Sophie Sackstein

Independent Small Group Discussion Write-up

1. What was the motivation for this study? (e.g. big picture questions motivating experiments, prior work motivating experiments, etc)

The motivation of this study came from previous research on TRN and multitasking in the PFC. In previous research, they had identified the TRN region of the brain and its individual neurons as possible regulators of the brain's ability to multitask but had until now been unable to successfully prove the hypothesis. In previous decades it was hypothesized that the TRN might function like a gate for the flow of sensory information. However, there are problems recording and analyzing the anatomical structure of the TRN deep within the brain. There was also no method of isolating behavior associated with the TRN from other surrounding area. This presents a novel setup to isolate activity from visTRN. The prefrontal cortex is thought to regulate attention to sensory stimuli through top-down control of sensory cortical areas. In this article, they had trained mice to attend to the appropriate stimulus by selecting between two competing auditory and visual stimuli and with optogenetic manipulation this sensory integration was diminished. Performance on this task required the prefrontal cortex and the subset areas of it, including the visual thalamic reticular nucleus (visTRN). They provide evidence that the visTRN controls visual thalamic gain through feedforward inhibition of the lateral geniculate nucleus, thus selecting the appropriate input for further processing.

2. List the key methodological details (species, preparation, recording/ anatomical techniques, data analysis methods)

They used a competing visual and auditory stimuli to test the effects of sensory integration with optogenetic manipulations on these mice. Some these manipulations included the genetic labelling of neurons with the Cl– indicator SuperClomeleon which is later described in figure 5. In their research in mice, they showed that TRN neurons, which have been previously implicated in the dampening of brain signals in people, were also less active when the mice were led to focus on a visual flash of light to get a milk reward. In contrast, when the mice were made to pay attention to a sound and ignore the flash of light, researchers say TRN neurons that controlled vision were more active, suppressing the visual signals in order to pay more attention to the sound. Earlier research showed that different TRN neurons controlled specific senses and which ones were payed attention to. In this study, they developed a new behavioral experiment in which they monitored the ability of mice to successfully collect a milk reward by paying attention to a light signal or a sound. The test was designed with this paradigm in order to gauge how well the area of the brain known to control higher behavioral functions, the prefrontal cortex, could direct the focus on one sense over another. As part of the test, researchers distracted the mice with opposing stimuli: If the mouse was expecting a flash of light to guide it to the milk reward, the researchers distracted it with a sound, and vice versa. Distracting the mice decreased their ability to collect the food reward to 70 percent from nearly 90 percent, even if the distracting stimulus was removed later. Concurrently, the research team recorded electrical signals from TRN neurons and also tracked the mice's behavior while at the same time inactivating various parts of the brain's neural circuits with a laser beam.

3. For each figure, describe the important points including how the authors interpret the findings and what the findings may actually show.

Figure 1)

a) This shows a model for visual gain in this experiment for cross-modal conditions. Models of neuronal gain propose that the activity of each neuron is normalized by the combined activity of its neighboring neurons.

b) This shows a basic schematic of how the experiment was performed. Brown noise suggests that they attend to vision whereas the blue noise that the mice attend to audition.

c) Visual and auditory trials show similar performance.

d) Visual detection performance showed detection threshold and peak performance was the same from the cross modal condition.

e) Getting rid of the auditory distractor did not effect the psychometric function- they seemed to sense the same.

f) Reversal learning- the ignoring of the auditory stimulus did not change the threshold but it did change the psychometric function. The detection threshold is higher.

g) The confidence of the psychometric function for d-f. The visual only had the lowest threshold and cross modal had a higher detection threshold. The distractor present had the lowest threshold.

Figure 2)

This showed top-down thalamic inputs for the cross modal task.

This shows that PFC–TRN activity is essential for visual gain control, the purpose of a gain control is to tune the input to stimuli levels.

a) Schematic of how the PFC activity was disrupted in the mice. The PFC activity was disturbed during stimulus anticipation. The competing tasks show huge decreases in activity during the presentation. This suggest a role of the PFC in inhibition of non-relevant stimuli.

b) This shows the visual-only task had little change as compared to the control task.

c) Disrupting the visual cortical activity had diminished visual performance only during stimulus presentation. You can see the large difference in visual performance and almost no effect on the baseline or audition.

Figure 3)

a) This shows the staining of visTRN neurons with ChR2–eYFP and stained with anti-GFP. This tested neurons that neurons that project to the LGN with retrograde lentiviruses2.

b&c) During 'attend to vision' trials or 'attend to audition' trials the areas were inhibited accordingly.

d) The PFC activity changed during stimulus anticipation and corresponding visTRN activity was then measured.

e) PFC disruption effected the visTRN activity.

f) This drove LGN inhibition in VGAT-ChR2 mice, visTRN firing reduces visual thalamic gain during the presentation of the stimuli.

g) Inhibiting visTRN function made similar performance on auditory trials, this made odd visual gain for the eNpHR3.0 mice.

Figure 4)

a) This shows a model of the multi-electrode targeting of the LGN.

b) This single LGN cell spiking when attention was directed to vision. This showed less of an effect for audition.

c&d) When attention was on the visual stimuli, LGN neurons showed increased response to anticipatory, and

e) Visual evoked potential (VEP) shows a strong depolarization to attending to visual stimuli and this is shown more clearly in the left figure.

Figure 5)

a) This is possible mechanisms for modulation of LGN firing rate, it is possible that presynaptic inhibition of feedforward excitation. visTRN inhibits LGN.

b) FRET photometry and diagram of CFP-to-YFP FRET. This included genetic labelling of neurons with the Cl– indicator SuperClomeleon. The CFP is FRET donor and yellow fluorescent protein (YFP) is a FRET acceptor. Both CFP and YFP emission data was collected under each photometric condition.

c) AAV-hSynSuperClomeleon was injected it into the LGN, and the dye is shown below in the highlighted image.

d) The injection of the GABA agonist reduced SuperClomeleon FRET. The green indicates this reduction.

e) The signals were stronger for contralateral side (contralateral to the recorded LGN)

f) The schematic of the photometry in the cross-modal task is shown here. The visually-evoked chloride photometry showed significantly larger responses in ‘attend to audition’ trials than in ‘attend to vision’ trials. The ‘attend to audition’ trials show an

earlier increase in [Cl–]i (decreased SuperClomeleon FRET). During TRN inactivation visual and audio has the same response- there is a clear effect of anticipation of audition. You can even see the earlier depolarization of this cell suggests that there is a clear effect of inhibiting non important stimuli info.

4. What is your assessment of the overall findings? Did the experimental data support the authors' interpretation? Why or why not?

The TRN, is likely responsible for the ability to multitask and respond to multiple parts of stimuli at once, binding them into a holistic percept. Individual TRN neurons that act like a switchboard, continuously filtering sensory information and shifting more or less attention onto one sense – like sight – while relatively blocking out distracting information from other senses, including sound. They found that inactivating the prefrontal cortex region of the brain, disrupted TRN neural signaling and reduced mice to only random success in obtaining a milk reward when presented with specifically cued light or sound signals. Inactivating the TRN, while leaving the cortical regions intact, also diminished success with obtaining the prompted food reward. These results demonstrate how the prefrontal cortex is essential to performing such behavioral tasks and how this part of the brain stores the knowledge ultimately communicated to the TRN to control how much visual or auditory sensory information is suppressed or not, and how the brain ultimately multitasks. These findings support a subcortical model of sensory selection in which sense specific thalamic reticular subnetworks can relay some top-down control for sensory thalamic processes.

5. Describe new insights that you gained from the small group discussion of this paper.

I learned about how the task was performed and it was different from other experimental paradigms- allowing them to isolate activity to distractibility in the TRN.

6. List all of your questions and/or points in the paper that you did not understand.

I don't understand why the line appears lower in figure 1f if the distractor was absent. I also don't get the task at all for figure 5.