1. Neuroscience Program, Vanderbilt University
2. Department of Biomedical Engineering, Vanderbilt University
3. Department of Neurological Surgery, VUMC
4. Brain and Behavior Discovery Institute, Department of Neurology, Medical College of Georgia, Augusta University
5. Department of Ophthalmology and Visual Sciences, VUMC
*These authors contributed equally

Intermittent Stimulation of the Nucleus Basalis Improves Working Memory in Aged Monkeys

Sophia Chung[1]*, Janki Bava[2]*, Zhengyang Wang[1]*, Clement Garin[2], Katelyn Clemencich[2], Kendyl Pennington[4], Sarah K. Bick[3], Dario J. Englot[2,3], David T. Blake[4], Christos Constantinidis[1,2,5]

Introduction

The forebrain cholinergic system plays an important role in regulating higher cortical functions. Degeneration of cholinergic systems correlates with cognitive performance loss due to aging. The nucleus basalis (NB) of Meynert is the only source of neocortical acetylcholine in primates. NB stimulation provides a potential alternative treatment to enhance cholinergic activation.

Here we test whether deep brain stimulation of the NB in a cohort of aged non-human primates (NHP) enhances working memory performance, as a potential model for treatment of Alzheimer's and age-related cognitive decline.

Surgery

Electrodes are placed bilaterally in the NB through hollow bone screws. A second surgical site is created in the subscapular region for the Implantable Pulse Generator (IPG). A micro-welded pigtail wire connects the IPG device and stimulation electrodes. To ensure functionality, the IPG is tested before the surgical sites are sutured and externally sealed.

Figure 1. Boston Scientific Spectra WaveWriter™ SCS system implantation.

Stimulation Parameters

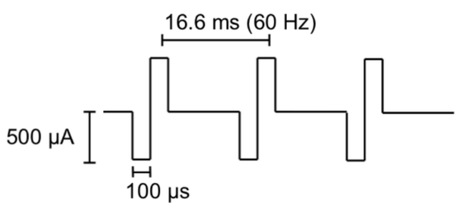

Figure 2. The stimulation parameters of biphasic pulses for 20 seconds every minute in a daily 1-hour window.

Task and Subjects

Seven rhesus monkeys (Macaca mulatta) 24-33 years of age were trained on a delayed-match-to-sample task and tested after reaching asymptotic performance. Two female animals (age 24 and 28 years) implanted with the Boston Scientific Spectra WaveWriter™ SCS system have completed 8 weeks of intermittent stimulation in the NB. The animals performed a match to sample task, using an adaptive tracking procedure (Fig. 3).

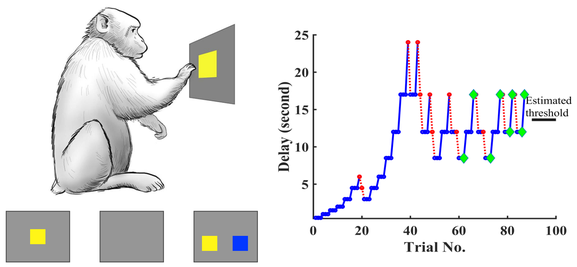

Figure 3. The adaptive match-to-sample task, and performance in one session, using an adaptive tracking procedure.

Results – PET Imaging

PET scans with fluorodeoxyglucose tracers were carried out after 8 weeks of NB stimulation in subject F and subject O (Fig. 4) SUVr (standardized uptake value ratio, normalized on the average of the cerebellar cortex) was significantly increased in the stimulated site, compared to the unstimulated one.

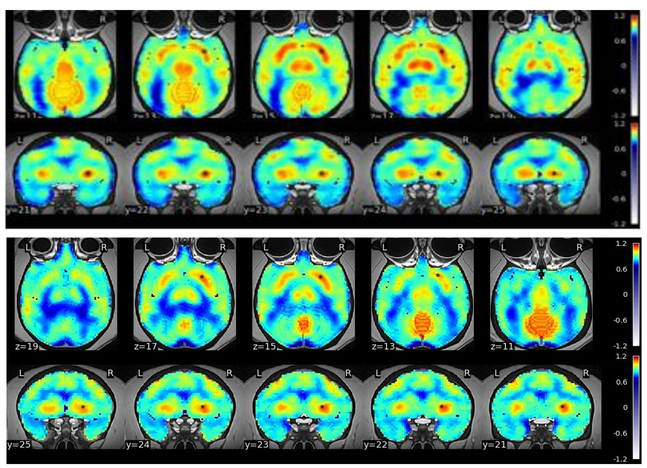

Figure 4. SUVr PET images of Fluorodeoxyglucose (18F) after unilateral (R) stimulation for subject F (first 2 rows) and subject O (bottom 2 rows).
The image shows a signal increase in right putamen (*).

Results – Behavior

The adaptive tracking procedure (Fig. 3) allows day-to-day estimation of the threshold level of working memory delay corresponding to 79% correct in each session. Results from different stimulation statuses are shown in Fig. 5.

Significant increases of 2.00 seconds (permutation test, p = 1.0E-03) and 1.9778 seconds (permutation test, p = 2.0E-02) in the average threshold delay durations were observed during the first 8 weeks of stimulation for subjects F and O.

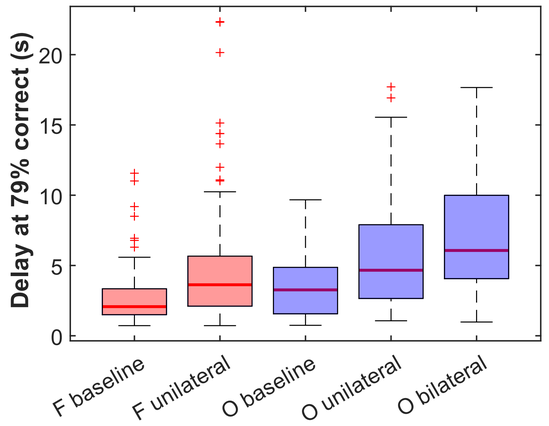

Figure 5. Task performance over different stimulation statuses for subjects F and O. Preliminary results of bilateral stimulation in subject O suggest further improvement over unilateral.

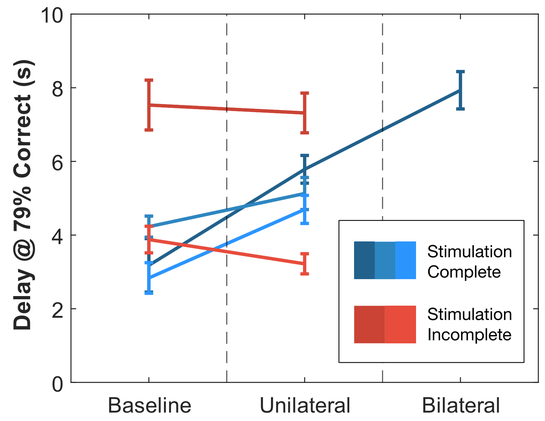

Figure 6. Comprehensive results of stimulation for all subjects. Each line represents average delays for one subject. Blue lines indicate completion of 8 weeks of stimulation. Red lines indicate incompletion.

Three subjects completed at least 8 weeks of unilateral stimulation as shown in Fig. 6. One subject (O) also underwent bilateral stimulation for over 8 weeks.

Performance of two control subjects who underwent the surgery but did not complete 8 weeks of unilateral stimulation are shown in red lines. For these subjects, the implanted electrodes either did not precisely target the NB or had out of range resistance values.

Summary

Current results show that intermittent stimulation of NB in aged NHP:

- Improves working memory performance.
- Is effective when applied for 1 hour daily.
- Appears to be more effective when applied bilaterally than unilaterally.
- Increases glucose uptake in the stimulated side.

Next steps:

- The efficacy of NB stimulation will be examined in contrast to and in conjunction with existing pharmacological treatments.
- Determine how long stimulation is effective in subjects.

Acknowledgements

This work was supported by the National Institute on Aging [RF1 AG060754].

Boston Scientific provided IPGs and supporting materials through a partnership modeled on the BRAIN Initiative Public-Private Partnership templates.

Thank you to Dr. Christos Constantinidis, Chrissy Suell, Katelyn Clemencich, Zhengyang Wang, and members of the Constantinidis Lab for your continued support and mentorship. Thank you to Dr. Jesse Spencer-Smith, Dr. Charreau Bell, and my fellow DSI-SRP participants for your advice and support as well.