Rhode Island COBRE Center for Central Nervous System Function: Progress and Perspectives

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ABSTRACT

The Center of Biomedical Research Excellence (COBRE) Center for Central Nervous System Function (CCNSF) was funded in 2013 by the National Institute for General Medical Sciences to establish a collaborative environment for basic and applied research in higher nervous system function with humans and experimental animal model systems. Since its inception, the COBRE CCNSF has funded junior faculty investigators as Project and Pilot Project Leaders and one established investigator on projects investigating fundamental properties of nervous system function using a range of tools spanning molecular genetics, neurophysiology, invasive and non-invasive brain stimulation, behavior and neuroimaging. The Administrative Core facilitates all Center activities with a focus on career development, grant proposal submission, and deployment of technology developed by our research cores. The Design and Analysis Core aims to provide principled study design expertise, statistical modeling, machine learning, inference, and computation. The Behavior and Neuroimaging Core provides project-specific collaboration and support to COBRE scientists to promote the acquisition of high quality behavioral, physiological, neuroimaging and neurostimulation data, to ensure the integrity of the data collection infrastructure and to help implement robust data processing and visualization pipelines. While the cores principally serve Center scientists, our Center and the core resources have availability to all Rhode Island researchers.

KEYWORDS: neural function, neural recording, neuroimaging, behavior, core services

INTRODUCTION

Higher brain function often refers to the general ability to plan, organize, and select behaviors in a goal-directed manner. Deficits in higher brain function are common in both neurological and psychiatric disorders. They can result in a wide range of higher-order behavioral deficits, including an inability to plan a purposeful sequence of actions, a failure to inhibit inappropriate or detrimental responses, and difficulty initiating or flexibly shifting to novel responses as task demands change. These high-level deficits can occur following a stroke, brain damage, or neurological diseases, including Alzheimer’s disease and Parkinson’s disease. Moreover, many psychiatric disorders result in high-level cognitive deficits, such as schizophrenia and attention-deficit hyperactivity disorder.

The American Psychiatric Association’s definition of dementia (DSM IV) includes executive dysfunction (synonymous with deficiencies in high-level brain function). However, specific diagnosis and clinical assessment remain difficult. The limited understanding of the neural systems’ specific organizations mediating high-level function and its underlying mechanisms may contribute to this problem. For example, the Research Council of the American Neuropsychiatric Association conducted a comprehensive, clinically-oriented review of research from 1966 to 2002 on higher brain function. It concluded that a lack of basic knowledge into its mechanisms, functional organization and diversity remained a persistent obstacle to clinical assessment and treatment. Since that time, the basic mechanisms of attention, decision, and action have received growing interest, and these have formed the core of our COBRE project.

Integration of psychophysics, genetic tools, and neuroimaging represents a fundamental approach to address clinically significant gaps in the basic understanding of high-brain function. A significant obstacle to understanding higher brain function arises from uncertainty about how defining its major components, some of which – attention, decisions and action – we focused upon in Phase 1 of our COBRE project. Functional neuroimaging methods can measure the impact of a particular cognitive manipulation on activation in a specific brain region. Therefore, differences in developmental and adult-level attention, decision and action functions may be indexed by changes in activation in different brain regions or networks. Second, functional neuroimaging, neural recording, and intracranial stimulation can reveal how brain areas interact during the elaboration of these key processes. Attention and decision-making often operate through top-down modulation of ongoing processing, such as in the primary visual cortex or lateral temporal cortex. The impact of these top-down modulatory effects on local processing is difficult to assess using behavioral measures alone. However, functional MRI, source localized EEG, and combined neural recording and intracortical stimulation,
coupled with contemporary analysis methods, can permit measurement of local changes in targeted regions, such as the primary visual cortex, due to top-down modulation. This offers a means of studying the mechanisms and dynamics of top-down control. Finally, the ability to precisely localize higher brain function to neocortical and subcortical sites using functional neuroimaging permits more specific predictions regarding the impact of neurological and psychiatric disorders on higher brain function and the potential effects of behavioral and pharmacological interventions on these deficits. Integrating genetic analysis provides the opportunity to probe how genetic variations shift the parameters of these various components of higher brain function, which is essential for understanding variability across natural human populations.

ORGANIZATION OF THE COBRE CCNS

When we considered applying to the National Institute for General Medical Sciences (NIGMS) for COBRE funding, Brown University had significant research activities concerned with higher central nervous system function. Nevertheless, we believed that Brown and its affiliated hospitals and the larger Rhode Island community, could benefit by establishing a research center focused on nervous system function especially that related to cognition in health and brain disorders. We, therefore, proposed establishing a Center for Central Nervous System Function (CCNSF) to develop infrastructure in two domains: faculty researchers, particularly junior investigators, who would serve as Project Leaders (PL) and Pilot Project Leaders (PPL), and research cores, designed to facilitate the development of the research programs of PLs and PPLs.

Like all COBRE Centers, we established the obligatory Administrative Core. This core, with input from our Internal Advisory and External Advisory Committees, aims to support the scientific, technical and mentoring goals of our COBRE Center by providing leadership and an administrative structure to facilitate and coordinate the activities of the leaders of each research project, the overall Principal Investigator, the Deputy, and Associate Directors, positions held respectively by David Sheinberg (professor, Department of Neuroscience) and John Davenport (Managing Director, Carney Institute for Brain Science). The Administrative Core, among other functions, provides administrative support for the Principal Investigator and all PLs, PPLs, and Core Directors, collection and maintenance of financial records for all projects and cores, prepares the annual Progress Report; coordinate activities of the Internal Advisory Committee, the University Advisory Committee, and the External Advisory Committee in their roles of mentoring and evaluating the research and personnel in each project and core; organizes the COBRE Center’s internal meetings, and assists in data dissemination and sharing. Additional activities may include interactions with relevant departments and programs in faculty searches, external seminar series, and internal journal clubs. Indeed, we have used COBRE funds for the recruitment of one PL (T. Desrochers) and have made commitments to two incoming tenure-track faculty.

For the initial four years of Phase 1, we had a single research core, the Design and Analysis Core (DAC), and this core has continued into Phase 2. Applied scientists from Brown’s Department of Biostatistics, Division of Applied Mathematics, and the Department of Computer Science have directed the DAC. The primary purpose of the DAC concerned developing novel analytic tools for designing experiments and analyzing data, all in the service of the specific experiments proposed and implemented by PLs and PPLs. This core had more of a research-slanted focus compared to the typical service-related emphasis of COBRE research cores, aiming to develop collaborations with PLs and PPLs. We expected that the DAC would also provide more prosaic statistical and data science queries related to experimental design and data analysis implements. The core has succeeded in generating many original publications, more than 10 during Phase 1, and DAC staff have provided valuable consulting services to our PLs and PPLs. As Phase 1 progressed, and particularly due to input from PLs and PPLs, we recognized a need to enhance services related to implementation of research, especially for developing best practices to conduct experiments using structural MRI, task-based and resting state functional MRI, diffusion imaging, transcranial magnetic stimulation, transcranial direct-current and transcranial alternating-current stimulation, galvanic skin response, electroencephalography, and eye tracking. Clearly, the complexity of these techniques and the challenges of mastering the infrastructure required for effective and efficient deployment of them can significantly impede research progress, especially in the case of relatively junior investigators. Therefore, we created the Behavior and Neuroimaging Core (BNC) to provide ongoing expert support, training, assistance, and advice to these investigators. 

Figure 1. Project flow. PL or PPL brings a concept to DAC (light blue shading) and BNC (orange shading), which initiates a series of sequential steps from experimental design to final realization. Boxes with both orange and blue coloring indicate a cooperation between the two research cores.

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the COBRE PLs and PPLs in the practical aspects of data collection, data management, and data processing.

Together, the DAC and BNC have provided support and assistance to COBRE PLs and PPLs and their research teams to promote and facilitate the acquisition of high-quality research data and facilitate analysis of COBRE research data through deployment of tools, analysis platforms, and training. Figure 1 illustrates the typical flow for research projects from project inception through its completion. One notes that the DAC and BNC have overlapping and non-overlapping functions.

RESEARCH ACTIVITIES OF THE COBRE CCNSF

Since the inception of our COBRE in 2013, we have supported 11 PLs, eight in Phase 1, with two of these PLs spanning Phase 1 and Phase 2 and three solely in Phase 2. We will soon recruit at least two new PLs to “replace” PLs who will rotate off COBRE support. In the final years of Phase 2, we may recruit up to three other PLs for the total of 13 to 16 PLs who have or will have benefitted from COBRE support. Table 1 lists Phase 1 and Phase 2 supported PLs, along with their primary academic department, their project title and their support term. The PLs have come from Brown University’s Division of Biology and Medicine (MCB, Neuroscience, Neurosurgery), Arts and Sciences (CLPS), and School of Public Health (Biostatistics). All but W. Asaad and M. Worden had tenure-track appointments, with Neurosurgery [W. Asaad] not having tenure-track options and M. Worden serving in the research track. Most of the PLs conducted research with humans, spanning systems and cognitive neuroscience questions and addressing a wide range of questions from basic visual processing [M. Worden] to brain mechanisms of social interactions [O. FeldmanHall]. Two PLs (W. Asaad and T. Desrochers) used non-human primates to investigate fundamental questions about learning, decision-making and mental sequences. Two PLs used other model systems (rodents and Drosophila) to investigate fundamental mechanisms underlying developmental disorders [E. Morrow] and the molecular genetics and neural circuit dynamics mediating reward behavior [K. Kaun].

Along with the eight awarded pilot projects (not listed), whose leaders had primary appointments in several different departments and Brown University divisions, including Neuroscience, CLPS, Psychiatry, and Behavioral and Social Sciences, the unifying theme of all projects and pilot projects concerned revealing brain mechanisms of higher central nervous system function in health and disease. The project led by K. Kaun exemplifies our approach. She uses fruit flies as a model system and employs standard and novel methods spanning behavioral analysis, neural circuit recording, and molecular genetics to learn basic reward mechanisms. For her COBRE project, Prof. Kaun proposed investigating a glutamate-dopamine feedback circuit responsible for reward prediction and the localization of dopamine-2 like receptors (D2Rs) within this circuit in Drosophila. She hypothesized that feedback from glutamate neurons would result in a sparse representation of reward dopamine neurons in-memory expression and that D2R localization in these dopamine neurons would change during memory consolidation. One aim focused on testing whether a mushroom body (a major component of the fruit fly’s brain) γ5β’2 glutamate to dopamine connection is required for memory expression. A second aim proposed to develop a new tool for in vivo localization of D2Rs within this circuit. Other projects funded by our COBRE had similar focused and important goals.

Not listed in Table 1 are the genders of all but Prof. Jones had junior investigator

Table 1. Project Leaders of the COBRE CCNSF

<table>
<thead>
<tr>
<th>Department*</th>
<th>Project Title</th>
<th>Tenure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amso, D.</td>
<td>CLPS Development of vision and attention in typical and ASD individuals</td>
<td>2013–2016</td>
</tr>
<tr>
<td>Worden, M.</td>
<td>Neuroscience Conflict adaptation and selective attention</td>
<td>2013–2017</td>
</tr>
<tr>
<td>Asaad, W.</td>
<td>Neurosurgery Cortical-subcortical interactions in attention and learning</td>
<td>2013–2018</td>
</tr>
<tr>
<td>Song, J-H.</td>
<td>CLPS Target selection for visually guided actions</td>
<td>2013–2018</td>
</tr>
<tr>
<td>Kaun, K.</td>
<td>Neuroscience Microcircuits for reward driven decisions in Drosophila</td>
<td>2015–2018</td>
</tr>
<tr>
<td>Desrochers, T.</td>
<td>Neuroscience The neural basis of sequence monitoring in human and nonhuman primates</td>
<td>2017–2021</td>
</tr>
<tr>
<td>Shenhav, A.</td>
<td>CLPS Mechanisms of cognitive interference from value-based choice conflict</td>
<td>2017–2021</td>
</tr>
<tr>
<td>FeldmanHall, O.</td>
<td>CLPS The neural and affective mechanisms of socially risky learning</td>
<td>2018–2021</td>
</tr>
<tr>
<td>Eloyan, A.</td>
<td>Biostatistics Quantitative methods for brain connectivity network estimation and interference in functional magnetic resonance imaging</td>
<td>2018–2021</td>
</tr>
<tr>
<td>Jones, S.</td>
<td>Neuroscience The causal role of neocortical beta events in human sensory perception</td>
<td>2018–2021</td>
</tr>
</tbody>
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* MCB: Molecular Biology, Cell Biology and Biochemistry; CLPS: Cognitive, Linguistic and Psychological Sciences
status when COBRE support began. Prof. Jones was included in Phase 2, since she proposed to extend her computa-
tional-driven work into empirically based data collection related
to predictions of her computational models. Similarly, we
considered all Pilot Project Leaders as junior investigators
since none had received an R01 or equivalent grant when
starting their pilot project, though one Pilot Project Leader
had a K99/R00 grant, which NIGMS consider as a research
project grant.

OUTCOMES OF COBRE CCNSF

Our PLs and PPLs and research core members have been
particularly productive in garnering external research
funds, publishing peer-reviewed papers, and advancing their
careers at Brown (and unfortunately for us, also elsewhere
via recruitment), while also receiving professional recogni-
tion. Collectively and to date, our cohort of faculty research-
ers have published nearly 90 peer-reviewed papers supported
by COBRE funds, including many in well-respected journals
such as *Annals of Neurology, Cell Reports, Current Biology,
elife, Genetics, Journal of Neuroscience, Nature, Nature
Communications, Nature Human Behaviour, Nature
Reviews Neuroscience, Neural Computation, NeuroImage
Neuron, PLoS Computational Biology, PLoS Genetics,
PNAS, and Psychological Review*, among others. As a group,
the PLs and PPLs have successfully leveraged their COBRE
support to garner more than $22 million in external research
support, mostly from the NIH, but also from the NSF and
other Federal agencies as well as from private foundations
[e.g., Simons Foundation]. As our Phase 2 PLs and PPLs pro-
gress in their research, we expect additional grant awards;
indeed, one of our PLs has received promising news of both
an NIH and an NSF award, thereby increasing, by about $3
million, the total grant awards of our COBRE cohort. Our
COBRE supposed PLs have also received recognition for
their outstanding work by being awarded tenure [Amso,
Kaun, Morrow, Song] at Brown. In contrast, those supported
in Phase 2 have made excellent progress toward tenure.
For a loss to Brown but their benefit, some PLs and PPLs have
been recruited to other institutions, even though Brown
made competitive counteroffers. Some of our PLs have
received national recognition, such as a PECASE award [E.
Morrow] and field-specific young investigator citations [O.
FeldmanHall and A. Shenhav]. Taken together, our research
cohort has made outstanding progress using the standard
metrics of scientific achievement.

THE FUTURE OF THE COBRE CCNSF

As we reach the mid-point of the Phase 2 funding period,
we have accelerated our Phase 3 application plans. To this
end, we have identified a small cohort of PLs to “replace”
graduating PLs for at least two years of project-level funding,
using the faculty recruitment mechanisms provided by the
COBRE program. Since Phase 3 COBRE grants provide only
for pilot projects and cores, we have continued our outreach
to inform department chairs and center and institute direc-
tors that we will have research funds for larger-scale pilot
projects. We have also undertaken a review of our research
cores’ effectiveness, as we position them for the Phase 3
application. First, we have opened our cores to the entire
Brown community, including Brown-affiliated hospitals
and, with time, the whole Rhode Island scientific commu-
nity, with an aim to demonstrate usage and need. Second,
we have begun discussing how to leverage expertise in other
COBRE Centers that use similar or related methodologies
employed by our CCNSF researchers. Along these lines, we
note that many NIGMS-funded IDEa programs have data
handling capabilities, sometimes in the form of cores. We
endorse efforts to coordinate data science expertise across
the many COBRE and other IDEa supported programs
(INBRE and CTR). The objective is to seek partners related
to leveraging resources, especially financial ones and to
demonstrate to the staff of NIGMS’s Division for Research
Capacity Building that the funds devoted to Rhode Island are
being used well. Regarding the future of our research cores,
in recognition that Phase 3 cores should focus on developing
sustainability, we will refocus the DAC more toward ser-
vice and less toward creating novel statistical approaches.
Recall that, at the end of Phase 1, we split our DAC into
two cores, one to develop theoretical approaches for experi-
mental design and data analysis, the original main feature
of the DAC, and the BNC to serve the practical needs of our
COBRE cohort for experimental implementation. We now
believe that we should reintegrate these two cores while
maintaining efforts on developing novel statistical tools and
integrating, but to integrate these efforts with those of other
COBRE and other IDEa programs in Rhode Island.

We close with gratitude toward NIGMS for providing gen-
erous funds to foster the careers of many junior investigators
in Rhode Island by providing direct support to their research
endeavors and supporting research cores that have served
our COBRE cohort.

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