Pilot study of cortical recording with synchronized limbic stimulation

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Numerous mental disorders are hypothesized to involve inadequate prefrontal regulation of limbic structures. We have proposed a neural prosthesis that interprets prefrontal cortex (PFC) activity and couples it to limbic stimulation, serving as a patient-controlled, artificial PFC-limbic connection. This closed-loop neural prosthesis could address clinical shortfalls of current brain stimulators (e.g., responding to rapid variations in symptoms; reducing the time required for the stimulator to be ON, perhaps minimizing side effects and preserving battery life by reducing stimulator-on time). In this pilot study, we demonstrated that animals can learn to modulate PFC unit activity to earn rewarding limbic stimulation.

Four Long-Evans rats were implanted with 16-electrode recording arrays within a single cerebral hemisphere, targeting the prelimbic-infralimbic border of PFC at 3.5 mm anterior to bregma. Bipolar stimulating electrodes were inserted bilaterally into the medial forebrain bundle (MFB). Animals were trained in a one-dimensional auditory brain-computer interface (BCI) task, adapted from Gage et al. [1] In this task, animals were cued in a series of trials to increase PFC single-unit firing rates to reach a target, and were rewarded with MFB stimulation if they satisfied the target in time. Thus, they were able to directly influence limbic electrical activation via PFC activity. We performed rigorous statistical testing to assess whether animals were successfully controlling the BCI and triggering MFB stimulation above chance performance. First, we designated 20% of on-line trials as "Catch" trials, where no BCI feedback was given. Second, we performed 10,000-fold bootstrap replication of each day's trials. Animals were only considered to have successfully and significantly controlled the system if both comparisons were above chance. As a third verification, we examined the time to trial success, which should be faster during Actual trials if animals were attending to and utilizing BCI feedback to control the stimulator.

All four subjects demonstrated successful control of the closed-loop stimulator, with control on 21 testing sessions out of 51 total. Across all testing sessions, the target acquisition rate was significantly higher during Actual trials (with BCI cursor present) than Catch trials or post-hoc Bootstrap trials (Fig 1, $p < 0.017$, paired-sample t-test). Success time analysis (normalizing to maximum trial length) showed that animals reached the target faster on successful trials when the BCI cursor was present (Fig 2, $p < 0.034$, paired-sample t-test). These results support the hypothesis that animals were aware of and actively attempting to control the neural cursor. Although mean success rate was less than 40%, this is impressive considering that we recorded from PFC, an area with no behavioral correlate to facilitate training, and utilized only one unit per session with unit-to-cursor mapping changed daily. Performance in clinical implementations is likely to be much higher.

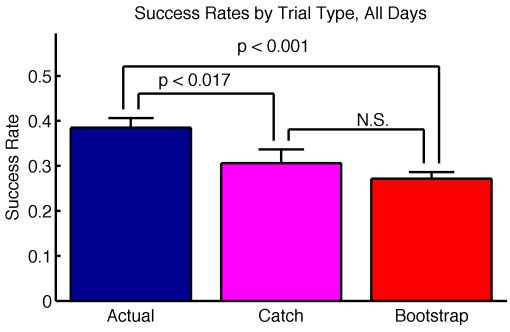

Fig 1

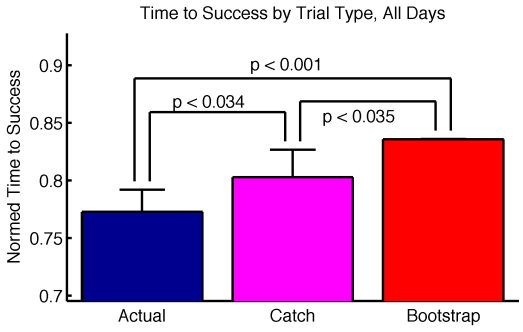

Fig 2

REFERENCES

[1] G. J. Gage, K. A. Ludwig, K. J. Otto, E. L. Ionides, and D. R. Kipke, "Naïve coadaptive cortical control," *J. Neural Eng.*, vol. 2, no. 2, p. 52, 2005.

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