions. These damaged structural networks will next be used as input for a neurophysiological model that simulates how the functional activity of the network changes based on the damaged structural connections.

In figure 3, the pipeline to implement a biomechanical model is depicted in the right panel. Experimental DWI and MPRAGE data are used to create a structural network of nodes (brain regions) and edges (streamlines). This experimentally-derived structural network is spatially aligned with the finite element model of brain tissue, and each element is assigned a fiber direction based on the dominant direction of the streamlines passing through it. The FEM is then used in blast or blunt impact simulations, which makes use of two-way coupling of Lagrangian

and Eulerian codes, and the strain in the direction of fiber is calculated for each element. Using empirical formulas for cell death, the strain in each element is linked to estimated tissue damage, and the amount of damage is then used to estimate changes to the edges of the structural network. The output of the proof-of-concept model is a damaged structural network in the same coordinate space as the initial experimental data, and ongoing research uses it as input for a neurophysiological model simulation. Future work could also compare it to experimental findings in clinical populations.

2.4 Technical Approach Summary

Critically, all of our research efforts are focused on large-scale brain networks, so network level results from the experimental studies can be used as input for the modeling work. Likewise, estimated network output from the modeling efforts can be used to inform hypotheses and analyses on the experimental networks. Thus, our focus on brain regions (nodes) and structural and functional brain connectivity (edge weights between nodes) enables the integration of modeling and experimentation efforts in order for theoretical insights from the modeling work to interact with the empirical relationships discovered in the experimental research. Each of the three main research areas has been scoped to produce scientific results that advance the state of the art in the field (see figure 1); however, the strength of this research program emerges from a focus on uncovering the fundamental relationships among brain structure, function, and behavior. Our highlighted accomplishments in the Results section summarize our contributions to a computational neuroscience field focused on understanding brain network connectivity and its relationships with task-dependent behavior.

3. Results

Projects over the first three years focused on integrated research across experimentation and modeling efforts: development of analysis pipelines for computing and quantifying individual differences in connectivity networks; design of experimental protocols and collection of novel structure, function, and behavior datasets in Army-relevant task domains; and implementation of computational brain models on ARL servers for novel simulations and analysis. Each of the following sections summarizes the main findings and highlighted accomplishments for each of our three main research areas. The first section (3.1) discusses our experimental research, and it is organized in three subsections to separately convey the unique challenges in our structural connectivity (3.1.1) and functional connectivity (3.1.2) research that serves as the foundation for understanding predictive relationships among structure, function, and behavior (3.1.3). Although the experimental results are organized into three subsections, the research was intertwined in its execution. The second section (3.2) reviews our neurophysiological modeling of oscillatory brain activity at multiple spatial scales and highlights its close integration with the experimental research. The third and final section (3.3) describes our finite element modeling that uses

structural connectivity information to inform estimated injury to brain tissue that is then linked back to damage in large-scale, structural brain networks. This proof-of-concept modeling approach enables its integration with the neurophysiological and experimental work to estimate changes in functional activity and/or behavior based on the structural network damage.

3.1 Neurophysiological Data Collection & Analysis

Our experimental research largely focuses on three intertwined domains: structural connectivity, functional connectivity, and predictive relationships among structure, function, and behavior. Across all three, we aim to identify robust metrics that quantify differences among individuals relevant for task performance outcomes, but the state of the art in each domain has required and will continue to demand a different research focus for the near-term.

3.1.1 Structural Connectivity

Methods to reconstruct structural brain networks from MRI scans are still an active area of research. Given these recent changes, one component of our structural research evaluates the imaging dataset itself, investigating the reproducibility of the data at varying time intervals. Our first structural project in conjunction with the ICB investigated reproducibility from triplicate scans collected from the same individual within the same month (Vettel et al., 2010). Our analysis compared brain-wide tract reconstructions (streamlines) from two types of diffusion weighted imaging scans, diffusion tensor imaging (DTI) and diffusion spectrum imaging (DSI). We examined reproducibility of the recovered structural network by comparing within-subject variability across three repeat scans to between-subject variability across scans. As expected, we found that both diffusion imaging techniques exhibited less variability within participants than between participants, indicating that the brain structure of any single participant was more similar to other scans from the same individual than to scans from other individuals. Importantly, the results also showed that this effect was greater for the DTI method than the DSI method. This suggested that DTI can better capture differences among individuals compared to DSI. This result, however, was likely tied to the tractography reconstruction algorithms available at the time of analysis.

Concurrent with these analyses, innovations occurred in the estimation of the water diffusion within each brain voxel (Yeh, Wedeen, & Tseng, 2008; Yeh et al., 2011). These improvements allow for a renewed focus on millimeter-scale, voxel-based analyses for an evaluation of reproducibility. Recently, we began collaborating with a lab pioneering this approach at Carnegie Mellon University, and we collected a new dataset to examine reproducibility that leveraged their innovations in the DSI acquisition sequence as well. This dataset contains duplicate scans from the same individual six months apart. Yu and colleagues are preparing a manuscript discussing our reproducibility analysis focusing on the test-retest validity of orientation distribution functions, quantitative anisotropy, and other associated metrics within the imaged brain voxels that are the basis for reconstruction algorithms of directional streamline estimates. This ongoing project leverages a summer internship analysis executed by Yu under the

mentorship of Vettel that explored the use of probabilistic tractography analyses to assess the integrity and reproducibility of white matter tracts.

Our research to confirm the reproducibility of structural imaging enables the development of our main interest—structural metrics that capture individual variability in anatomical networks. Ongoing research examines both voxel-based variability in structural directionality estimates as well as network variability from tractography. One project investigates a method that preserves variability in the shape of the estimated streamlines (Cieslak & Grafton, 2013). Prevalent analysis methods focus on the start and end points of structural connections—i.e., do participants have the same number of fiber tracts connecting two brain regions? This conventional approach discards the information about the shape of the tract and whether its path between regions passes through the same cortical voxels between individuals. We leverage a different method in our $(DSI)^2$ toolbox under development in order to preserve this additional tract information. Researchers draw a region anywhere in the imaged 3D brain volume and compare the fiber tract pathways (position vectors) across individuals; an example is shown in figure 4. This provides a more detailed comparison of tract similarity between individuals, and it is one promising method to better quantify individual differences in structural networks and examine if these differences explain the functional and/or behavioral variability. A joint publication is in preparation by Cieslak, Jaswa, Vettel, and Grafton to accompany a public release of this toolbox.
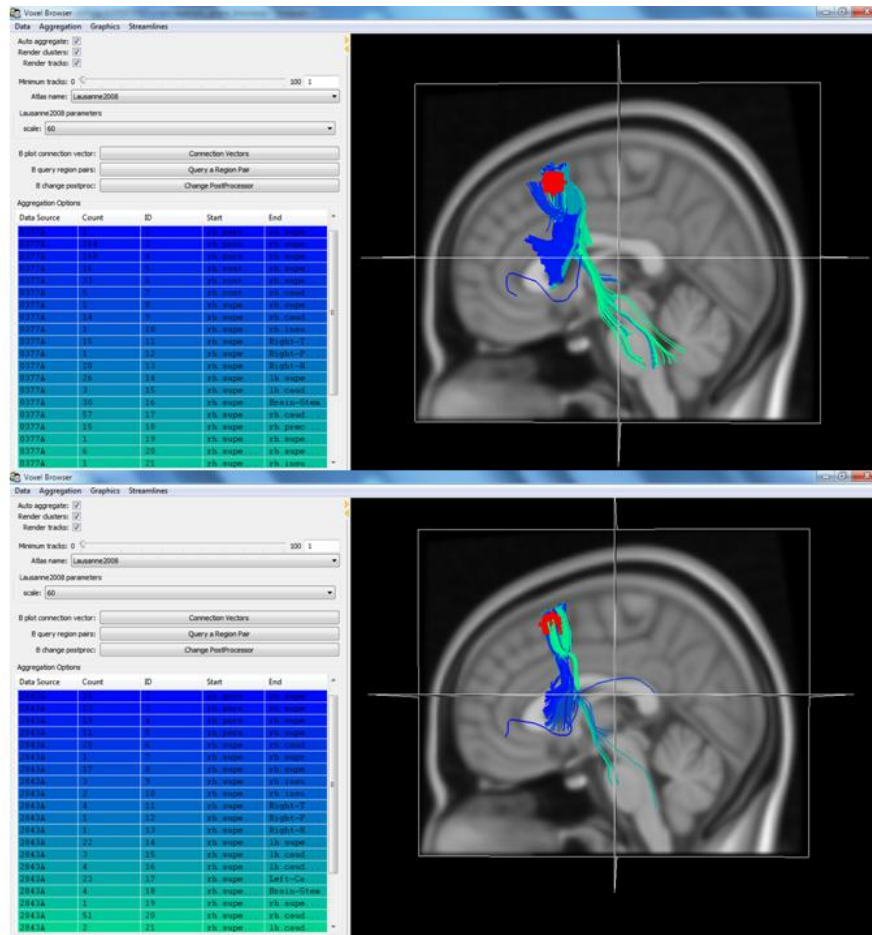
Figure 4. Images from the (DSI)[2] toolbox that show the same search sphere (red) in two different individuals plotted on the same standardized MNI template image. The toolbox identifies a difference in both the number and trajectory of the fiber tract streamlines that pass through the red region of interest.

In addition to research on the shape of streamline trajectories, another ongoing project focuses on the topology of the streamline endpoints within a brain region. Reconstructed networks of structural connectivity typically contain several hundred thousand streamlines, and several hundred streamlines terminate in well-studied gray matter regions of the cortex. The topology of these endpoints likely captures variability in the functional network they support (Pyles, Verstynen, Schneider, & Tarr, 2013; Verstynen, Badre, Jarbo, & Schneider, 2012; Verstynen, Jarbo, Pathak, & Schneider, 2011; Wang et al., 2012), and this variability may also capture the individual differences in structure relevant for differences in task performance. We leveraged a method for density-based clustering (the DeBaCl toolbox; (Kent, Rinaldo, Yeh, & Verstynen, 2013) from our academic collaborators that builds level set trees using a data-driven metric for similarity among the sampled endpoints. This allows for a concise description of streamline clusters as a hierarchical structure, and we are currently determining whether it captures variability in streamline endpoints that has predictive relationships with function and/or behavior.

Our structural work focuses on the development of methods to quantify structural variability, ensuring that the structural estimates are reproducible and sensitive to individual differences. This research lays the foundation for determining a set of structural metrics of individual differences that can be examined for their predictive relationship with variability in functional networks and behavioral performance.

3.1.2 Functional Connectivity

A majority of our functional connectivity research projects examined whether functional connectivity measures can reliably measure brain dynamics when intermixed with signal artifacts generated from biological and environmental sources. Promising results using phase-based connectivity measures heavily influenced our initial research (e.g., Stam, Nolte, & Daffertshofer, 2007).

In our first functional connectivity project, McDowell et al. (McDowell, Kerick, & Oie, 2010) examined the performance of a nonlinear connectivity measure, Phase Lag Index (PLI), in a dataset with varying levels of motion characteristic of operational environments. Five volunteer subjects performed an auditory target detection task in six motion environment conditions: (1) sitting stationary on a ride motion simulation (RMS) platform; (2) traversing a paved washboard road surface on the RMS; (3) traversing cross-country terrain on the RMS; (4) standing stationary on a treadmill; (5) walking at 3 mph on a treadmill; and (6) jogging at 5 mph on a treadmill. The analysis examined the susceptibility of PLI to the motion artifacts generated in these six motion conditions across six common frequency bands: delta, theta, alpha I, alpha II, beta, and gamma. On a global level, low-frequency PLI showed slight sensitivity to self-generated motion (i.e., walking and jogging), but mid- and high-frequency PLI did not show such sensitivity to any motion condition. The slight sensitivity of PLI in the lower frequencies could reflect either the neurocognitive processing associated with self-generated motion or could reflect some susceptibility to movement-based artifacts from these conditions. Overall, these results suggest that PLI can be used to reliably examine brain networks in certain operational environments such as driving, but additional work is needed to examine their utility for ambulatory motion environments. This led to additional research on walking with an improved version of the phase-based connectivity measure.

Lau and colleagues (Lau, Gwin, McDowell, & Ferris, 2012) used an extension of Stam's PLI measure known as the weighted phase lag index (WPLI) that introduced a phase-difference weighting normalization to mitigate the effects of zero-lag phase relationships that are characteristic of volume-conducted noise (Vinck, Oostenveld, van Wingerden, Battaglia, & Pennartz, 2011). In this study, eight volunteer subjects performed a similar target detection task as McDowell et al. (2010), but with visual instead of auditory stimuli. All subjects performed the task in two conditions: standing on a treadmill and walking at 1.8 mph on a treadmill. The analysis examined whether WPLI could detect neural activity akin to a well-characterized neural signal for detecting a target stimulus, known as the "P300," across these two conditions. Results

found that WPLI was less sensitive to walking artifacts related to the gait cycle (heel strike and toe off during a stride) than conventional EEG channel voltage analyses. However, WPLI responses that were time-locked to the appearance of a visual oddball stimulus during walking were highly variable across subjects and trials. Consequently, Lau and colleagues introduced a temporal stability measure of WPLI (i.e., WPLIS) that identifies periods of high/low WPLI variability. The WPLIS measure enabled us to detect a more robust P300-like cognitive event to the visual stimulus during walking. Thus, this study also confirmed the promise for phase-based connectivity measures to recover event-locked cognitive activity from artifact-contaminated EEG recorded during a walking task.

Two ongoing projects continue to explore connectivity-based approaches to understand cognitive control of walking. One project investigates functional neural connectivity during walking on uneven terrain, using a combination of experimental EEG data and neural mass modeling approaches (Snyder, Vindiola, Vettel, & Ferris, 2013). This research has calculated connectivity using three different phase-based measures: the imaginary component of coherence (ImC) (Nolte et al., 2004), the phase locking value (PLV) (Lachaux, Rodriguez, Martinerie, & Varela, 1999), and the debiased weighted phase lag index (dWPLI) (Vinck et al., 2011). Using experimental results to parameterize the model, a simulated brain network is constructed to examine different possible connectivity patterns that could underlie and, thus, replicate the experimentally-derived functional networks. Preliminary results found that simulation matched only one of the two connectivity patterns found in the experimental results: it captured an 8 Hz alpha modulation driven by the anterior cingulate, but not the alpha modulation by the posterior parietal node. The simulation results also revealed that the dWPLI measure may produce spurious connections for indirect connections, e.g., three unidirectional connections from cingulate to parietal cortex to sensorimotor nodes manifests as connection between anterior cingulate and sensorimotor nodes. These results were published and presented at the IEEE Engineering in Medicine & Biology Society (EMBS) Neural Engineering Conference (Snyder et al., 2013). Analysis for the journal publication is still ongoing with focused refinement on the simulated networks to examine if different network connections and timing patterns will better replicate the experimental results; in addition, we are exploring the addition of directed connectivity measures to complement the phase-based measures.

The second ongoing project investigates whether electrocortical dynamics are different for incline walking compared to level surface walking. This project combines experimental EEG data and electromyography (EMG) data recorded from seven muscles of the leg, three below the knee (*tibialis anterior, medial gastrocnemius, and soleus*) and four above the knee (*rectus femoris, biceps femoris, gluteus maximus, and gluteus medius*). Preliminary analyses focused on qualitative relationships between the EMG data and spectral power in estimated single sources in sensorimotor areas, and these results were presented by Bradford and colleagues at Society for Neuroscience. Ongoing analyses move from single sources to functional task networks to examine cortico-muscular coherence, and Bradford and colleagues are preparing a manuscript on

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this analysis. The project explores whether we can replicate the published, predictive relationship between EMG from the lower leg (*tibialis anterior*) and changes in functional EEG networks for level surface walking, and then extend this result to other EMG sensors and incline walking. Both of these ongoing walking projects will advance our knowledge about the role of cortical neural sources during locomotion, particularly over complex surfaces.

We have also examined the performance of phase-based connectivity measures in another Army-relevant task domain—shooting. Two complementary, EEG functional network analyses were performed on a previously published dataset where 18 volunteer participants (17 U.S. Marines and 1 U.S. Army Ranger) performed eight shooting conditions that manipulated the complexity of the task environment and a mixture of enemy and friendly targets (Kerick, Hatfield, & Allender, 2007). The participants identified visual, pop-up targets in a simulated environment and used a demilitarized weapon (i.e., emitted laser beam instead of live fire) to enable dynamic movements and simulate the recoil immediately following weapon triggering. The complementary projects examined whether phase-based measures could recover functional brain signals of interest at different experimental timeframes. In an analysis by Kerick, Vindiola, and McDowell (section 3, Vettel, Dagro, et al., 2012), PLI and WPLI was derived and examined on data epochs consisting of three types of events: non-event locked artifacts (i.e., primarily non-brain activity), non-event locked alpha bursts (i.e., primarily brain activity), and trigger-locked activity (i.e., a mix of brain activity and artifact induced by recoil). Analyses were run separately for six common frequency bands: delta, theta, alpha I, alpha II, beta, and gamma. Both measures found similar, statistically significant results showing the expected increase in PLI/WPLI values in alpha frequency synchronized across electrode recording sites in the alpha analysis (but not other frequency bands), as well as decreased PLI/WPLI values during high movement artifacts across five of the six frequency bands in the trigger-locked activity when the measure was correctly eliminating the near-zero phase relationships from volume conduction. Results also showed an unexpected increase in gamma for the non-event locked artifacts, but this effect was substantially smaller than the two event-locked conditions. The conclusion emphasized the success of the measure to capture distributed alpha connectivity—i.e., task-related activity—while the measure mitigated false-positive connectivity values during periods of high movement artifact. As a complement to these findings, a summer internship project led by Rawal in collaboration with Vettel, Luo, and McDowell (section 2, Vettel, Dagro, et al., 2012) directly compared the performance of WPLI on experimental epochs centered around the trigger pull event to traditional time-frequency analyses. Results showed that the channels that were identified as significant in WPLI data were different from the ones identified in the time-frequency analysis. Differences also included a left lateralization of paired network communication among brain regions only seen in the WPLI analysis but consistent with research on expert marksmanship (Kerick et al., 2007). Combined, both of these analyses on the shooting data indicated that the WPLI measure appears to be largely insensitive to the large artifacts found in dynamic human movements, while simultaneously being sensitive to functional connectivity associated with cognitive processing.

Related methodological research by Gordon and colleagues (2013) examined whether the detection of phase synchronization in EEG data with EMG noise and volume conduction effects could be improved using a parametric estimation technique based on autoregressive (AR) modeling. The research compared the performance of three methods WPLI, PLI, and ImC in their standard form with the performance of their parametric versions on two simulated datasets and one experimental dataset. The first simulation was developed using a simplified sinusoidal model, while the second simulation was developed using a neural mass model. Four levels of simulated EMG noise were added to the simulation, ranging from a no-noise condition to a high-noise condition. The experimental data came from one person performing a visual target detection task who had strong EMG signals emanating from the forehead in the second half of the dataset, providing a set of trials with minimal noise and a set with high noise. The results for both the simulation and actual EEG data showed that in the low-noise conditions the parametric and nonparametric approaches performed similarly. However, in conditions with high-power EMG noise, the parametric approaches were superior to their nonparametric counterparts at detecting statistically significant periods of phase synchronization. These results suggest that parametric approaches to connectivity measures are able to capture task-related phase synchronization in EEG data collected in real-world environments, including mobile tasks, where strong movement-related noise will be concurrent with the neural activity of interest.

Although the bulk of our initial work focused on phase-based connectivity measures, ongoing work also examines a family of directed connectivity measures, including Partial Directed Coherence (PDC), Directed Transfer Function (DTF), and direct Directed Transfer Function (dDTF). This class of directed connectivity measures was inspired by Granger-Geweke causality (Geweke, 1982; Granger, 1969), and further extends the concept of connectivity by allowing researchers to determine the causal directionality of connections. Originally used in economic time series analysis, Granger causality is used to study dependencies in bivariate signals. If incorporating the components of the model of the first signal helps reduce the error of prediction in the second signal, then the first signal is said to have caused the second signal. Brooks and colleagues are preparing a manuscript that describes a study employing DTF to examine relationships among functional connectivity, time on task, and driving performance. In a driving simulator, participants were asked to maintain their vehicle centered in the lane and quickly correct heading errors caused by lateral perturbations to the vehicle that randomly occurred throughout the task. As time on task increased, the amount of heading error before correction increased. A connectivity analysis of scalp electrodes identified connections with greater power in the alpha frequency band during trials with larger heading errors than ones with smaller heading errors. The identified connections originated in left posterior regions on the scalp and terminated in both ipsilateral and contralateral anterior regions (figure 5). Furthermore, regression analyses found a relationship between heading errors and the DTF connectivity values from connections emanating from posterior to anterior regions. These results indicate the potential for functional connectivity metrics to estimate differences in task performance. The benefit of using directional connectivity measures lies in the ability to draw inferences about the

underlying functional networks; in this case, connections from posterior to anterior regions on the scalp capture time-on-task effects that manifest in slower response time during a driving task.
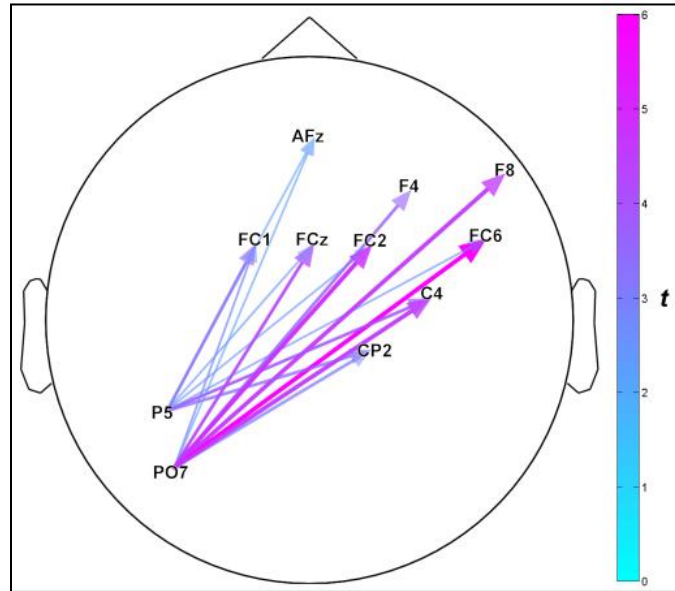
Figure 5. Significant channel pairs exhibiting greater DTF values for the quartile of trials with slowest response times than the quartile with fastest response times. Varying *t* values are displayed on the basis of line thickness, color, and transparency with lower values corresponding to thin transparent cyan lines and larger values corresponding to thick opaque magenta lines.

Thus far, our experimental work has only investigated classes of connectivity measures independently, such as a set of phase-based measures or a set of directed connectivity measures. However, our evaluation of these connectivity measures in our modeling research (4.2) indicated that measures are likely best used in concert with one another to maximize sensitivity to brain activity and increase interpretability of the results. For example, some of the measures are able to detect weak synchrony missed by other measures, but they are also susceptible to false positives arising from external noise sources. Thus, using these measures in concert with ones resilient to volume conduction in datasets with variable external noise will likely improve detection of underlying functional networks and improve interpretation of the connectivity results. We expect other pairings among the measures to be informative in other situations based on the sensitivities and susceptibilities of the measures; ongoing experimental work employs multiple types of functional connectivity measures to understand the relative strengths across connectivity measures both within and across cognitive domains.

Two ongoing projects address additional task domains to the ones described previously. Vettel and colleagues are preparing a manuscript on results presented at the Society for Neuroscience conference that examine the functional networks supporting multisensory integration.

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Participants wore a 128-channel EEG cap and watched audio-visual movies of everyday events, such as tapping a pencil. The movies had varying levels of congruency between the auditory and visual information. Some movies were real-world impact events with sights and sounds from the same object occurring at the same time, while others had a temporal offset between the visual and auditory impacts and/or a semantic mismatch between the object seen and the object heard. This work investigates the functional networks that determine whether auditory and visual information should be bound together in a coherent percept using temporal and semantic cues to integration. Multisensory integration processes allow us to understand the constant bombardment of perceptual information about concurrent, but distinct, events in the world around us, and understanding these processes will enable a better understanding about sense-making of audio-visual scenes. Another project is collecting data from a simple finger movement paradigm in order to investigate whether the expected "ground-truth" laterality effects in motor cortical activity are accurately detected with various classes of functional connectivity measures. Participants are presented with identical stimuli and asked to press a button with either the left or right finger, depending on the trial block. Analyses examine whether the measures can accurately recover the expected laterality in neural responses for each hand and its contralateral hemisphere. Both task domains support ongoing work to understand how multiple connectivity measures can be used in concert to better capture temporal dynamics of functional networks that are predictive of task-relevant brain states or behavioral performance.

A recurrent challenge across our research on functional connectivity measures centers on how to easily view the results of the analysis. Our high-density EEG datasets have 32, 64, 128, or 256 electrodes, and our current experimental paradigms involve tasks that last from 10 min to several hours. Connectivity analyses are performed on all possible channel pairs, and time-evolving functional connectivity examines the continuous time series data. Thus, as the number of channels, frequency resolution, and/or temporal resolution within a trial increases, the total number of analyzable data points increases from hundreds and thousands to many millions. With this magnitude of points, connectivity results become increasingly difficult to view and interpret. We designed a toolbox to facilitate connectivity data viewing and analysis. Input can be three-dimensional connectivity data with channel x channel x frequency to examine frequency-evolving effects collapsed across time, or input can be a four-dimensional connectivity matrix with channel x channel x frequency x time to investigate frequency by time effects. The toolbox shows the time-frequency connectivity plot for each channel pair in a grid format, allowing the user to dynamically select the connectivity pair of interest. The user can then draw a box around the number of timepoints and/or frequencies of interest to view in the connectivity map. As shown in figure 6, this map shows a layout of electrode locations with plotted functional connections between electrodes that meet criteria specified by the user. A user guide for the toolbox by Fernandez, Passaro, and Vettel is in preparation using simulated EEG-like data to demonstrate features of the toolbox.
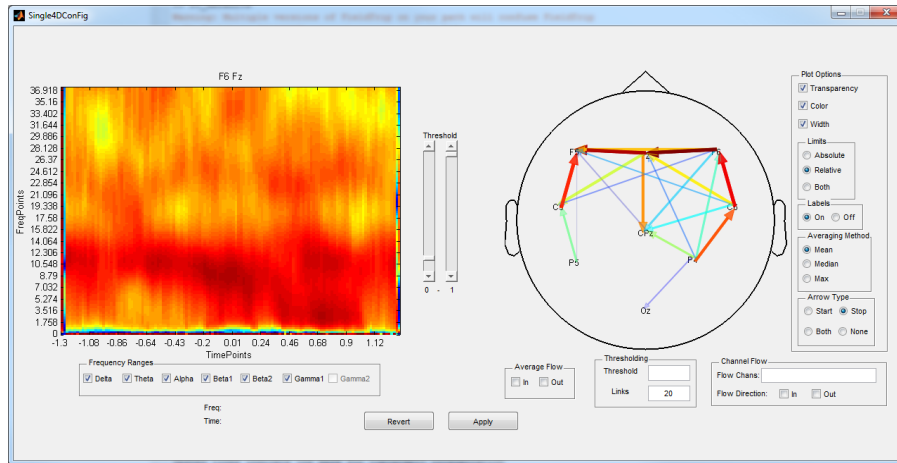
Figure 6. A single channel pair connectivity plot containing the time-frequency connectivity power on the left hand side and a connectivity topography plot on the right.

Our research over the past three years has focused on implementing, comparing, and evaluating functional connectivity measures, including a concentrated effort to establish the applicability of functional connectivity measures for understanding unconstrained behavior in mobile environments. Although substantial work remains to understand the limits of these approaches, our research indicates the promise of using functional connectivity measures to understand task-dependent brain activity in mobile, real-world settings.

3.1.3 Structure, Function, and Behavior Research

We are interested in the situations when variability in structural connectivity can be used to predict differences in task-dependent functional networks. This work requires datasets measuring structure, function, and behavior in the same individual. As discussed in section 2.1, we rely on our academic partners with MRI scanners to collect structural (and fMRI) data, and we jointly develop experimental paradigms and analyze the resulting datasets. Our research over the past three years has focused on identifying Army-relevant task domains for our initial structure-function-behavior research.

One collaborative project with the ICB examines individual differences in decision making. The paradigm translates previous adaptive decision making work to a more complex stimulus set, as well as a more complex task paradigm, and incorporates additional neuroimaging methods (fMRI, EEG, and DWI). This will allow us to examine relationships between fMRI and EEG functional activity networks as well as DWI to link these relationships to structural variability. In the previous research, collaborators at the ICB used pictures of cropped faces and found fMRI neural markers identifying military and civilian personnel who were able to use changing probability information about targets to improve their performance as determined by signal detection theory (Aminoff et al., 2012). An initial behavioral study employed our novel stimuli, which consist of computer-rendered full-body human models embedded in a desert metro environment (Vettel et al., submitted), to investigate whether different task scenarios, rather than

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target probability information, would encourage individuals to shift their decision criterion (i.e., their willingness to say that they recognize a target) and thereby improve their target recognition performance (Kantner et al., submitted). In one condition, adaptive decision making was encouraged using a security patrol scenario: in order to avoid critical misses, participants were encouraged to not let dangerous people go free. In a different condition, participants were encouraged to avoid false alarms, i.e., not to harm innocent people. We intentionally designed our task to be extremely difficult with highly confusable human targets, which allowed us to determine whether participants increased their reliance on scenario information (as opposed to information in memory). Across 389 participants, we found that the majority of individuals resisted shifting their criteria; that is, they failed to follow the performance-enhancing instructions given in the cover story. We speculate that people would rather try their best to use memory to respond to each item, even when their ability to do so is extremely poor. Put another way, people would rather attempt to be *correct* than be *correctly biased* in their decision criterion. Despite the overall resistance to shifting, when considering the subject population as a whole, these new stimuli also elicited a high degree of variability in the amount of shifting across individuals. These behavioral results confirm the applicability of this stimulus set for the ongoing neuroimaging work that examines whether neural markers indicative of individual differences in criterion shifting in prior work using simplistic stimuli will translate to more complex task paradigms. Our upcoming simultaneous fMRI/EEG dataset will facilitate comparative functional network analyses across two neuroimaging methodologies: one with high spatial and low temporal resolution (fMRI) and the other with low spatial and high temporal resolution (EEG). Likewise, these two functional imaging methods provide different technical approaches to link with variability found in structural networks. A large set of personality measures will also be collected in addition to the neuroimaging data, so this dataset will provide a rich set of individual difference measures across structure, function, and behavior.

A collaborative project with CMU has a different emphasis. In this effort, we will focus on fMRI functional networks and their relationships with structural and task performance data. In pilot work, we identified two task domains that are well suited for studying complex networks of roughly 12–20 fMRI regions. The first is an inhibitory control task where participants must inhibit a speeded response based on delayed visual information, and the second is multisensory task where participants watch a continuous audiovisual movie with variable levels of congruency between sensory modalities. Planned analyses will examine the utility of incorporating structural information to improve the prediction of task-dependent activity in this recovered network and examine structure-function-behavior relationships for fMRI networks.

These two tasks in CMU data collection also hold promise for complementary modeling work. Our ongoing modeling work requires experimental data from a task heavily influenced by the functional dynamics from a small node (4–8) network; however, the functional data must also vary based on task performance between participants. These two tasks may match both of these needed features. This would facilitate the implementation of individual-specific models of the

task-dependent small node network, and research will examine if the variability in the structural connections among the network nodes accounts for experimental variability in subject function and/or performance.

Finally, the multisensory task in the Carnegie Mellon data collection effort will feed into an upcoming analysis project in conjunction with the University of Pennsylvania. During the experiment, the perceptual information evolves from a congruent audio-visual movie to a visual-only movie to an auditory-only storyline to an incongruent audio-visual movie. These manipulations are known to recruit different sensory brain regions, and our joint analysis will look at the stability in the network configuration itself and how membership in the network evolves during changes in the complexity and congruence of the perceptual information.

In any of our structure-function-behavior datasets, however, a substantial technical challenge remains: narrowing the search space for the types of structural and functional metrics that capture statistically meaningful differences in individuals. We have investigated a machine learning approach to examine features predictive of task performance, and Vettel and colleagues presented these results at the Society for Neuroscience conference. This project used the previously collected decision making dataset at the ICB from 95 Army Officers and civilians, where participants were sorted into two groups based on their performance on the task (adaptive decision making or not). We computed 183 individual difference measures, including behavioral measures from standardized, published questionnaires (Aminoff et al., 2012), as well as structural and functional measures predominantly derived from graph property metrics based on their relevance for clinical populations (Stam & Reijneveld, 2007) and motor sequence (Wymbs et al., 2012). Results using this feature set to predict decision making performance were only slightly better than chance, but this lackluster finding likely reflects the lack of variability in the structural and functional features. Ongoing work continues to improve our structural and functional metrics to increase their sensitivity to variability between individuals. In addition, our collaboration with the ISN focuses on enhancing the machine learning methods employed, leveraging their expertise in characterizing clinical populations and identifying individual differences measures that are predictive of treatment outcomes (Doehrmann et al., 2013). We expect that improved individual difference measures and analytic methods will identify predictive structure-function-behavior relationships with variability in task performance.

During the last three years, our work has focused on identifying task domains for investigating brain structure-function relationships, securing funds to collect these datasets with our academic partners who have the research MRI scanners needed for structural imaging, designing collaborative experimental protocols, conducting joint data analysis, and leveraging existing structure-function-behavior datasets to examine technical approaches to investigate relationships among these three classes of individual difference metrics.

3.2 Neurophysiological Modeling

Three research projects have used the neural mass model to examine time-evolving functional networks. Two of them were discussed in the functional connectivity section of this report (3.1.2). The work by Gordon and colleagues (2013) used the neural mass model to examine whether a parametric estimation technique improved detection of phase synchronization in the presence of simulated EMG noise. Published and ongoing work by Snyder and colleagues (2013) constructs several time-evolving network models to investigate which pattern best replicates the experimentally-derived functional networks during a walking task. The work highlighted here by Vindiola et al., in press used neural mass models to simulate EEG-like experimental trials to examine how well three phase-based connectivity measures recover a time-evolving connectivity pattern across a set of experimentally relevant conditions, including the same simulated EMG noise employed by Gordon and colleagues (2013).

In this project (Vindiola et al., in press), two neural mass nodes were parameterized to oscillate at experimentally relevant frequency bands (alpha in the 8–12 Hz range and gamma in the 30–70 Hz range), and they were coupled with either unidirectional or bidirectional connectivity to examine detection of feed forward connections with or without feedback. We compared how well three phase-based connectivity measures (PLV, ImC, and dWPLI) can recover the timeframe and frequencies of the underlying connectivity pattern across a set of 14 experimentally relevant conditions. We also compared the performance of the measures on simulated signals with and without volume conduction to evaluate robustness to volume conduction for experimental use in mobile, operational environments. Across these 28 simulated conditions, the three phase-based connectivity measures (PLV, ImC, and dWPLI) performed reasonably well, with no one measure outperforming the others in all simulations. Expected differences were seen in the no volume conduction case: both ImC and dWPLI were insensitive to synchronizations occurring in the bidirectional connected configurations when the two regions oscillated in same frequency range ($10 \leftrightarrow 10$, $43 \leftrightarrow 43$) since they explicitly ignore phase differences of $\pm 0°$ or $\pm 180°$, while PLV captured this connectivity in this bidirectional, within-frequency condition. However, this sensitivity has its tradeoff in performance since PLV was much less selective and detected spurious synchronizations across a wide range of frequencies and times. More variability in performance among the three measures was observed in the volume conducted cases. For PLV and ImC, the addition of noise affected the measures differently, and even within measure, the effect of added noise varied across the experimental configurations. In contrast, dWPLI was consistent across all configurations in our analysis, and our results confirmed the expected behavior that volume conduction did not increase or decrease the detected synchronizations (although this result may also reflect the permutation statistical test used). The clear finding from this work was that no particular measure clearly dominates. The amount of volume conduction, the magnitude of environmental noise, the underlying network connectivity, the frequency interactions, and the method of statistical correction all influence the performance of these measures. Rather than selecting a single measure to use as a sole method

for detecting synchronizations, a richer understanding of the integrative network underlying cognitive performance will be possible by looking at multiple measures in combination. Doing this will not only provide a richer picture of the types of interactions that occur, but over time it will also lead to a better understanding of the relative strengths of the measures within and across cognitive domains.

Vettel and Franaszczuk are preparing a report describing a similar measure comparison project that was performed on the biophysical models of signal neurons. This work focused on three directed connectivity measures—PDC, DTF, and dDTF—as measured from a simulated EEG-like signal generated from several thousand nonlinear conductance-based neuron models. We simulated six EEG-like networks that consist of four interacting nodes oscillating in experimentally relevant EEG frequency bands (alpha and gamma). Four of these networks were simple feed-forward networks, with one node projecting to the other three nodes, and two of these networks had more complex interactions with additional feedback connections and a ring structure. For each of the six simulated networks, we computed a multivariate autoregressive (MVAR) model and calculated the effective connectivity measures—the PDC, DTF, and dDTF—to evaluate whether the effective connectivity measure correctly captured the underlying network connectivity. Results found little qualitative difference among the three measures for the networks tested, and they demonstrated that these functional connectivity measures can provide useful information about causal influences among network nodes; however, they should be applied conservatively and interpreted carefully since they detect spurious connections even in simplified network configurations. Two guiding principles were proposed for application and interpretation of these measures on experimental EEG data: (1) analyze only those frequency bands with substantial overlap in the power spectra of the experimental recordings from investigated nodes and (2) apply a conservative statistical threshold. The measures performed best on the simple feed forward networks, so they are likely most applicable for recovering less complicated network interactions and may perform better when knowledge about anatomical connections can be used to constrain their application or interpretation.

Ongoing modeling work focuses on building models with structural network data from experimental research. In a new collaboration with the University of Pennsylvania, one project examines structural constraints on brain state reconfigurations using computational modeling. The project implements functional constraints in the model that are dependent on experimentally-derived structural network data, and we will examine the propagation of synthetic electrical stimulation. We will employ network control theory to quantify the time-varying change in connected brain regions, as well as the energy needed to obtain the subsequent reconfiguration of the system. This work will inform the expected variability of brain networks within a single state and the expected energy of network transitions between different states.

Our multiscale modeling approach provides a research foundation that is enabling a new research program at ARL to investigate the effects of traumatic insults on brain structure and function at sub-cellular and cellular levels. The initiative uses liposomes and 3D cell cultures in realistic

blast environments to understand structural and functional changes under controlled blast conditions; however, the research focuses on potential neural injury mechanisms tied to traumatic insults that lead to mild cognitive impairments in humans. Currently, the available noninvasive neuroimaging technologies to study human cognition and link structure-function-behavior parameters only exist at the large-scale network level, a higher level of organization than the liposome and 3D cell cultures. Thus, this new research program requires a link from the lower subcellular and cellular scales up to the large-scale networks in order to identify potential injury mechanisms that are tied to decrements in human behavior. Therefore, at the heart of the technical approach in the new research group is intertwined modeling and experimental efforts, where parameters from the lower scales can be used in neurophysiological models of large-scale networks. We can use knowledge about changes in membrane permeability from the sub-cellular research as a parameter in our models at the higher scales to see how this influences larger networks. Likewise, experimentation and modeling at the cellular level identifies changes in the amount of neurotransmitter release that may modulate network level electrochemical activity that can one day be linked to behavior. Ultimately, multiscale modeling provides a framework to link results across scales and connect neural injury to changes in human behavior.

Across these modeling efforts, we aim to understand dependencies between structural topology and functional oscillations in networks of simulated nodes. Our initial efforts built our computational modeling expertise by focusing on small-scale networks, utilizing them to investigate the performance of functional connectivity measures to recover underlying network topologies. Ongoing work actively seeks experimental data that is well-suited for current modeling and analysis capabilities that will provide insight on theoretical relationships between structural connectivity and the resulting functional connectivity. A central focus across all of these projects is a constant interaction between the modeling and experimental research areas to ensure that the projects complement and constrain one another.

3.3 Biomechanical Modeling

Our biomechanical modeling work implemented a proof-of-concept approach that links simulated damage to neural tissue with changes in structural network connectivity. A constitutive model was first created to improve the mechanical response of white matter tissue for finite element (FE) simulations and implemented into the SIERRA (Sandia National Laboratories) solid mechanics code (Kraft & Dagro, 2011). DWI is used to account for the direction of white matter tracts and allows for the creation of a transversely isotropic hyperelastic constitutive model. Each element is assigned a fiber direction based on the localized fibers that pass through it. This allows for the calculation of an axonal strain value and an improvement of the deviatoric response based on the assigned fiber direction. Using this method, we are able to capture a portion of the anisotropy that exists within the complex geometry of the brain.

This constitutive model was then implemented in a FE model that was developed at ARL based on MRI and DWI neuroimaging data (Kraft, Mckee, Dagro, & Grafton, 2012). The transversely

isotropic model is used to improve the mechanical response of simulated brain tissue and to allow for the calculation of strain in the direction of axonal tracts. Frontal impact was simulated to investigate the response of the brain through metrics such as axonal strain, strain rate, and pressure. Axonal strain and strain rate are applied to empirical formulas for cell death developed at Columbia University (Morrison, Cullen, & LaPlaca, 2011). This formula accounts for the biological factors that take place to estimate the cell death up to 96 h after an injury. This cell death value is used as a threshold to estimate localized regions of the brain that may have been damaged. In addition, the fiber tractography from DWI allows for the creation of a structural network model that is coupled to the mechanical response. Damage is related to the structural network by tracking the fibers that pass through regions above the set threshold, as well as the gray matter regions that they connect. The number of fibers that pass through a region that is above the threshold is used as a means to degrade the edge between nodes. Measures from network science were used as a means to quantify changes in the network. The global and local efficiency represent the network's capability to transfer information between nodes in parallel (Latora & Marchiori, 2001). These values were calculated for the structural network before and after degradation to show a reduction in the capacity for communication. There were specific nodes that showed a greater reduction, including regions within the frontal lobe. To understand how these specific regions would affect the network as a whole, the betweenness was calculated. Betweenness is a measure of how often a region is part of a short path that connects two other regions and has been used to determine the node's importance to network integrity (Rubinov & Sporns, 2010). For this simulation, we found that many of the nodes with the largest reduction in local efficiency also had a low betweenness value. By investigating such measures, we gain a better understanding of how localized damage from a traumatic impact may have widespread effects to the brain.

The fidelity of the network degradation model was further improved by the implementation of the fiber segment-based degradation method (McKee, Dagro, Vindiola, & Vettel, 2013). This method treats all fibers as a series of fiber segments. Only fiber segments in a region above the threshold contribute to the degradation of a network edge. This allows for a varying level of degradation based on the length of the fiber that is within the damaged region. Previously, the entire fiber was removed from the model if any part of it passed through a region above the threshold. This resulted in many edges where all fibers were removed, which is problematic for the calculation of some network measures. The use of fiber segments allows for a larger range of degradation to better quantify different severities of loading conditions. This proof-of-concept method was implemented to evaluate the sensitivity of network measures for a frontal blast loading and a side blast loading. An illustration of the fiber segment removal process is shown in figure 7 for these two loading conditions. The black represents segments of fiber that pass through areas above the threshold. This image also demonstrates the time evolving nature that results from the use of the empirical cell death formula. The side blast loading shows a larger number of fiber segments removed at 96 h, as well as a high concentration of removed fiber segments connected to the occipital lobe in panel H. The frontal blast loading resulted in the

removal of fewer fiber segments with a more even distribution throughout the volume of the brain at 96 h, as shown in panel D. These differences in fiber segment removal are reflected in the resulting network measures. The global measure of connectivity change was higher in the side loading, with a particularly high concentration of degraded edges connecting to nodes located in the occipital region. In comparison, the frontal blast produced a more widespread pattern of damage where edges had a lower reduction in connectivity. Based on the results, it was determined that changes in individual edge weights are the most sensitive to loading direction when using the fiber segment method. However, there were also differences in global measures such as efficiency. In addition to the sensitivity analysis, the consistency of network measures was assessed for differently sized networks. It is known that network measures are often topology- and scale-dependent when applied to the brain (Bassett, Brown, Deshpande, Carlson, & Grafton, 2011). Degraded networks are normalized based on the undamaged network, so it is important to investigate if the normalized network measures were reduced by the same percentage across all network scales. Network measures were calculated on networks between 12 and 1002 nodes. It was found that the normalization produced a similar reduction in the total edge strength and efficiency for all networks for both the frontal and side blast loadings, suggesting that our measures are a relatively scale-free (i.e., generalizable) approach to modeling blast damage.
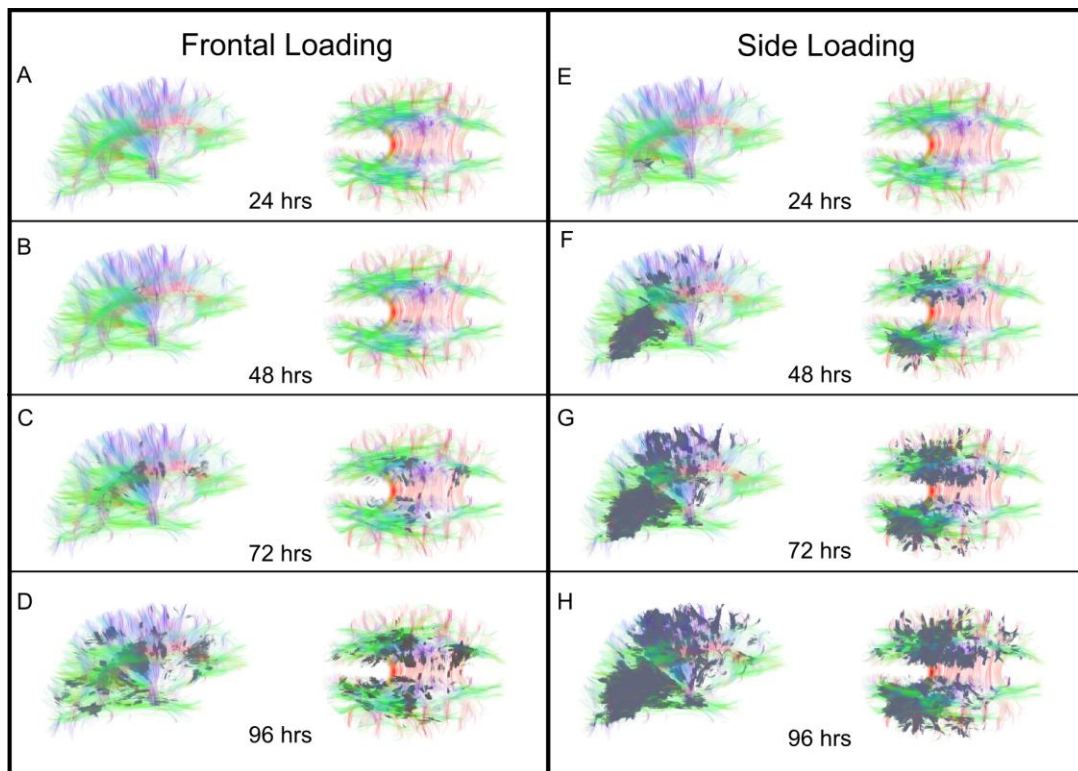

Figure 7. Fiber segments, illustrated in black, show where fibers pass through a region above the damage threshold for frontal and side blast loading. In this proof-of-concept approach, the cellular death damage parameter is calculated up to 96 hours after insult based on the initial strain and strain rate.

Our biomechanical modeling work implemented a proof-of-concept approach that links simulated damage to neural tissue with changes in structural network connectivity. This project sets the foundation for ongoing work that uses the resulting structurally damaged network as input in a neurophysiological model that links structural connectivity with simulated functional connectivity. Linking these two modeling efforts enables an examination of the functional effects of simulated traumatic insults to the brain.

4. Conclusions

Our collaborative, cross-disciplinary research team has developed an integrated research portfolio to examine predictive relationships in large-scale brain networks among white matter structural connectivity, functional network activity, and behavioral performance on Army-relevant tasks. Specifically, we focus on variability in connectivity, both between individuals and within individuals over time, which will give us the ability to predict and shape outcomes relevant to task performance. Our three research areas intertwine experimental and modeling projects and use a uniting framework from network science with brain regions as nodes and brain connectivity data as edge weights. Experimentally-derived structural networks are used as input for simulated brain networks in the neurophysiological modeling of oscillatory brain activity dependent on underlying structural connectivity and in the finite element modeling of biomechanical response of brain tissue dependent on blast and blunt impact loading conditions. Likewise, estimated damage to structural networks from the biomechanical modeling is used as input for the neurophysiological modeling to estimate the effect on functional activity, or in clinical and experimental research that links variability in structural connectivity with variability in task performance. Insights about structural constraints on functional activity from the neurophysiological modeling inform hypotheses and interpretations of connectivity results on experimental data. Our three research areas were built from a common technical approach to ensure theoretical insights from modeling and empirical relationships from experimentation can inform and constrain one another.

Our overall results indicate that structural and functional connectivity measures hold promise for understanding behavioral variability in real-world task environments based on differences in healthy individuals. In the experimental studies, our research emphasizes the development and/or identification of robust imaging and analysis methodologies to quantify individual differences in connectivity. Our structural connectivity work examines the reproducibility of innovative imaging methods, and we investigate whether structural metrics derived from the fiber trajectory or from topology of streamline endpoints capture robust variability among individual subjects. Our functional work focused on technical challenges inherent to the use of a mobile neuroimaging method, EEG, to recover task-dependent functional networks from electrical signals intermixed with task-irrelevant signals generated from biological and environmental

sources. Published results from target detection and shooting paradigms have indicated the promise of a class of phase-based measures for detecting task-related connectivity while mitigating false positive connectivity results from artifacts resulting from volume conduction. Ongoing work examines the applicability of these methods for additional task domains, including locomotion over complex terrains, multisensory integration, and motor execution. We are also investigating a complementary class of directed connectivity measures inspired by Granger-Geweke causality to investigate the contribution of both phase-based and directed connectivity methods for the interpretation of large-scale networks. Ongoing research found that a directed connectivity measure can detect decrements in task performance when response time increases in a reactive driving task. These initial experimental results suggest connectivity approaches are able to detect task-dependent variability, and several neurophysiological modeling projects have shown the successful detection of underlying network connectivity in small 2–4 node networks. Ongoing work actively seeks experimental data that is well-suited for current modeling and analysis capabilities that will provide insight on theoretical relationships between structural connectivity and the resulting functional connectivity. Our data collections at ARL and in conjunction with academic partners address this need.

Thus far, our research on structural and functional connectivity has largely examined structural metrics in isolation or links between functional connectivity and behavior; however, these research projects provide the foundational knowledge about structural and functional metrics that capture individual differences. These metrics will enable ongoing work that examines predictive relationships among structure, function, and behavior. In the past three years, we have jointly designed experimental paradigms on decision making, inhibitory motor control, and audio-visual integration with academic collaborators who have the MRI technology needed to collect structural imaging data. Additional datasets are available from collaborative relationships with UARCs at UCSB (the ICB) and at MIT (the ISN) that extend to other paradigms on healthy individuals, such as language and motor sequence learning tasks, as well as paradigms on clinical populations, including mTBI patients. Thus, these datasets provide a rich research opportunity to look for predictive structure-function-behavior relationships in healthy and clinical populations with our academic collaborators, as well as burgeoning collaborations with researchers at the Medical Research and Material Command (MRMC). We are invested in narrowing the search space for the types of structural and functional metrics that are predictive of decrements in performance and/or diagnostic of injury. Preliminary work has examined the utility of machine learning techniques to identify predictive metrics of individual differences, but additional approaches will be explored as the quality of the individual difference metrics of connectivity improve.

These collaborative opportunities dovetail nicely with validation data needed for the finite element modeling research, as well as a new ARL research program focused on brain structure-function coupling to understand neural mechanisms of injury at the cellular and sub-cellular scales. We have developed a finite-element (FE) model of the brain that was informed by

structural, white matter tractography to build a transversely isotropic material model and replicated experimental test data from blunt impact to the head (cadavers). We have developed a proof-of-concept approach to convert estimated damage to brain tissue into estimated damage to a structural network, but future research will focus on improving the cellular injury models to better estimate tissue damage. Additionally, experimental data is needed to understand how cell injury translates to structural damage in large-scale networks and impairments to long-range functional connectivity. The new ARL research program on traumatic insults will study structural and functional effects of well-characterized blast waves on changes in cellular morphology and electrochemical signaling in 3D brain cell cultures. By using these experimental parameters in multiscale modeling efforts, future research will examine how localized structure-function changes scale up to effect the functional activity of large networks. By linking up to the network level, our technical approach enables a link between the estimates of damaged connectivity and neural injury mechanisms at lower scales and associated changes in network connectivity and task performance.

Emerging from a review of our highlighted accomplishments, our research program evidences a multi-scale approach to link experimental and modeling efforts. Our models span multiple spatial and temporal scales that can be flexibly adapted for experimental insights expected in the coming decades. The scope of the unknown about the human brain is strongly evidenced by the many ongoing, multi-million-dollar international research efforts that have blossomed in the past decade, including President Obama's B.R.A.I.N. initiative, the European Human Brain Project, the Allen Institute for Brain Science, the NIH Human Connectome Project, etc. These same initiatives, however, also indicate the potential for revolutionary neuroscience insights, for technological advancements for imaging the brain, and for innovative approaches for modeling and analysis of big data from billions of active neurons.

As our collaborative, multidisciplinary research team goes forward, we plan to actively participate in these endeavors, and advance the start of the art in the use of connectivity approaches to understand brain function in real-world task environments. In addition, we plan to advance neurotechnology design for optimized Soldier-system performance by developing new approaches to quantify individual differences and recover time-evolving functional networks that can enhance algorithms for real-world contexts. We emphasize advancements needed for improved designs of protection equipment that will minimize neural injury by improving material models of brain tissue for use in simulations of blast and blunt force impact. However, the strength of this research program results from a focus on uncovering the fundamental relationships among brain structure, function, and behavior. In the long term, this foundational neuroscience knowledge can have broad-based applications to the Army, including individual-specific training protocols to optimize skill acquisition and decrease time to train, analytic tools to triage, diagnose, and/or mitigate neural trauma, and metrics to quantify Soldier traits that address critical needs in the Army's Ready and Resilient campaign.

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6. Transitions

We have divided our transitions into sections, with summary statistics listed in parenthesis when appropriate. Over the course of three years, we have supported several postdoctoral fellows and interns with onsite research projects, and we have hired contractors to work onsite, including two who have been converted to full-time civilian employees. We have an established transition agreement with MRMC to share methods developed that can quantify differences in structural, functional, and behavior measures across individuals, and we have a regular teleconference to communicate ongoing projects and identify additional avenues for collaboration; in addition, as our connectivity algorithms continue to improve and influence neurotechnology development for real-world settings, we expect to also contribute to existing agreements with TARDEC and NSRDEC that integrate neurotechnology development with system development for crewstation design and equipment for dismounted Soldiers, respectively. We have four published journal publications, two under review, and seven in preparation for submission in the next few months. We have four published tech reports and two ready for OPSEC review. Despite the significant restrictions on civilian personnel attending conferences in the past two years, our research collaborators have enabled representation at international conferences to disseminate our results with the larger neuroscience community, including five published, peer-reviewed conference proceedings and ten conference poster presentations and talks.

6.1 Personnel

We have built an in-house research group through several mechanisms in order to enhance ARL's in-house capability to perform translational neuroscience research. We have hired several contractors to work onsite with the needed expertise for this research, including P. Justin McKee, Antony Passaro, Rob Fernandez, and Matt Jaswa. Two researchers came on as contractors and have been converted to civilian employees (Amy Dagro and Manny Vindiola). In addition, several postdoctoral fellows, summer interns, and a Davies fellow have collaborated on onsite projects for this research effort.

6.2 Technology Program Annex (TPA) Agreements

We have established transition deliverables from our research program to MRMC under an ongoing TPA agreement with Combat Casualty Care Research Program in their Neurotrauma Research portfolio; under this agreement, we provide MRMC with complementary analytic approaches for identifying predictive relationships among brain structural connections, brain functional activity, and behavioral measures. We also have regular teleconferences to discuss ongoing research and identify additional avenues for collaboration; for example, our joint discussion about an MRMC initiative to stand up an integrated product team for radiologic imaging identified a role for ARL's expertise in neuroimaging to address subject matter expert

needs as part of their review panel (Vettel served as a panelist on MRMC's Department of Defense (DOD) Traumatic Brain Injury (TBI) Imaging In-Progress Review). In addition, as our algorithms continue to improve and contribute to the design of neurotechnologies for use in real-world settings, this research will influence and contribute to our existing TPA agreements with both TARDEC and NSRDEC that integrate our research on neurotechnologies to improve performance with their applied research on crewstation development and novel devices for dismounted Soldiers.

6.3 Journal Publications (4 published, 2 under review, 7 in prep)

Gordon, S. M.; Franaszczuk, P. J.; Hairston, W. D.; Vindiola, M.; McDowell, K. Comparing Parametric and Nonparametric Methods for Detecting Phase Synchronization in EEG. *Journal of Neuroscience Methods* **2013**, *212*, 247–258.

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Kantner, J.; Vettel, J. M.; Miller, M. B. Extreme Criterion Shifting: Not On Your Life. Psychological Bulletin & Review, (submitted).

Vettel, J. M.; Kantner, J.; Jaswa, M.; Miller, M. Animated 3D Human Models for Use in Person Recognition Experiments. Behavioral Research Methods, submitted.

Vindiola, M.; Vettel, J. M.; Gordon, S. M.; Franaszczuk, P. J.; McDowell, K. Applying EEG Phase Synchronization Measures to Non-linearly Coupled Neural Mass Models. *Journal of Neuroscience Methods* **in press**.

In preparation:

Bradford, J. C.; Lukos, J. R.; Passaro, A. D.; Vettel, J. M.; Franaszczuk, P. J.; Ferris, D.P. Cortical Involvement in Human Walking on Flat and Incline Surfaces. *Journal of Neurophysiology,* in preparation.

Brooks J.; Passaro A. D.; Vettel J. M.; Kerick S. E.; Franaszczuk P. J. Directed Alpha Connectivity Associated with Driver Fatigue. Journal of Neuroscience, in preparation.

Cieslak, M.; Jaswa, M.; Vettel, J. M.; Grafton, S. (DSI)[2]: An Open-Source Platform for Local termination Pattern Analysis. Frontiers in Neuroinformatics, in preparation.

Good, C.; Passaro, A. D.; Bird, C.; McDowell, K.; Curran, T.; Vettel, J. M. Anticipation and Fatigue: Insights from prestimulus alpha. *Journal of Cognitive Neuroscience*, in preparation.

Snyder, K. L.; Vettel, J. M.; Vindiola, M.; Ferris, D. P. Integrated Modeling and Experimention to Examine Cortical Connectivity During Uneven Terrain Walking. *NeuroImage*, in preparation.

Vettel, J. M.; Yu, A. B.; Bird, C.; Tarr, M. J.; McDowell, K. M.; Franaszczuk, P. J.; Curran, T. Network Dynamics Underlying Multisensory Integration of Real-World Audiovisual Events. *Experimental Brain Research*, in preparation.

Yu, A. B.; Vettel, J. M.; Grafton, S.; Verstynen, T. Long-Term Reproducibility of Diffusion Spectrum Imaging. *Neuroimage*, in preparation.

6.4 Technical Reports (4 published, 2 in preparation)

McKee, P. J.; Dagro, A.; Vindiola, M.; Vettel, J. M. *Fiber Segment-Based Degradation Methods for a Finite Element-Informed Structural Brain Network*; ARL-TR-6739; U.S. Army Research Laboratory: Aberdeen Proving Grounds, MD, 2013.

Kraft, R. H.; Dagro, A. M. *Design and Implementation of a Numerical Technique to Inform Anisotropic Hyperelastic Finite Element Models using Diffusion Weighted Imaging*; ARL-TR-5796; U.S. Army Research Laboratory: Aberdeen Proving Grounds, MD, 2011.

Vettel, J. M.; Vindiola, M.; Dagro, A.; McKee, P.J.; Kraft, R. H.; McDowell, K.; Franaszczuk, P. J. *Brain Structure-Function Couplings: Year 2 Accomplishments and Programmatic Plans*; ARL-SR-268; U.S. Army Research Laboratory: Aberdeen Proving Grounds, MD, 2013.

Vettel, J. M.; Dagro, A.; Gordon, S.; Kerick, S.; Kraft, R. H.; Luo, S.; Rawal, S.; Vindiola, M.; McDowell, K. *Brain Structure-Function Couplings (FY11)*; ARL-TR-5893; U.S. Army Research Laboratory: Aberdeen Proving Grounds, MD, 2012.

In preparation:

Fernandez, R. J.; Passaro, A. D.; Vettel, J. M. *ConnVis: Connectivity Visualizer, A Visualization Tool for Large Connectivity Datasets*; in preparation; U.S. Army Research Laboratory: Aberdeen Proving Ground, MD.

Vettel, J. M.; Franaszczuk, P. J. *Evaluating Multivariate Directional Connectivity Measures for Use in EEG Network Analysis using a Conductance-Based Neuron Network Model*; in preparation; U.S. Army Research Laboratory: Aberdeen Proving Ground, MD.

6.5 Conference Proceedings (5 published)

Kraft, R. H.; Dagro, A. M.; McKee, P. J.; Grafton, S.; Vettel, J. M.; McDowell, K.; Vindiola, M.; Merkle, A.C. Combining the Finite Element Method with Structural Network-Based Analysis for Modeling Neurotrama. *11th International Symposium, Computer Methods in Biomechanics and Biomedical Engineering*, 2013.

Kraft, R. H.; Dagro, A. M.; McKee, P. J.; Vettel, J. M.; Vindiola, M.; McDowell, K.; Chung, P. Connectome Neurotrauma Mechanics for Impact and Blast. A*RL 2012 Research in Ballistic Protection Technologies Symposium*, Aberdeen Proving Ground, MD, 2012.

McDowell, K.; Kerick, S.; Oie, K. Non-linear brain activity in real-world settings: movement artifact and the phase lag index. In *Proceedings of the 27th Army Science Conference*, Orlando, FL, 2010.

Snyder, K. L.; Vindiola, M.; Vettel, J. M.; Ferris, D. P. Cortical Connectivity During Uneven Terrain Walking. *6th International IEEE EMBS Neural Engineering Conference*, 2013.

Vettel, J. M.; Bassett, D.; Kraft, R. H.; Grafton, S. Physics-Based Models of Brain Structure Connectivity Informed by Diffusion-Weighted Imaging. In *Proceedings of the 27th Army Science Conference*, Orlando, FL. Reprinted as ARL-RP-0355 U.S. Army Research Laboratory: Aberdeen Proving Grounds, MD, 2010.

6.6 Conference Presentations (10 presented, 1 accepted)

Bradford, J. C.; Lukos, J. R.; Ferris, D. P. Electrocortical Activity During Human Walking on Flat on Incline Surfaces. Poster presented at the *Annual Society for Neuroscience Conference*, San Diego, CA, 2013.

Kantner, J.; Vettel, J. M.; Turner, B. O.; Schubert, M. L.; Elliott, J. C.; Giesbrecht, B.; Miller, M. B. Electrophysiological Correlates of Induced Liberal Versus Conservative Decision States in Recognition Memory. Poster accepted for presentation at the *21st Annual Meeting of the Cognitive Neuroscience Society*, Boston, MA, 2014.

Kantner, J.; Vettel, J. M.; Miller, M. B. Limits on Criterion Flexibility in Recognition Memory. Poster presented at the *54th Annual Meeting of the Psychonomic Society*, Toronto, ON, Canada, 2013.

Kantner, J.; Vettel, J. M.; Miller, M. B. What Does it Take to Induce Extreme Criterion Shifts in Recognition Memory? Talk given at the *10th Annual Bay Area Memory Meeting*, San Francisco, CA, 2013.

Kraft, R.; Vettel, J.; Lance, B.; McDowell, K. A Structural Mechanics-Based Approach for Predicting Neural Deficits. Presentation given by R. Kraft at the *Neural Restoration Workshop*, Albuquerque, NM, 2009.

Urban, A. D.; Vettel, J. M.; Franaszczuk, P. J. Testing Multivariate Directional Connectivity Measures Using a Conductance-Based Model Framework. *Rhythms and Oscillations Workshop at Mathematical Biosciences Institute*, Columbus, OH, 2013.

Vettel, J. M.; Vindiola, M.; Aminoff, E. M.; Tipper, C.; Frithsen, A.; Johnson, A.; Grafton, S. T.; Miller, M. B. Predicting Individual Differences in Decision Making Based on Structural, Functional, and Behavioral Measures. Poster presented at the *Annual Society for Neuroscience Conference*, New Orleans, LA, 2012.

Vettel, J. M.; McDowell, K.; Bird, C.; Nestor, A.; Gordon, S.; Kerick, S.; Heller, L.; Tarr, M. J.; Curran, T. Network Dynamics of Multisensory Integration of Real-World Environmental Events. Talk given at the *Annual Society for Neuroscience Conference*, Washington, DC, 2011.

Vettel, J. M.; Bassett, D.; Grafton, S. Reproducibility of Diffusion Weighted Imaging Across Multiple Scanning Sessions. Poster presented at the *Annual Meeting of the Society for Neuroscience*, San Diego, CA, 2010.

Verstynen, T.; Vettel, J. M. Indirect Influence of Medial Orbitostriatal Projections on Response Selection: Check Yourself Before You Rectus Yourself. Abstract presented at the *Annual Cognitive Neuroscience Society Conference*, San Francisco, CA, 2013.

Vindiola, M.; Lau, T.; Chung, P.; Vettel, J. M.; McDowell, K. Neural Mass Model Validation of a Graph-Theoretic Approach to Identifying Effective Connectivity of Brain Regions From Functional Connectivity Measures in EEG. Talk given at the *Annual Society for Neuroscience Conference*, Washington, DC, 2011.

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