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

This progress report is organized “by project” for each of the Center’s four funded projects.

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

Overview:

Objective 1 remains behind schedule as the result of setbacks associated with the renegotiation of prices of the equipment being purchased with our Montana-based business partner, delays in equipment setup and training, changes in vendor personnel, and continuing delays in the acquisition of the remainder of the hardware from the vendors.

We have received our head caps, but remain engaged in talks with TechEn and Veridical Research and Design to integrate the stimulus presentation software collection of EEG and fNIRS data. At this point, it does not seem feasible to integrate these hardware, retrain personnel, and complete the project within the scheduled timeframe.

As previously indicated, the fNIRS portion of this study can will still be run despite setup delays on the integration of the EEG and fNIRS systems. Pilot data collection for this work is complete. Recruitment of subjects for the fNIRS is underway. As a result of personnel turnover, two RAs are being trained that will be dedicated to fNIRS data collection during the summer months. There are expected to be fully trained before June 1, 2017, at which time data collection will re-commence.

A project coordinator has assembled all recruitment materials, identified and created digital copies of study measures for computerized administration, and has programmed an online signup option for study participants. An IRB protocol has been submitted and approval has been obtained. Undergraduate research staff has been recruited and trained. Approval has also been obtained for the use of the Psychology subject pool and the recruitment of community participants.

Equipment purchased:

Equipment has been purchased from Neuralynx, Inc. and TechEn, Inc. as described in the research proposal. Software has been ordered, received, and set up to begin processing EEG data as soon as it is collected. Brain Vision Analyzer software has been purchased for EEG data cleaning. Presentation stimulus presentation software has been purchased for the task to be used during data collection. Consumable supplies for the application of the fNIRS optodes have also been purchased.

Progress towards milestones (since previous update):

- Practice data has been sent to TechEn for feedback regarding procedural adjustments
- 3 pilot participants have been run
- 1 study participant has been run

- An online sign-up system for study participants has been assembled

Total amount of expenditures by report date:

Salaries:

- Project coordinator salary: $6,282.50
- Project coordinator benefits: $2,206.05

Contracted Services/Consultation:

- Veridical Research and Design: $5,800.00
- Veridical Research and Design parts reimbursement: $12.39

Equipment:

- Neuralynx, Inc.: $65,000 for EEG setup and caps
- TechEn, Inc: $134,000 for fNIRS setup
- ActiCap for data collection: $6,969.00

Software:

- Software for EEG data processing: $7,902.80
- Neurobehavioral Systems software programming for experimental task: $900.00
- Presentation software license for stimulus presentation: $511.65

Other Costs:

- Facilities services charge to move equipment shipped from vendors: $58.50
- Shipping cost for EEG data processing software: $30.00
- University charges for purchasing hardware: $158.88
- Secure safe for storing participant payments: $16.81
- Wooden sticks to use for optode application: $12.65
- Human subjects payment advance: $2,000
- Lab supplies: $100.40

Objective 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.

Overview:

Enrollment for the study ended in mid-March and we were able to screen five study participants. Two of the five subjects passed screening and were enrolled into the study. The remaining three were all screen fails (did not meet inclusion/exclusion criteria). One of the two enrolled subjects completed all study procedures on 5/18/17. The other enrolled subject completed all TMS treatment visits and will return to the clinic in late June for the follow-up study visit.

Hirings (since previous update):

No new hirings have occurred since our last update.

Equipment purchased:

No new equipment has been purchased since our last update.

Progress towards milestones (since previous update):

- Two subjects have successfully enrolled into the protocol (another 3 subjects were screen fails).
- One subject has completed all procedures in the study.
- One subject has completed all TMS treatments, and still has a follow-up visit scheduled for late June 2017.

Total amount of expenditures by report date:

- Neuralynx, Inc.: $58,484.70 for EEG setup
- TechEn, Inc.: $133,650 for fNIRS setup
- Brainsway, Inc: $283,000
- BrainVision: $10,618
- Payroll of Research Managing Director, Business Manager, and Faculty Consulting: $43,920.96
- Travel expenditures: $881.73
- Supplies, Shipping, and Communication expenditures: $458.67
- Western Montana Mental Health Center: $94,864.14
- Consultants: $8,779.63

Objective 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.

Overview:

We have successfully tested 2 SiteOne clinical candidates in the primate model, demonstrating strong analgesia with no notable off-target toxicology signals. ST-2257 and ST-2262 have both demonstrated a dose-dependent analgesic response with a complete block of pain at the higher doses. These findings provide important validation of our technology and we are further characterizing these compounds and others as potential clinical candidates. In December 2016, SiteOne closed a $15M Series B financing and strategic collaboration with Amgen which provides the resources to accelerate the development of our compounds and complete an initial clinical trial within the next 3 years.

Additionally, the SiteOne team has designed and tested a histamine-induced itch protocol for the primates while they are fully awake. This approach has been reported to work well in humans, rhesus macaques and rodents. In this model, itch is induced by subcutaneous or intradermal injections of histamine followed by observational analysis of scratching response. We were able to test reactions to histamine in four monkeys and concluded that histamine is not an effective pruritic agent in our model of

cynomolgus monkeys. In two remaining monkeys, we tested responses to capsaicin, which is known to activate heat-sensitive sensory fibers in the skin. Topical application of capsaicin resulted in robust scratching response in both monkeys. We concluded that topical capsaicin evokes robust scratching response and that it can be further explored in testing the ability of NaV1.7 blockers to block capsaicin-induced scratch. Both of these exploratory studies were conducted in compliance with the MSU IACUC protocol.

We also conducted a protocol to validate our noxious heat model in lightly anesthetized monkeys with buprenorphine, a known strong opioid analgesic. The study design was similar to previous protocols with our test drug candidates. Four monkeys participated in this study. IV administration of 0.3 mg/kg buprenorphine produced strong analgesia resulting in inhibition of heat-induced hand withdrawal. We concluded that our noxious heat model activates classic pain pathways. The study was also conducted in compliance with the MSU IACUC protocol.

Hirings:

SiteOne is utilizing two Senior Scientists from our San Francisco based research facility, in addition to Dr. Yeomans, to design and conduct research activities with the model. At least one of these positions will relocate to Montana during 2017 and additional pre-clinical hires are being evaluated for 2017.

Equipment purchased:

Cardiac/respiratory monitor at $3,000.

Progress towards milestones:

- Screening of ST-2262, a novel, non-opioid drug candidate, has been successfully completed in this primate efficacy and safety model. Additional in-vitro and in-vivo characterization of this potential clinical candidate are ongoing. Several additional related new compounds have been synthesized and are undergoing initial pre-clinical evaluation for testing in the primate model in 2017.

Total amount of expenditures by report date:

- Total expenditures to date are ~$223,000
- Payroll of MSU Faculty Consultant: $4,999.83

Objective 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.

Overview:

Objective 4 continues to be on track for timelines. Since March, we've completed all baseline assessments, 3 month follow-up assessments, and YAM delivery in all 8 schools. We've also received questionnaires from parents, teachers, and staff/administrators, and the feedback to date has been mostly positive.

Hirings (since previous update):

No new hirings have occurred since our last update.

Equipment purchased:

None.

Progress towards milestones (since previous update):

- We continue to have the support of the Office of Public Instruction and DPHHS for the proposed study.
- We have completed baseline assessments, YAM delivery, and follow-up assessments in 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 (Miles City).
- We have started entering baseline and follow-up survey data into MS Excel with the plan to have it completely entered by mid-June.

Total amount of expenditures by report date:

- Contracted Services (YAM Training): $25,186.12
- Participant Payments: $1,325
- Travel & School Recruitment Costs: $28,756.27
- Services: $3,244.85
- Supplies: $17,562.82
- Payroll of YAM Facilitators and Assistants: $64,059.19
- Payroll of Research Managing Director, Research Study Coordinator, & Business Manager: $105,009.10