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| **Fiscal Year:** | FY 2021 | **Task Last Updated:** | FY 09/22/2020 |
| **PI Name:** | McKinley, Richard Ph.D. | | |
| **Project Title:** | Effects of Transdermal Vagal Nerve Stimulation (tVNS) on Cognitive Performance Under Sleep Deprivation Stress | | |
| **Division Name:** | Human Research | | |
| **Program/Discipline:** | | | |
| **Program/Discipline--Element/Subdiscipline:** | | | |
| **Joint Agency Name:** | | **TechPort:** | No |
| **Human Research Program Elements:** | (1) **HFBP**:Human Factors & Behavioral Performance (IRP Rev H) | | |
| **Human Research Program Risks:** | (1) **Sleep**:Risk of Performance Decrements and Adverse Health Outcomes Resulting from Sleep Loss, Circadian Desynchronization, and Work Overload | | |
| **Space Biology Element:** | None | | |
| **Space Biology Cross-Element Discipline:** | None | | |
| **Space Biology Special Category:** | None | | |
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| **PI Organization Type:** | GOVERNMENT | **Phone:** | 937-938-3598 |
| **Organization Name:** | United States Department of the Air Force | | |
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| **Zip Code:** | 45433-7951 | **Congressional District:** | 10 |
| **Comments:** | | | |
| **Project Type:** | Ground | **Solicitation / Funding Source:** | 2018 HERO 80JSC018N0001-Crew Health and Performance (FLAGSHIP, OMNIBUS). Appendix A-Flagship, Appendix B-Omnibus |
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| **No. of Post Docs:** | 0 | **No. of PhD Degrees:** | 0 |
| **No. of PhD Candidates:** | 0 | **No. of Master' Degrees:** | 0 |
| **No. of Master's Candidates:** | 0 | **No. of Bachelor's Degrees:** | 0 |
| **No. of Bachelor's Candidates:** | 1 | **Monitoring Center:** | NASA JSC |
| **Contact Monitor:** | Whitmire, Alexandra | **Contact Phone:** | |
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| **Flight Program:** | | | |
| **Flight Assignment:** | | | |
| **Key Personnel Changes/Previous PI:** | | | |
| **COI Name (Institution):** | McIntire, Lindsey M.S. ( Infoscitex, Inc ) | | |
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| **Task Description:** | Objective: To evaluate the efficacy of transdermal vagal nerve stimulation (tVNS) to mitigate the effects of fatigue induced by sleep deprivation on aspects of cognition including attention, arousal, multitasking, and memory in populations of Department of Defense (DoD) subjects.<br>Primary Objective: Demonstrate a >20% improvement in at least one cognitive skill during sleep deprivation stress when compared to the control population.<br><br>Secondary Objective: Assess effects of tVNS on subjective mood.<br><br>Methods: This study will utilize a single factor, between subjects, double blinded experimental design. The factor will be "stimulation type" and will be tested at two levels: active and sham. Participants will be randomly assigned to one of two experimental groups (n=20 for each group). Group 1 will receive active tVNS on the skin over the left and right cervical vagus nerve (neck) at 25 Hz for 2 minutes on each side (with a 2 minute break in between) at 1800. Group 2 will receive sham tVNS at 1800 on both the left and right cervical vagus. The sham will be conducted with a separate sham tVNS device provided by the manufacturer. The sham provides similar sensations (e.g., vibrations) without providing stimulation of the nerve.<br><br>After consenting to participate in the study, participants will fill out the medical screening questionnaire. Two days prior to their scheduled experimental trial, participants will be given an activity wrist monitor and instructed that their daily schedules should include a minimum of seven hours of sleep per night between the hours of 2300 and 0600. Also during this time participants will receive training on all four performance tasks to be utilized in the study. Participants will be trained to asymptote on the performance tasks to guard against learning effects during experimental testing. Therefore, more training may be administered if necessary. Participants will also become familiarized with the subjective questionnaires at this time.<br><br>On the day of their experimental trial, participants will be required to awaken at 0600 and perform their daily activities as normal. They will be instructed to not consume any caffeine or central nervous system (CNS)-altering medications/substances on the experimental test day. Each participant will arrive at the test facility at 1530 hours. Upon arrival, their activity data will be analyzed to ensure that proper sleep cycles were maintained. Starting at 1600 hours, participants will complete one session of the vigilance task (30 mins), one session of the working memory task (20 mins), one session of the psychomotor vigilance test (PVT) task (10 mins), one session of the Multi-attribute task battery (MATB) task (20 mins), and fill out the Profile of Mood States-Brief (POMS-B), Visual Analogue Scale (VAS), and side–effects questionnaire. Afterwards, participants will then be provided a break of approximately 90 minutes where they can talk, watch TV, walk, read, or play video games. The second session will begin at 1900 hours. These procedures will be repeated every three hours with the final session occurring at 1600 the following day (36 hours continuous wakefulness). At 1900, participants will be given active or sham tVNS depending on their experimental group.<br><br>Impact: High levels of performance at all times is a requirement for success in both military and space exploration populations. Non-invasive vagal nerve stimulation has been shown to augment cognitive performance such as learning, memory retention, attention, and arousal. The results from this research will help determine the feasibility of tVNS to limit the effects of fatigue stress on NASA and military operators. While there is no substitute for adequate sleep, this may substantially reduce errors and attention lapses caused by increased fatigue when rest is not an option. |
| **Rationale for HRP Directed Research:** | |
| **Research Impact/Earth Benefits:** | Impact: High levels of performance at all times is a requirement for success in both military and space exploration populations. Non-invasive vagal nerve stimulation has been shown to augment cognitive performance such as learning, memory retention, attention, and arousal. The results from this research will help determine the feasibility of tVNS to limit the effects of fatigue stress on NASA and military operators. While there is no substitute for adequate sleep, this may substantially reduce errors and attention lapses caused by increased fatigue when rest is not an option. |
| **Task Progress:** | The study data collection has now been completed, the data analyzed, and the journal manuscript has been drafted. Two groups of participants with twenty in each group completed the procedures of this study. One group received either non-invasive tVNS over the left and right cervical vagal nerve (neck), or sham tVNS at 1900 hours during 34 hours of sustained wakefulness. Every 3 hours throughout the night, until 1700 the next day, participants completed a battery of cognitive tasks and subjective mood questionnaires. The task battery included the Mackworth Clock Test (Sustained Attention Task), the N-Back working memory task, the Psychomotor Vigilance Task (PVT), and the Air Force-Multi-Attribute Task Battery (AF-MATB). The Mood Questionnaire was a 15-item mood questionnaire where the participants checked a box closer to the mood on the scale that they most identified with at the moment. For example, "Fatigued or Energized," "Happy or Sad," and "Optimistic and Pessimistic" were items on this questionnaire. Depending on the box selected, the questionnaire would output a numerical score (1-7) to quantify the mood.<br>The purpose of this study was to investigate the use of peripheral nerve stimulation on the cervical vagus as a fatigue countermeasure. One of the primary findings from this study was a significant interaction for the multi-tasking test that occurred later in the testing at the 0700 and 1000 sessions. Participants had been awake for 24 to 27 hours during these two testing sessions, respectively, which represents a traditional low point for circadian rhythms; further analysis showed that the group receiving tVNS stimulation had a significantly higher throughput capacity than the sham group. In fact, the tVNS group's throughput capacity decreased only 5% from their baseline at 1600 (when they first arrived at the lab, 9 hours awake) whereas the sham group's capacity fell 15%. Twelve total minutes of non-invasive stimulation delivered at 1900 hours appears to be providing a long-lasting benefit to multi-tasking performance, 15 hours post-stimulation, when performance should be at its worst.<br><br>To our knowledge, the present study is the first to assess multi-tasking cognitive performance during VNS, and the first to do so under conditions of lengthy sleep deprivation. Given the results from the AF-MATB task that indicates the greatest performance benefit is found for tasks requiring visual attention, it is not surprising that a performance benefits for the visually-based psychomotor vigilance task (PVT) was also detected. The PVT is a simple reaction time test that requires visual attention, rapid detection and response, and more generally, measures physiological arousal levels. Our results indicated that the tVNS group performed significantly better than sham on the PVT for the duration of the testing, which by the end of the study was 19 hours after stimulation. In our previous research with tDCS and sleep deprivation, we repeatedly found that tDCS enhanced arousal levels (as measured by the PVT) compared to caffeine and sham stimulation for as long as 24-hours post stimulation (McIntire et al., 2017; McIntire et al., 2014). Furthermore, |

when we delivered cervical tVNS on 4 consecutive days using the same device and stimulation procedures from this study, we found elevated PVT accuracy scores as long as 90 days post-stimulation (McIntire et al., 2019).

Another interesting finding from this study was the smaller increase in subjective fatigue rating by participants who received tVNS when compared to sham. It is possible, if not likely, that this reduction in fatigue is caused by activation of the locus coeruleus (LC). This brain region is involved with attention, memory, wakefulness, and arousal. These are all aspects of behavioral that we showed to be influenced by tVNS. Future research should investigate other forms of cognitive enhancements and consider biomarker or imaging analysis to more deeply explore the mechanisms of action, determine why low-current neural stimulation seems to be effective, and what neural sites and regions are being differentially activated.

References

McIntire, L.K., McKinley, R.A., Nelson, J.M., & Goodyear, C. (2017). Transcranial Direct Current Stimulation versus Caffeine as a Fatigue Countermeasure. Brain Stimulation, 10(6), 1070-1078.

McIntire, L.K., McKinley, R.A., Nelson, J.M., & Goodyear, C. (2014). A Comparison of the Effects of Transcranial Direct Current Stimulation and Caffeine on Vigilance and Cognitive Performance during Extended Wakefulness. Brain Stimulation, DOI: 10.1016/j.brs.2014.04.008.

McIntire, L.K., McKinley, R.A., & Goodyear, C. (2019). Peripheral Nerve Stimulation to Augment Human Analyst Performance. IEEE Research and Applications of Photonics in Defense Conference (RAPID), Miramar Beach, FL, USA, 1-3.

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| **Bibliography Type:** | Description: (Last Updated: 07/01/2021) |
| **Articles in Other Journals or Periodicals** | McIntire LK, McKinley RA, Goodyear C, McIntire JP, Brown RD. "Effects of Transcutaneous Vagal Nerve Stimulation (tVNS) on Cognitive Performance under Sleep Deprivation Stress." Scientific Reports, submitted as of September 2020. , Sep-2020 |
| **Articles in Peer-reviewed Journals** | McIntire LK, McKinley RA, Goodyear C, McIntire JP, Brown RD. "Cervical transcutaneous vagal nerve stimulation (ctVNS) improves human cognitive performance under sleep deprivation stress." Commun Biol. 2021 Jun 10;4(1):634. https://doi.org/10.1038/s42003-021-02145-7 ; PMID: 34112935; PMCID: PMC8192899 , Jun-2021 |