MREDI Final Report: SYNERGISTIC IMPROVEMENT IN THE DIAGNOSIS & TREATMENT OF MENTAL ILLNESS, DEMENTIA, & CHRONIC PAIN
July, 2017

This report is organized "by project" for each of the Center's four funded projects.

Project 1: Combine EEG and fNIRS for clinical diagnostic development for anxiety and depressive disorder.

Accomplishments
The successes of Project One lie in the setup and use of a new technology for mental health research in the state of Montana. One project coordinator and three research assistants were trained to collect fNIRS data in psychological research, a skill that is rare in Psychological Science. The placement of this technology, and the knowledge for its use in basic scientific research, at MSU puts the university in a position to do cutting-edge neuroscience that can both extend basic scientific knowledge about the neural processes underlying mental health (or illness) and lead to large external awards from federal funding sources.

Four jobs were created in the state of Montana as a result of this award. These positions provided an opportunity for keeping and attracting high-achieving young scholars to the state and offering them training in the use of fNIRS technology.

Quantitative accomplishments associated with project milestones include the following:
- The purchase of equipment from external business partners identified in the proposal. The construction of this equipment is complete and has been delivered to Montana State University.
- The setup of an EEG/fNIRS lab in the Department of Psychology on the MSU-Bozeman campus.
- Integrating fNIRS data collection with stimulus presentation for the acquisition of neural activity data during a computer task.
- The hiring of a project coordinator (1), research assistants (2), and the recruitment of volunteer aides for data collection (2).
- Training study personnel to collect EEG and fNIRS data, including obtaining practice data and receiving individualized feedback from TechEn, Inc.
- Obtaining IRB approval for study.
- Assembling recruitment and study materials, including programming experimental task.
- Collecting fNIRS and mental health data from 3 pilot participants and 45 participants for the study.

Comparison of results with original objectives
Although the overarching goals remain the same, results differ from those of the original objectives. Once analyzed, the data collected will enable us to answer questions about how neural resources are utilized by individuals who are high in depression and anxiety symptoms relative to individuals who are low in depression and anxiety symptoms. The placement of the fNIRS detectors will allow for a comparison of those results traditionally obtained using EEG measures, but both types of data (fNIRS and EEG) will not be available for this sample.

Additionally, this sample utilized young adults rather than children for data collection. The delay in hardware acquisition and setup made it unlikely that we would be able to recruit a sample of children large enough to conduct data analysis. In order to preserve the possibility of obtaining meaningful outcomes from these procedures, we targeted young adults rather than

children. Although the population and data are different than anticipated, we will still be able to begin to identify neural markers that may suggest a person is at risk for psychological disorder that requires a specialist's attention. This is consistent with the primary aim for this project.

Long-Term Impact
Two projects are already in place to follow up this work. The first is a new collaboration between Dr. Rebecca Brooker and Dr. Monica Skewes (MSU Department of Psychology) to examine the role of neural markers of regulation (obtained through fNIRS technology) in the manifestation of substance abuse behaviors. Dr. Skewes is an expert in substance abuse and addictions and has been actively working with Native American communities in Montana to understand the origins and perpetuation of substance use and abuse.

A second project will be for Dr. Brooker to extend the current work to include a sample of young children. This will enable an understanding of the ways that early neural markers of regulation may contribute to the development of depression and anxiety in early life.

Project 2: Conduct a breakthrough study on the use of Deep TMS for Alzheimer's Disease (AD) in order to improve the lives of Montana families affected by AD and make Western Montana Mental Health Center in Butte a treatment destination for patients from across Montana.

Accomplishments
Through our partnership with Western Montana Mental Health Center (WMMHC), we were able to help them conduct their first clinical research study in their Butte clinic. Although we fell short in recruiting the number of research subjects that were needed, we learned a great deal about how to effectively conduct this type of research in Montana. Two subjects passed screening and enrolled in the study, and they were both able to successfully complete all study procedures. Neither subject complained of study participation nor experienced any concerning adverse events.

Long-Term Impact
Although the Alzheimer's study did not meet the objectives from the original proposal, we do believe that several positive outcomes have come from this study that will be long lasting for Montana. By bringing this new technology to this part of the state, we now have expertise in conducting research combing EEG/fNIRS. The EEG/fNIRS equipment used in the study will be transferred to MSU and made available for other researchers on campus for their new/ongoing projects. Additionally, we have trained and certified four individuals in the state to deliver TMS. We also formed a partnership with Neuralynx, Inc., the Bozeman-based company who provided the EEG equipment and training.

The study coordinator who was hired to conduct this project at WMMHC was also able to attend a training to become a Certified Alzheimer's Disease and Dementia Care Trainer. Since completing her certification, she has gone on to train 35 people in the Butte community through an 8-12 hour seminar focusing on topics specific to Alzheimer's Disease including communication, repetitive behaviors, depression, personal care, and family relationships.

She also received an education grant of $1,000.00 to promote Alzheimer's Disease education in the community from the Montana Geriatric Education Center at the University of Montana. She plans to team up with another grant winner in Butte at the Belmont Senior Center and focus on educating EMTs, police, and family members providing in home care for those with Alzheimer's. The seminar will take place in Butte sometime in September 2017.

Project 3: Establish efficacy and safety in a non-human primate model to facilitate clinical candidate selection of non-opioid therapeutic agents for acute and chronic pain, common correlates of anxiety, depression and neurodegeneration.

Accomplishments
The non-human primate model established with the support of the MREDI grant has resulted in ground-breaking advancements in the development of SiteOne Therapeutics' small molecule NaV1.7 inhibitors. This model represents one of only a handful of non-human primate models for evaluating efficacy in pain therapeutic candidates in the global drug development community. With the MREDI grant support and the leadership of Dr. David Yeomans and the entire team at the Animal Resource Center at Montana State University, SiteOne achieved the following objectives:

- Successfully demonstrated the efficacy and initial safety of 2 SiteOne clinical candidates (ST-2257 and ST-2262), demonstrating strong analgesia with no notable off-target toxicology signals
- Designed and tested a histamine-induced itch protocol for the primates while they are fully awake, paving the way for more robust efficacy evaluation of pain therapeutic candidates
- Designed and conducted a protocol to validate SiteOne's noxious heat model in lightly anesthetized monkeys with buprenorphine, a known strong opioid analgesic
- The grant provided funding for research equipment, including a cardiac/respiratory monitor, video monitoring equipment and other equipment to evaluate sensory response to noxious stimuli
- The grant provided support for Dr. Yeomans, a Stanford Hospital anesthesiologist and two Senior Scientists from SiteOne's San Francisco based research facility to travel to Montana to design, validate and conduct the protocols. It also supported critical staff at the MSU Animal Resource Center

In summary, the support provided by the MREDI grant resulted in ground-breaking research in SiteOne's NaV1.7 inhibitors and, along with the other critical advancements made by the SiteOne research team, proved to be a significant catalyst in securing our $15M Series B financing and research collaboration with Amgen.

Long-Term Impact
Based on this success, SiteOne will continue to support the non-human primate model in Montana and has plans to evaluate several more therapeutic candidates in the coming months. Also, SiteOne will be bringing our partners from Amgen to participate in future protocols, providing excellent exposure and increased awareness of the research being done in the state of Montana.

Finally, SiteOne is developing plans to bring additional animal models to the ARC at MSU and plan to hire support staff that will help manage these research activities.

Project 4: Investigate the ability of the Youth Aware of Mental Health Program (YAM) to prevent suicidal behaviors and improve mental health in freshmen high school students in Montana.

Accomplishments
The CMHRR gained support and partnered with 8 schools (Gardiner High School, Pryor High School, Helena High School, Capital High School, Terry High School, Browning High School, Lodge Grass High School, and Custer County District High School), delivering the YAM

intervention to 60 classes of 1,387 mostly freshman students in Montana. We successfully recruited 515 of those students to give assent (with parent consent) to participate in the research study which involved completing mental health assessments before YAM began (Baseline) and 3 months after the program ended (Follow-up). Parents, teachers, and staff/administrators also completed 3 month acceptability surveys. We hired and trained 12 YAM Facilitators and 19 YAM Assistants, creating jobs for a total of 31 Montanans.

Results are not yet available from the Baseline and Follow-up surveys completed by students as we are still in the process of analyzing the data. We do have some preliminary data available related to the acceptability surveys completed by parents, teachers, and staff/administrators. Of the 48 parent surveys that were returned, 65% "agreed or strongly agreed" that they were pleased with the program, 71% "agreed or strongly agreed" that they would suggest this program to other schools, and 73% "agreed or strongly agreed" that they would want their school to participate again. Of the 21 teacher surveys that were returned, 48% "agreed or strongly agreed" that they were pleased with the program (52% were "undecided"), 52% "agreed or strongly agreed" that they would suggest this program to other schools (43% were "undecided" and 5% "disagreed"), and 57% "agreed or strongly agreed" that they would want their school to participate again (38% were "undecided" and 5% didn't answer the question). Of the teachers who provided "undecided" ratings, the majority stated that they were unable to determine the acceptability of YAM due to their limited involvement with its delivery. Teachers were included in the evaluation, despite their minimal involvement, to detect any potential negative impact on the classes (which did not occur). Of the 18 returned staff/administrator surveys (those who were much more involved than teachers), 94% "agreed or strongly agreed" that they were pleased with the program, 94% "agreed or strongly agreed" that they would suggest this program to other schools, and 100% "agreed or strongly agreed" that they would want their school to participate again.

Long-Term Impact
Our pilot YAM study has already begun to make a lasting impact on Montanans. Through the CMHRR's partnership with MSU Extension, we were able to receive 2 additional grants and bring our YAM efforts to 17 additional schools across the state. This funding also led to 17 MSU Extension faculty members now trained and certified as YAM Facilitators.

Future activities include plans to apply in summer 2017 for state legislative funding (MT House Bill No. 118) to continue YAM in the same 8 schools who participated in the pilot. The CMHRR is currently in discussions with Bozeman Health to potentially receive funding to deliver YAM in Bozeman, Belgrade, and Big Sky starting in the fall of 2017. We also plan to apply this October for National Institute of Mental Health (NIMH) funding for a large scale randomized control trial of YAM in both Montana and Texas. Lastly, we are starting the process of adapting the YAM program to make it appropriate for testing in college-aged students/young adults.

Potential future activities for expanding YAM across the state would necessitate the hiring and training of additional private sector mental health-related professionals to be YAM Facilitators and Assistants. We've already begun the process for long-term rollout of YAM through a YAM Trainer Workshop that took place in February/March 2017. Following completion of the workshop, we now have four of our original YAM Facilitators certified to be YAM Trainers. These four YAM Trainers will be able to train additional YAM Facilitators in Montana for years to come.

Final Metrics

- *Total additional grants received*: 5
    - USDA-NIFA, $362,378 (directs), Preparing Montana Extension to Address Mental

Health in Non-clinical Settings
    - Montana Mental Health Trust, $91,771 (directs), Expanding Extension's Role in Serving Montana in Non-Clinical Mental Health Services
    - Private donor/MSU, $25,000/matched by MSU, for YAM-related efforts in Native American communities
    - Montana Geriatric Education Center, $1,000, for a seminar to educate EMTs, police, and family members providing in home care for those with Alzheimer's
    - Amgen, $15,000,000 Series B financing and research collaboration, to accelerate the development of SiteOne's compounds and complete an initial clinical trial within the next 3 years
- *Total additional grants in progress*: 3
    - MT House Bill No. 118, Revise and provide additional funding for suicide prevention activities, CMHRR plans to apply for this funding to continue delivering YAM in the 8 pilot schools
    - NIMH R01, CMHRR plans to apply in Oct 2017 for federal grant funding for a large scale randomized control trial of YAM
    - Bozeman Health, CMHRR is in discussions with Bozeman Health about receiving funding to deliver YAM in Bozeman, Belgrade, and Big Sky
- *Number of partnerships formed (private and public sector)*: 6
    - Public sector – 3 for Objective 4 (MSU Extension, OPI, pilot schools)
    - Private sector – 2 for Objective 2 (Western Montana Mental Health Center and Neuralynx, Inc), 1 for Object 3 (SiteOne Therapuetics)
- *Number of new Montana businesses created*: n/a
- *Patents awarded or in progress*: n/a
- *Commercial products developed*: n/a
- *Jobs created*:
    - Private sector – 31 for Project 4
    - Research coordinators – 1 for Project 1, 1 for Project 2, 1 for Project 4
    - Student Research Assistants – 4for Project 1

Photos (see following page)

Project 2

EEG Machine

fNIRS Machine

Project 4

YAM Facilitator Training, Bozeman, April 2016