Analysis of Spiking Activity in the Frontoparietal Network of the Ferret during Optogenetic Stimulation

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Background and Rationale

- Cognitive control is the intentional selection of thoughts, emotions, and behaviors based on current task demands, and the concomitant suppression of inappropriate habitual actions [1].
- Impairments in cognitive control (i.e., attentional deficits) are observed in psychiatric disorders including ADHD, schizophrenia, and bipolar disorder [2].
- Noninvasive brain stimulation (NIBS) therapies have effectively alleviated symptoms associated with neuropsychiatric disorders by targeting the relevant neural networks [3].
- A mechanistic understanding of how neurons respond to exogenous stimulation is needed to increase targeting effectiveness of NIBS.
- Single unit analysis of animal electrophysiology data provides a rigorous investigation of endogenous neural dynamics during behavior.
- Parameters of the 5-CSRTT were manipulated to engage animals in a low ("Easy") and high ("Hard") cognitively demanding environment, eliciting two distinct brain states.
- Optogenetic stimulation is one method of influencing neural activity in animal models by targeting cortical oscillations - rhythmic activity patterns extracted from extracellular recordings - known to play causal roles in higher cognitive processes [4].

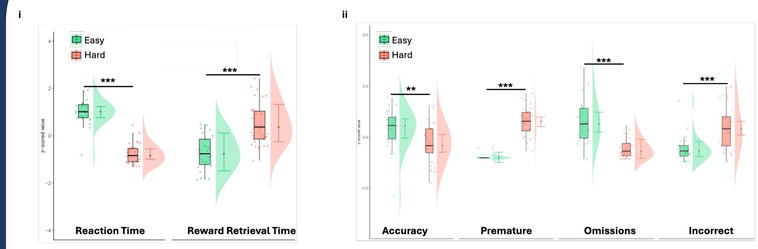
Conclusions

- We observed distinct clusters of single units that were either responsive or not responsive to optogenetic light stimulation in the premotor cortex.
- A cluster of parietal single units exhibit firing patterns that suggest stimulation in the premotor cortex effects parietal activity.
- Differences in single unit responses to exogenous stimulation may be due to state-dependency effects.

Future Directions

- Further visualize single unit subtypes and segregate them based on the stimulation protocol (i.e., theta (5 Hz) or alpha (11 Hz)).
- Establish causality between optogenetic stimulation and seemingly response unit type in the PPC.
- Correlate activity of single units prior to stimulation to post-stimulation changes in firing rate, to establish causal role of endogenous activity on response to optogenetic light stimulation.

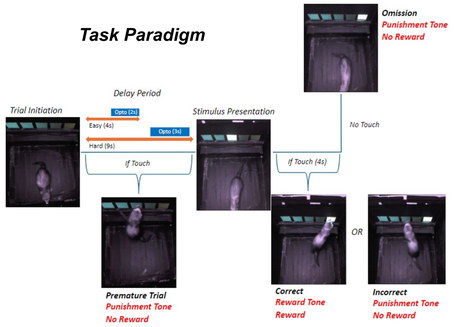
Behavioral Analysis



**p-value = 0.02, *** p-value <0.001
3 animal data combined, animal ID random effect in linear mixed model.
Reaction and Reward Retrieval Time computed from Correct trials.

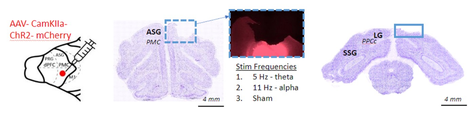
- The longer delay in "Hard" sessions is more demanding on top-down inhibitory control *(higher percent premature and incorrect, fewer omissions)*.
- Performance decreases as cognitive load increases in the Hard condition *(lower accuracy)*.
- Animals are more engaged *(lower reaction time)*, but more exhausted and take longer breaks in-between trials *(higher reward retrieval time)*.

Methods

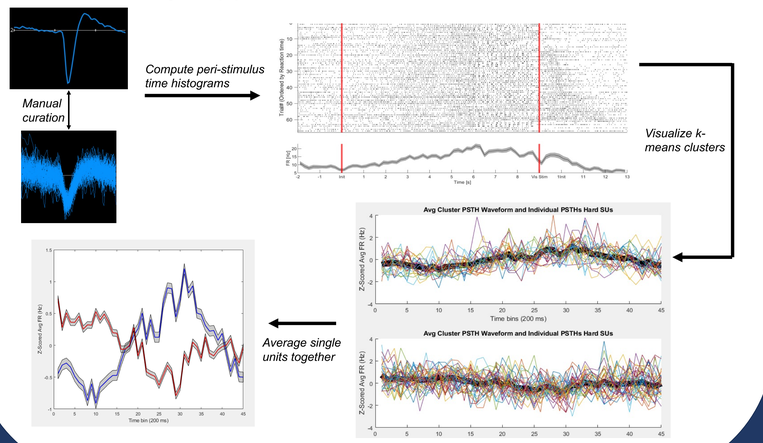


5-CSRTT is a behavioral paradigm that can be modified to probe multiple dimensions of cognitive control. Here, we varied delay period to stress top-down inhibitory control. Subjects begin a trial by initiation, followed by a variable delay period of either 4 s or 9 s delay for "Easy" and "Hard" sessions, respectively. A screen lights up that must be touched to give a water reward. Optogenetic stimulation duration illustrated in blue.

Simultaneous electrophysiological recordings at the PMC and PPC



Analytical pipeline



Results

Fig 1. Four distinct frontal patterns of response to optogenetic light stimulation in "Easy" task condition.

Fig 2. Four distinct frontal patterns of response to optogenetic light stimulation in "Hard" task condition.

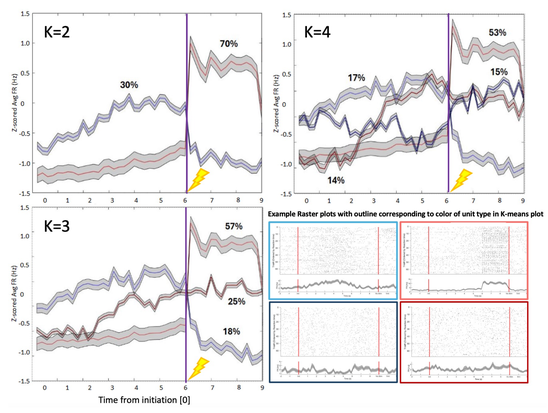
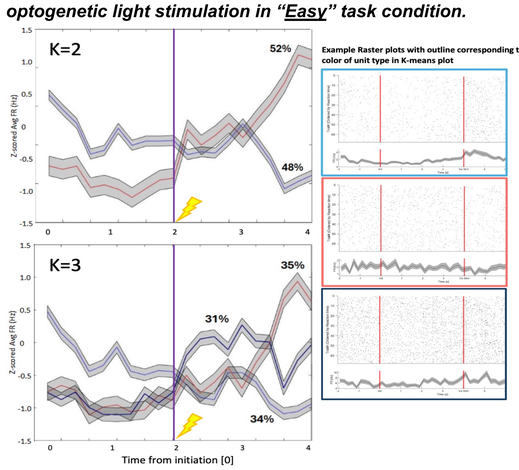


Fig 3. Three distinct parietal patterns of response to optogenetic light stimulation in "Easy" task condition.



Above (Fig. 3): K=2,3 for 134 SUs from PPC during the Easy condition. Units are evenly distributed between a group increasing in activity, a group decreasing in activity, and a third group that increases in activity following the stimulation period onset in the PMC.

Upper Left (Fig. 1): K=2,3,4 for 196 SUs from PMC during the Easy condition. Majority of units increase in activity in response to stimulation, next largest decreases in activity in response to stimulation, and two trends of increasing and decreasing activity that are not responsive to activity.

Left (Fig. 2): K=2,3,4 for 248 SUs from PMC during the Hard condition. Majority of units increase in activity in response to stimulation, next largest group decreases in activity in response to stimulation. Two trends that do not respond to stimulation have mirroring parabolic activities with one reaching a maxing near the middle of the delay period and the other a minimum.

Fig 4. Three distinct parietal patterns of response to optogenetic light stimulation in "Hard" task condition.

Above (Fig. 4): K=2,3 for 134 SUs from PPC during the Easy condition. Units are evenly distributed between a group increasing in activity, a group decreasing in activity, and a third group that increases in activity following the stimulation period onset in the PMC.

Acknowledgements

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