Retraining Neural Pathways Improves Cognitive Skills After A Mild Traumatic Brain Injury (mTBI)

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Research has found that the effects of a mTBI reflect disruptions of the neural networks for attention and working memory. After a mTBI, patients have trouble in sustaining attention and remembering. Cognitive deficits in those with a mTBI are hypothesized to result from neural timing deficits. Compensation for timing issues by increased prefrontal cortical recruitment would be manifest as increased distractibility, working memory deficits, and problems with balance and coordination. Visual timing deficits, resulting from magnocellular (motion) deficits are persistent in individuals with a mild TBI, manifesting as timing deficits in the dorsal pathways, and attention and executive control networks. Thus, daily living is dramatically impaired after a mTBI.

The magnocellular deficits persistent in those having a mTBI were remediated quickly (Lawton & Huang, 2019) by completing a short amount of movement-discrimination (*PATH*) training designed to optimally activate magnocellular (left-right movement) neurons in the dorsal stream relative to parvocellular (stationary background) neurons in the ventral stream. It is likely that the patented *PATH* movement-discrimination training paradigm improves not only magnocellular function, attention, and memory, but also feedback, that can be measured by the strength of coupled theta/gamma and alpha/gamma frequency oscillations, and measured by Dr. Huang and his team. MEG functional brain imaging that measured responses evoked from an N-back WM test on mTBI patients confirmed this improvement over their baseline in brain function after *PATH* training (Lawton & Huang, 2019). This pilot study illustrates the brain plasticity found in mTBI patients, that is, they show neurophysiological reorganization as evidenced by the MEG findings. Dr. Huang's innovative methods for MEG source imaging enable measuring timing changes, in terms of delta, theta, alpha, beta, and gamma oscillations, as well as changes in cognitive function following intervention training more precisely than any other methods. Statistical methods being used in this study to analyze MEG recordings and behavioral results utilize state-of-the-art techniques.

Furthermore, there is evidence that improvements in cognitive skills after this movement-discrimination training that is more rapid and effective than the competition are sustained over time. Our pilot study found that *PATH* exercises improved attention and working memory so less effort was spent decoding information, and more effort was spent on interpreting the information, improving timing by using most efficient working memory network, skills that improve a person's quality of life after a mTBI.

Proposed Study

The proposed study tests the feasibility of *PATH* neurotraining to improve working memory and attention in mTBI patients rapidly and effectively to provide clinical testing of therapeutic training for the remediation of cognitive disorders caused by a concussion. The scientific premise of this project is that remediation of a fundamental visual processing deficit affecting motion discrimination in the visual dorsal pathways generalize to high level cognitive abilities reliant upon motion processing as a foundation. Magnetoencephalography (MEG) brain recordings will be used to determine whether *PATH* training improves the function of the visual and cognitive networks, more than after Sham training, that activates the visual ventral pathways, and whether *PATH* neurotraining strengthens coupled (amplitudes locked in-phase in same brain regions): 1) theta/gamma activity, and 2) alpha/ gamma activity. This study will compare *PATH* training, presenting dim gray patterns moving left or right to activate the magnocells in the dorsal stream, with Sham training, presenting high contrast colored stationary patterns tilted left or right to activate the parvocells in the ventral stream. We predict that Sham training does not improve working memory and attention in mTBI. This will be measured using both neuropsychological standardized tests of cognitive skills and MEG recordings. MEG recordings before and after training will provide a biomarker (to determine whether *PATH* training improves the function of the dorsal, attention, and working memory networks more than found after a Sham treatment. MEG recordings will also be used to determine whether *PATH* neurotraining strengthens feedback, to be measured by the magnitude of increased coupled theta/gamma and alpha/gamma frequency oscillations using a sensitive metric of neural functioning, namely the delta (1-4 Hz), theta (4-7 Hz), alpha (8-12 Hz), beta (15-30 Hz), and gamma (30-80 Hz) frequency oscillations.

We plan to study 14 mTBI subjects between the ages of 18-55 with half doing PATH training and half doing Sham training. mTBI subjects will be recruited by posting brochures, approved previously, and by getting referrals from neurologists: Dr. Mohammed Ahmed, M.D. who sees the largest number of mTBI subjects in this area. The PI, having extensive experience conducting controlled validation studies, and the Senior Research Assistants (SRA)will be in charge of training all staff, running daily operations which requires scheduling and supervising: 1) pre-post standardized testing, 2) pre-post MEG exams at UCSD, and 3) administering the treatment and control interventions.

To evaluate whether *PATH* training improves working memory and attention in those with a mTBI more than after Sham training, changes in both behavioral, using standardized percentiles on neuropsychological tests as the primary outcome measure, and biomarkers, using MEG physiological brain recordings as the secondary outcome measure, will be analyzed, taking into account subject variability. Biomarker changes using MEG physiological brain recordings are critical to provide biological evidence for proposed mechanisms by which *PATH* training works. Behavioral improvements in cognitive skills will be analyzed by comparing pre- and post- 1) standardized percentiles on neuropsychological tests, 2) questionnaires, and 3) scores on the MoCA screening test.

Changes in test performance for the primary (VWM) and secondary outcome measures (attention, cognitive flexibility; *WAIS-4* processing speed, reading speed, MoCA, and questionnaires) will be analyzed using mixed-factors Analysis of CoVariance (ANCOVAs). These ANCOVAS will compare standardized test percentiles, reading rates, MoCA and questionnaire scores, controlling for age, before and after treatment and control interventions. The mixed factors ANCOVAs will be performed with the between subjects factor of Training Group (*PATH* vs. Sham Training) and the within subjects factor of Time (Time1, Time2). The SRAs will enter in all tests results, and contrast sensitivity data from those doing *PATH* neurotraining, and the dates and times of intervention training into the HIPPA and FERPA certified REDCap database. Based on our previous MEG study of mTBI subjects (Lawton & Huang, 2019), we expect large effect sizes ($d > 0.98$) for the MEG measures of improvements in: 1) brain function, increased response magnitude measured at hubs of the attention and executive control networks, and 2) different brain oscillations following *PATH* training.

Specific Aims

Specific Aim 1: Establish the feasibility of an innovative, computer-based program (*PATH to Reading/Insight* (*PATH*) neurotraining) to improve cognitive skills in mTBI subjects.

Go-NoGo Milestone: We will show that *PATH* neurotraining improves visual working memory (primary outcome) in mTBI subjects significantly more (at $p \leq 0.05$) than after Sham training. The go-nogo milestone will be evaluated by measuring whether subjects doing *PATH* neurotraining improve on visual working memory standardized percentile scores at least 15% more than those doing the Sham training, based on previous results in a pilot study (Lawton & Huang, 2019). Secondary outcomes like attention will also be evaluated.

Specific Aim 2: Use MEG source imaging in a working-memory (WM) test to validate that dorsal stream, attention, and memory networks improve in function significantly more following *PATH* neurotraining than following Sham training.

Go-NoGo Milestone: Compared with the baseline, an MEG WM exam from individuals treated with the *PATH* neurotraining will show significantly stronger neuronal signals, better performance accuracy, and shorter reaction times, than those doing Sham training, in different visual areas and in most efficient WM network, including the dorso-lateral prefrontal cortex (dlPFC), and anterior cingulate cortex (ACC). We will also see more significant increases than when doing Sham training in their magnitude of responses and significant increases in coupled theta/gamma and/or alpha/gamma oscillations, as predicted previously in our pilot study.

Since intervention training is being followed by a complementary strategy to provide practice on Visual Working Memory (VWM), one that was not used in the pilot study, it is highly probable that these Aims will be obtained, significantly improving cognitive skills after a mTBI. In addition, we will determine whether mTBI subjects who have neural timing deficits determined by MEG imaging data improve in cognitive function the most. Our preliminary data in just a few subjects has shown that MEG imaging was sensitive in detecting brain functional changes in dlPFC and ACC which are part of the VWM network. With more subjects in the proposed study than in our pilot data, we have confidence that these changes in dlPFC and ACC can be detected reliably. This study will be published in a leading scientific journal and provide data to show PATH provides proven solution.

Pilot Study: Lawton, T. & Huang, M.X. (2019) Dynamic cognitive remediation for a traumatic brain injury (TBI) significantly improves attention, working memory, processing speed, and reading fluency. *Restorative Neurology and Neuroscience,* 37, 71-86.