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參展科別 **行為與社會科學**

作品名稱 **建立大鼠模式之新行為派典以研究跨模式注意力的動態轉換歷程 Rapid switching of attention modality in a novel cross-modal selective attention paradigm in rodents**

得獎獎項 **二等獎**

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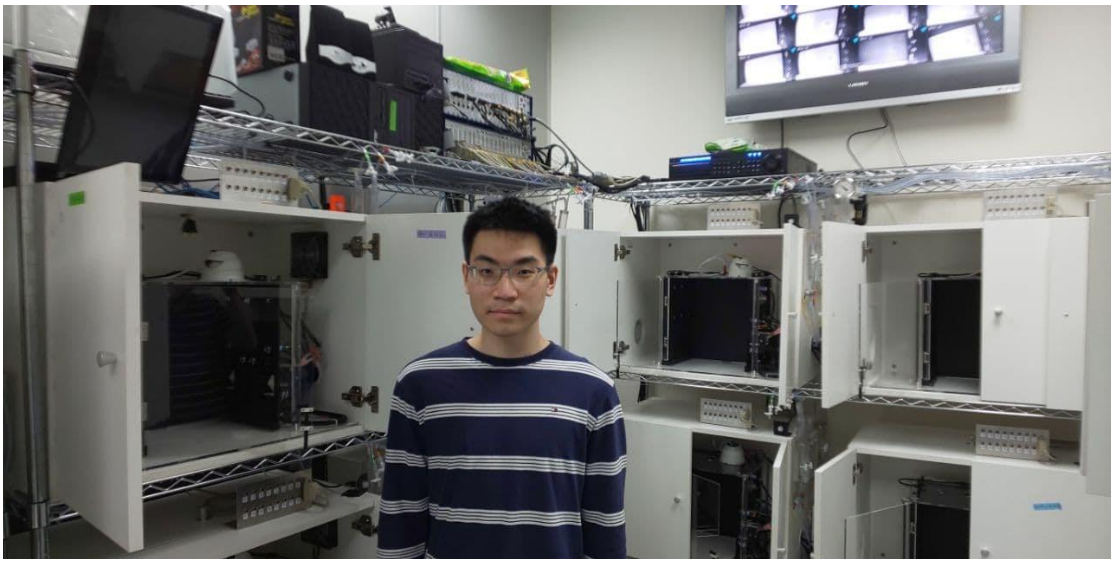
關鍵詞 **<u>rat model、cross-modal selective attention、behavior task</u>**

作者簡介



我是林煒哲，台北市私立復興中學雙語部高二學生。從小便對注意力有興趣，注意力能幫助我們完成任務，舉凡學習到對弈一盤完美棋局，更不用說注意力影響許多人的生活甚至造成疾病。一直尋找機會探索大腦相關課題，很高興進入實驗室動手尋找答案，從老鼠訓練到實驗裝置障礙排除，最後從實驗數據分析逐步解答，有說不清的辛苦更有狂喜。雖然離解開大腦奧秘還很遙遠，但希望藉由一步步的努力能慢慢替因注意力受苦的人提供線索。

摘要

我們的感官不斷地提供超過大腦可以處理的信息，所以需要注意力來選擇性的處理重要的感官信息。雖然研究指出，人類有能力處理在同時呈現的不同感官刺激中集中注意力在一種感官，但對於這樣的跨模式注意力如何快速移轉在感官間仍不理解。要回答這些問題，首先要建立良好的行為派典，我們才能夠從中研究跨模式注意力的轉換歷程。在本研究，我們設計了一個新的派典，允許自由行為的老鼠在同時呈現的聽覺和視覺刺激間動態地轉移注意力，並透過老鼠的行為選擇反映出他們當下的注意力焦點。我們觀察到老鼠面對同樣的聽覺與視覺刺激時，能在不同的狀況下，將注意力焦點專注於其中一個感官刺激，並忽略另外一個; 且能在單一次刺激呈現之間快速的移轉注意力焦點。這些結果證實我們建立了一個新的跨模式注意力派典，我們能在未來的實驗中研究背後的神經迴路機轉。

Abstract

Our senses constantly provide us with more information than we can process and that’s why we need a cognitive function to direct processing toward the more relevant sensory information. There are several ways sensory input can be sorted but one of the broadest would be by the sensory modality of the input stimuli. While many studies have clearly demonstrated that humans and animals have the ability to selectively focus their attention among simultaneously presented sensory inputs from different modalities, it has remained unclear how cross modal selective attention is dynamically deployed and how such attention can be rapidly switched from trial to trial. A critical step in answering these questions is a good behavioral paradigm that allows us to study the dynamic switching of cross modal selective attention in single trials. In this project, we developed a novel crossmodal selective attention task that allows freely behaving rats to dynamically shift their attention between competing auditory and visual modalities. Most importantly, their covert shifts in the attended sensory modality can be revealed by the reward port they chose to approach. We found that, when faced with the same auditory and visual stimulus combination under different attention demands, the performance of rats was guided by target stimuli in the relevant sensory modality while ignoring the irrelevant ones. Moreover, rats were able to rapidly switch their behavioral choices, reflecting the fast dynamics of attention shifts from trial to trial. These results establish a new behavioral paradigm for cross-modal selective attention, which can be used to study underlying neural circuit mechanisms in the future.

一、前言

（一）研究動機

Attention is our ability to focus on a select few sensory stimuli and enhance the processing of those stimuli. We have a limited processing capacity and thus can't process every sensory stimulus to their utmost. Instead, attention allows us to focus on those important stimuli and suppress processing of another irrelevant sensory stimulus to make full use of our limited processing capability. However, all such attentional function is internal and difficult to study from pure observation. The primary method to study attention has been behavioral tasks that force the use of some form of attention and indicate the attention through some behavioral differences depending on the focus of attention. Previous rat cross-modal selective attention behavior tasks cannot unambiguously show the attended modality of the rat or suffer from low accuracy while humans would not allow more invasive neurorecording techniques needed for studying the mechanisms behind cross-modal attention.

（二）研究目的

Our goal is to develop a new cross-modal selective attention task in rats that allows the animal to dynamically switch attention modality multiple times within a session and reveal its covert attention focus with two distinct response ports. This task design feature may allow the animal to learn more quickly, switch more rapidly, and allow experimenters to directly observe the sensory modality the animal attends to.

1.**Specific Aim:**

(1) Create a cross modal selective attention task that shows clear indication of attended modality from rat licking.

(2) Create a cross-modal selective attention task that allows for within session switching.

（三）名詞解釋

1. Modality (Sensory Modality): A form of sensory perception (visual or auditory modality in our task)
2. Session: One run of the task (We do one 2 hours session a day, Monday to Friday)
3. Trial: We define it as the cue and its associated response within the 2-second timeframe
4. Signal Detection Theory

	Oddball	Standard
Lick (Perceive Oddball)	Hit	False Alarm
No Lick (Perceive no Oddball)	Miss	Correct Reject

Table 1. Table of Responses in a Signal Detection Theory Experiment

Hit trial: An oddball cue was issued and we presume that it is perceived if the rat licks

False Alarm Trial: The rat licks to a standard cue

Miss trial: The rat does not lick when an oddball cue is played

Correct Reject: The rat correctly does not lick when it is a standard cue

Cross modal attention:

（一） Past Cross-modal attention task paradigms

In Michael Halassa's cross-modal task (2 Alternative Forced Choice), mice are trained to insert their nose into a central initiation port to start a trial. After the mouse inserted its nose, the task rule is given by a short sound, high frequency (11kHZ to indicate vision) or low frequency (10 kHz to indicate audition). After the task rule is given, the mouse needs to attend to that indicated modality and follow the cue, licking the left or right reward port depending on which side the cue for that modality appears. The cue for the other modality would be presented simultaneously on either side, chosen randomly. If the visual and auditory cues appear on the same side, the trial is defined as congruent whereas if the visual and auditory cue appear on a different side, then the trial is defined as incongruent.

Figure 1: Task Diagram

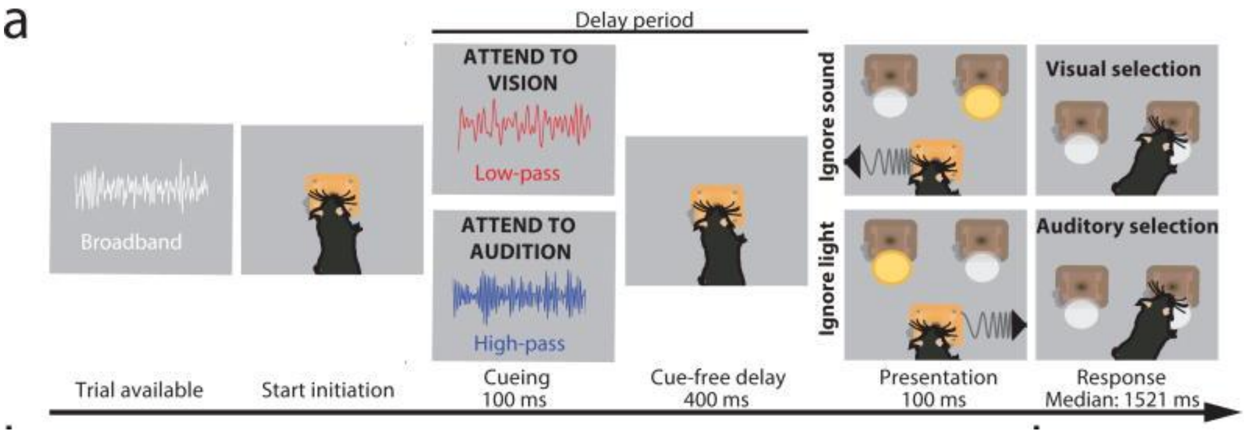


Figure 1: from "Thalamic amplification of cortical connectivity sustains attentional control" by Schmitt, L. I., Wimmer, R. D., Nakajima, M., Happ, M., Mofakham, S., & Halassa, M. M. (2017).

This task allows for incredible dynamic modality switching, but it also does not necessarily reveal the attended modality. On congruent trials, it would be impossible to differentiate which modality is attended to from the behavior readout; however as attending to either modality would give the same response. Then in incongruent trials where the cues would be on different sides, the mouse is still capable of getting the same answer to the auditory cue by choosing the side without the light or by choosing the opposite side to the light cue.

To solve this issue of ambiguity, Halassa trained a 4 AFC (Alternative Forced Choice) task where there would be four reward ports, two on the right and two on the left. Similar to the previous task, the mouse would have to choose left or right following the modality indicated by the rule cue but after choosing left or right, the mouse would have to choose between whether it is choosing left by following auditory cue or visual cue.

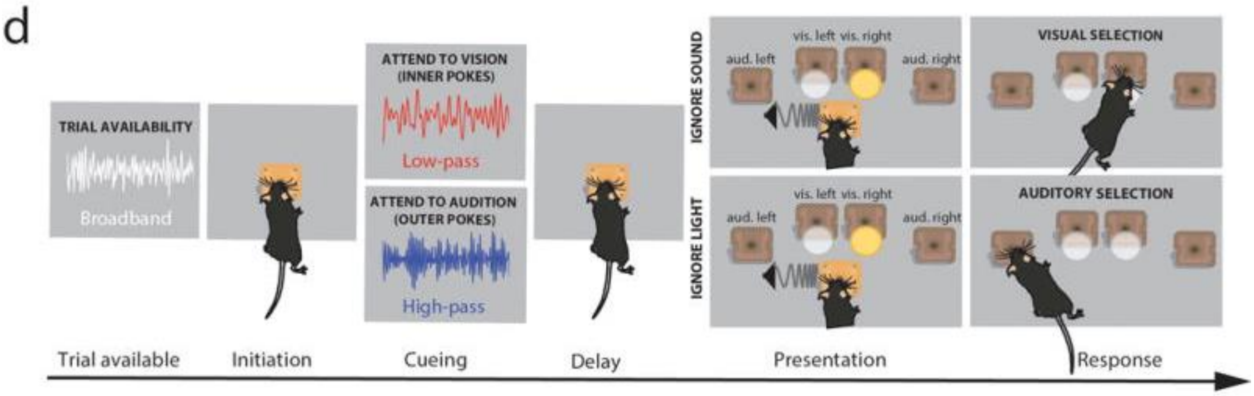


Figure 2: From "Thalamic amplification of cortical connectivity sustains attentional control" by Schmitt, L. I., Wimmer, R. D., Nakajima, M., Happ, M., Mofakham, S., & Halassa, M. M. (2017).

This, however makes the task far more complicated, and the success rate is far lower, around 0.42 (f), compared to around 0.72 for the 2AFC task.

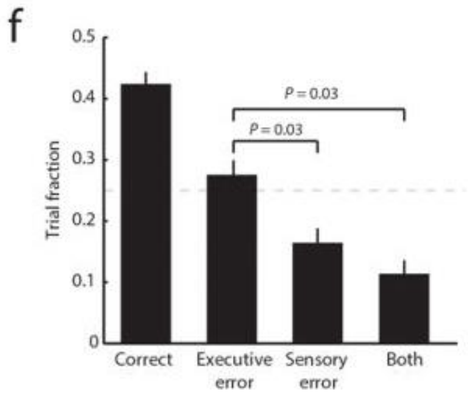


Figure 3: From “Thalamic amplification of cortical connectivity sustains attentional control” by Schmitt, L. I., Wimmer, R. D., Nakajima, M., Happ, M., Mofakham, S., & Halassa, M. M. (2017).

We developed an oddball GO/NO GO, that eliminates the ambiguity of attended modality in Halassa’s task. In this task, two cues are presented every 2 seconds: an odd light or a standard light cue, an odd sound, or an standard sound cue. The mouse would have to pay attention to one modality and lick the reward port when the odd cue of the task-relevant modality appears. This task has a high hit rate, and the licking would reveal the modality being attended with the few exceptions of odd-odd cues. Unfortunately, the rat is incapable of the dynamic within session modality switching in Halassa’s task.

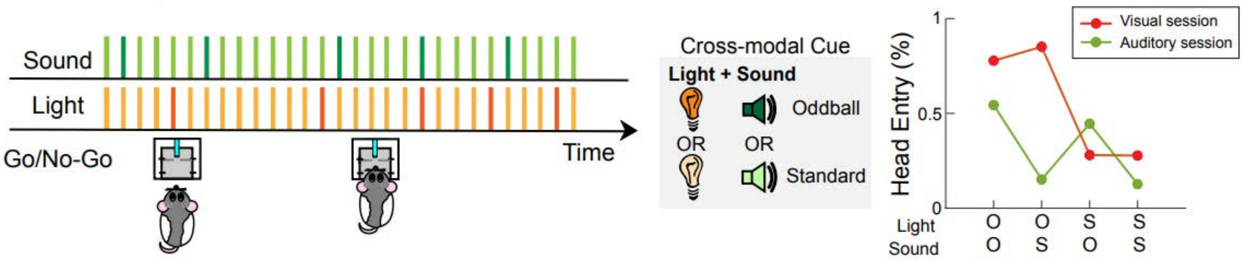


Figure 4: Schematic of Go/NO GO selective attention task

Based on these two behavioral tasks designs reviewed above (Halassa and oddball), we combine their features to develop a novel cross-modal selective attention task.

Halassa’s task allows dynamic switching between modalities through 2 reward ports but does not definitively show which sensory modality the rat is attending to while the oddball task does not allow for the dynamic within-session switching between modalities of Halassa’s task but reveals the attended sensory modality. In the new task we are able to know which modality is being attended to through the cue type the rat licks to, and we can know when the rat becomes aware of the change in target modality through the change in licking

side.

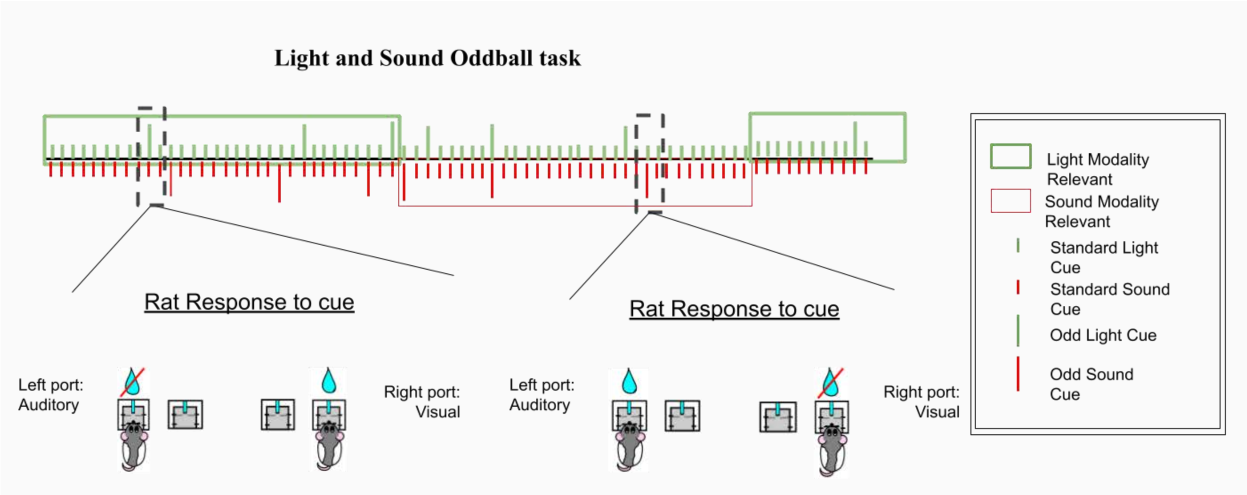


Figure 5: schematic of two reward ports cross-modal selective attention task. Every 2 seconds, a cue would be given from both sound and light modality. If the block modality is light and an oddball light cue is given, the rat is to lick the right reward port to receive water (a reward for the rat as the rat is water-deprived). The first two licks of the rat would not receive water to ensure that the rat is deliberately licking because it has learned the task instead of receiving the water by chance.

Sound: 6kHz as the oddball cue and white noise as standard cue/ Light: House Light as the oddball cue and two center light as standard

Response window of 2 seconds.

二、研究方法與過程

（二） Materials and Methods

1. Materials

(1) **Behavior Box**:

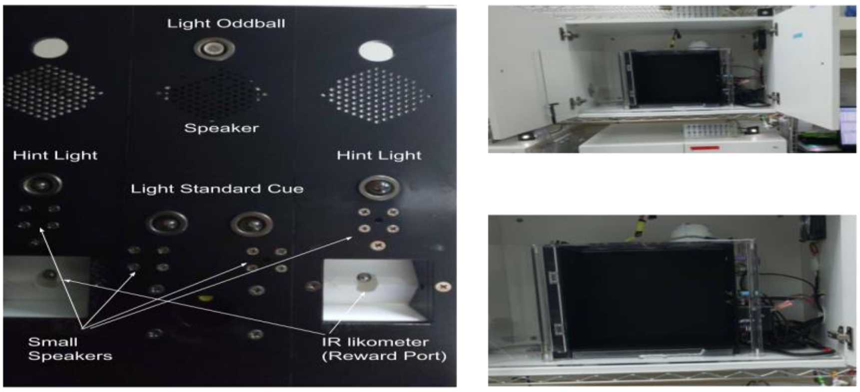


Figure 6: The front panel of the behavioral box (left) The behavioral box from the outside (right)

We use Med-PC version V program (Med Associates Inc®, Fairfax, VT) to control the behavior task.

(2) Animals:

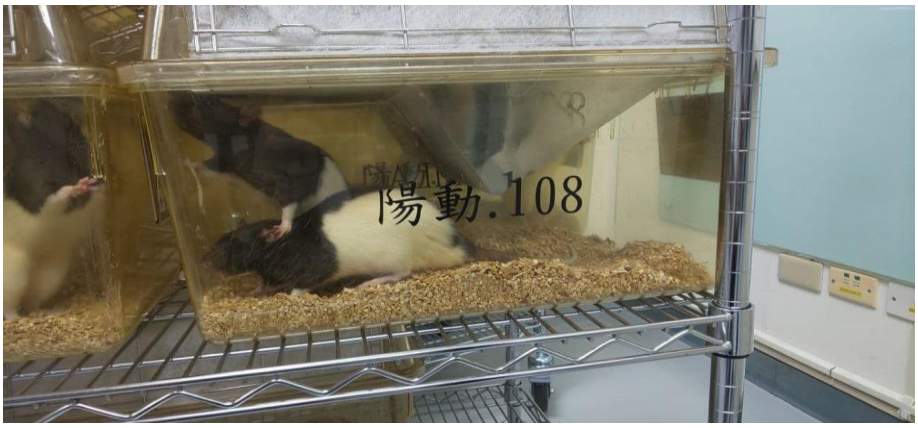


Figure 7: Picture of Long Evans rat being trained in the behavioral task

Age: 10 weeks

Sex: male

Mass: Around 400 gram

2. Methods

⑴ Water and Food Deprivation:

The rat is allowed 15 minutes of non-restricted water a day and 18 grams of food. The rat is weighed each day to ensure no abnormal change in weight which might suggest health issues. The rat is water restricted to increase the rat's desire for water which is used as a reward in the task.

⑵ Task Design:

We have designed a two reward port cross-modal selective attention task. Every 2 seconds, a cue would be given from both sound and light modality. If the block modality is light and an oddball light cue is given, the rat is supposed to lick the right reward port to receive water (a reward for the rat as the rat is water-deprived). The first two licks of the rat would not receive water to ensure that the rat is deliberately licking because it has learned the task instead of receiving the water by chance.
Sound: 6kHz as the oddball cue and white noise as standard cue/ Light: House Light as the oddball cue and two center light as standard. We have set the Response window of 2 seconds so that the response to a specific cue would not be interfered by the next stimulus. A schematic view of task design is shown in Figure 5.

(3) Training procedure: Figure 8

To teach the rat the final cross modal task, we teach each component of the task step by step. First, we teach it to associate the right reward port with reward when it perceives light oddball cues. Then we change sections of visual oddball cues into auditory oddball cues to teach the rat the block structure essential as well as to associate auditory cues with the left reward port. After it learned to associate the right side with visual and left side with auditory, we added in standard light and sound cues, teaching it to ignore standard cues. Finally, we played the visual and auditory oddball at the same time. Before this point, there would've only been a block of either visual or auditory cues at any moment.

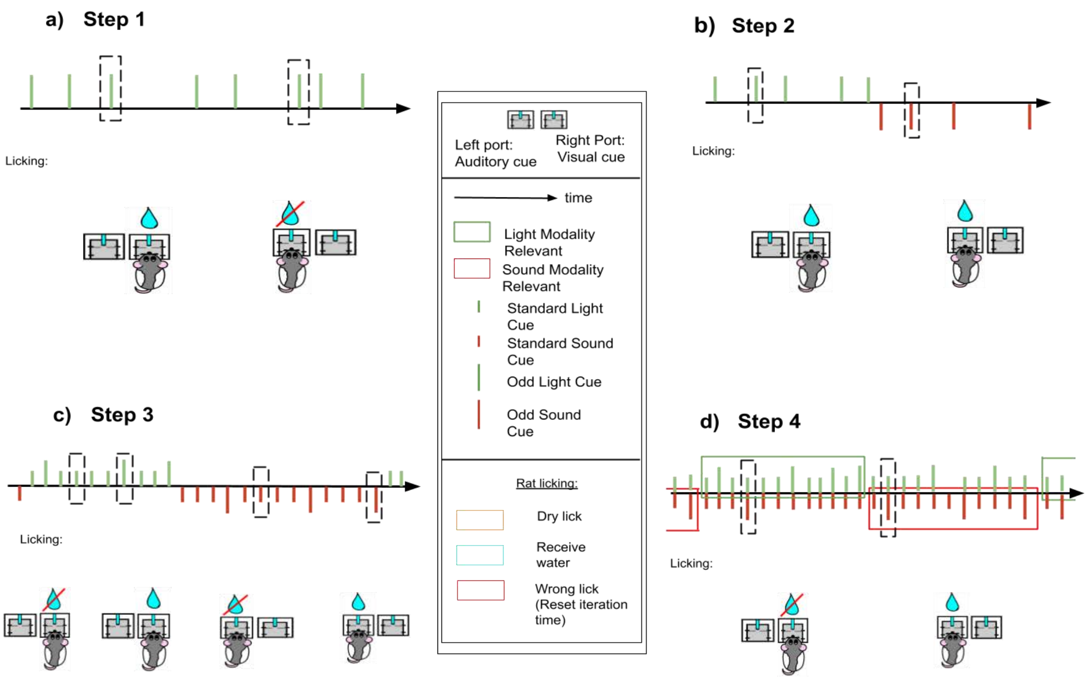


Figure 8:A-D) schematic of each step of the training to teach the rat to do the crossmodal oddball task, a modification of the single modal oddball task. (A) The rat receives oddball light cues and learns that it gets rewarded when it licks the right side and only gets water on the third lick. (B) Introduce auditory oddball cues, to which the rat needs to lick the left reward port. Gaps are added between oddball cues. (C) Adds standard cues between the oddball cues. (D) plays both oddball tasks at the same time in parallel and adds modality blocks (the relevant modality) that switches after every 20-40 hit trial for that modality.

(4) Data Analysis:

The plots and graphs are drawn using Matlab R2020b (The MathWorks, Inc®,Natick, MA)with the licking defined as only the first lick.

三、研究結果與討論

(一) Results-

1. the rat showed different learning curves about visual and auditory stimuli

From the first day of training to the second, the rat was able to improve its hit rate to visual cues. In step 2, while the hit rate to visual cues fluctuated and seemed to trend downward, its performance to auditory cues stably improved (Figure 9). Separating the rat performance to visual and auditory stimuli, we can see the rat performance (hit rate) to auditory cue improve over time. On the other hand, the hit rate to visual cues worsened at the start then started to improve in the latter half of training. Overall, it can be seen that the training procedure was a success, and the rat was able to improve in hit rate in addition to each additional task condition added in each step of training.

Hit Rate = Correct licking / total possible correct licking

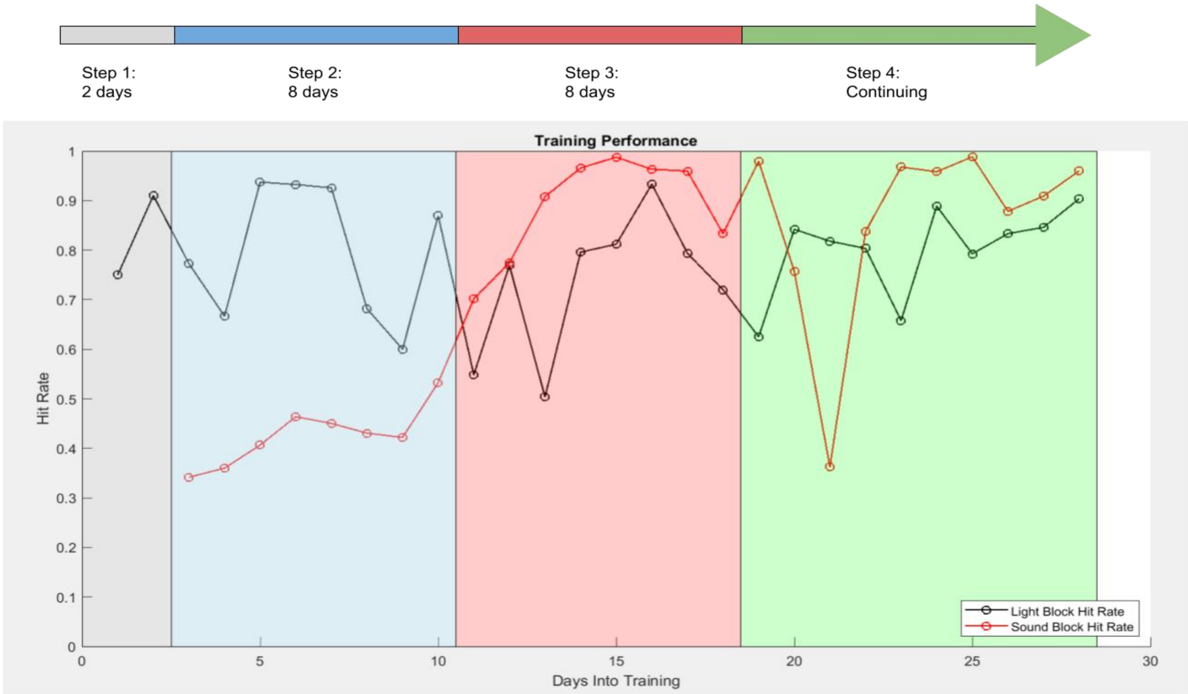


Fig 9: A graph of the hit rate of the rat to light cue, hit rate to sound cues during training. The steps represented by the background color in the graph is each step described in Figure 5

3. the rat selectively responded to either visual or auditory cues after the four step training procedure

In Figure 9, we only examined the hit rate, which showed that the rat was able to correctly lick a high proportion of trials where the oddball cue of relevant modality was present. However, this does not consider the possible error when the rat is not supposed to lick. Thus, to affirm that the rat correctly selectively attended to one sensory modality and not to both, we look at the false alarm rate. From Figure 10, we can see that the false alarm rate is around 0.2, similar to the miss rate, indicating that the rat is indeed preferentially attending to the target modality.

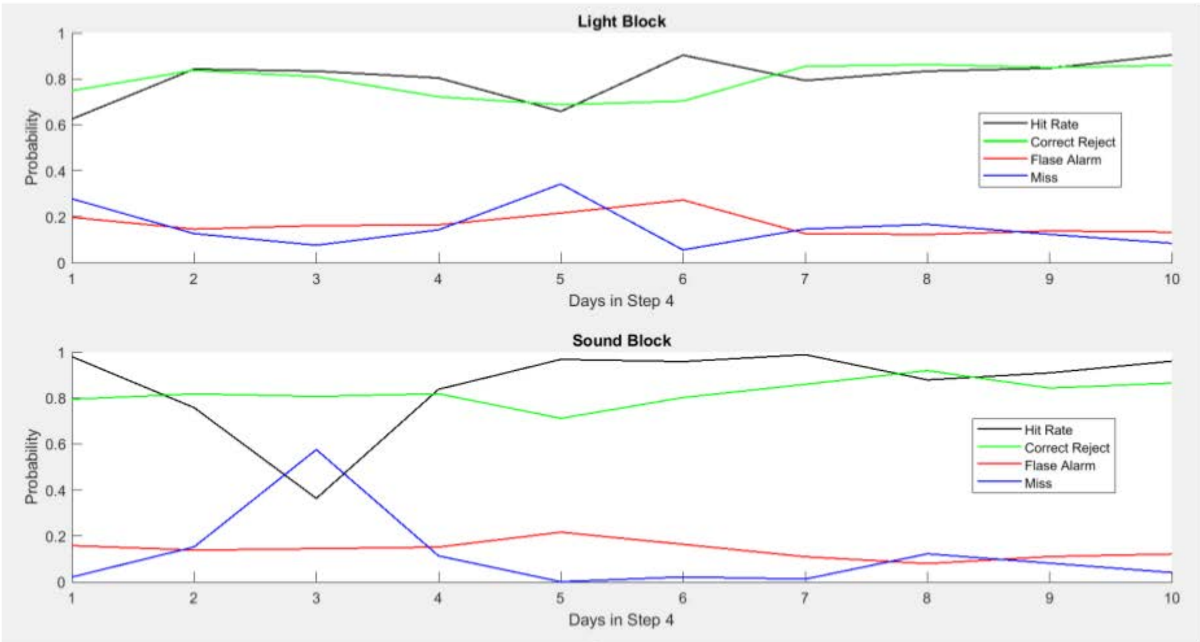


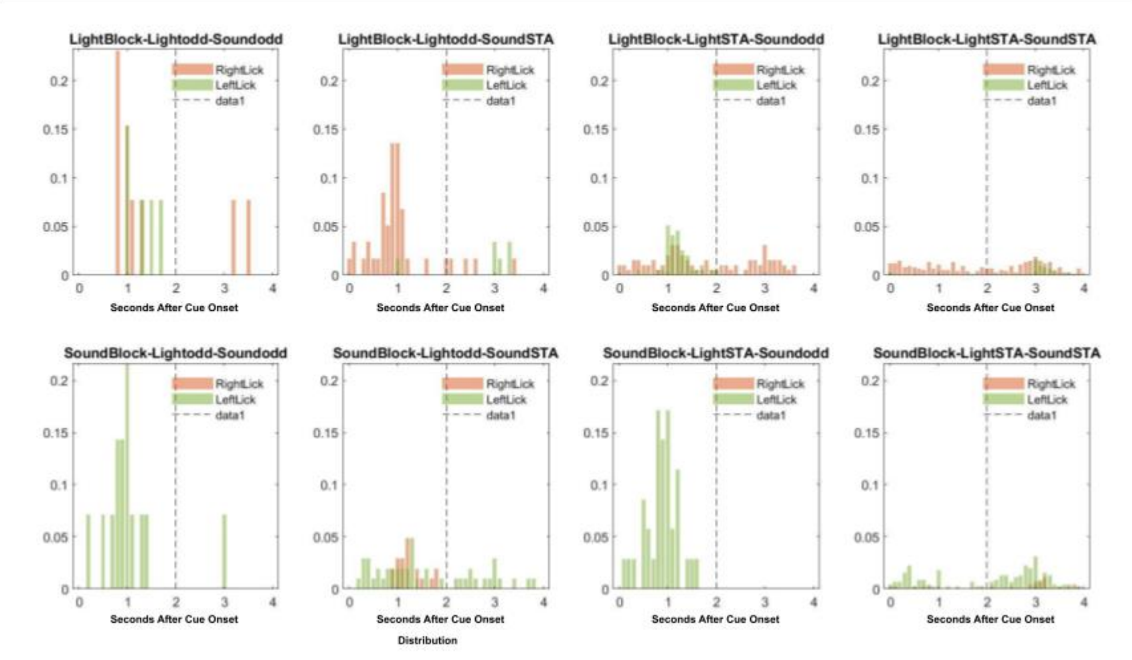
Figure 10: A plot of the Hit, miss, False Alarm, and Correct Reject rate of the rat during each day of step 4 of training (final completed task but with hint light). The performance on Light and Sound Blocks are separated and shown separately.

Note: Opposite side licking is not counted in hit, miss, false alarm, or correct reject. Due to this, the hit rate and miss rate do not add up to 1. Similarly, the Correct reject and False alarm rate do not add up to 1.

4. Clear evidence of task performance

When the rat is presented with the same pair of cues, we can observe a clear difference in behavior depending on the modality block. When Light oddball cues appear in the light block there is concentrated clustering of licking around 1 second after cue presentation. In contrast, there is diffused licking when standard light cues are presented in the light modality block. The diffused licking shows that the licking is spontaneous and not as a reaction to the cue presented. The same licking pattern is seen in the sound modality block ,except there's concentrated licking when the oddball sound cues are presented and similarly, diffused licking when standard cues are presented. Furthermore, we can see that for the most part, the rat is licking right in response to the light oddball cues in the light block. The response time of the rat can also be seen to be around 1 second showing that our 2-second response window is reasonable.

Day 1 of step 4



Day 10 of step 4

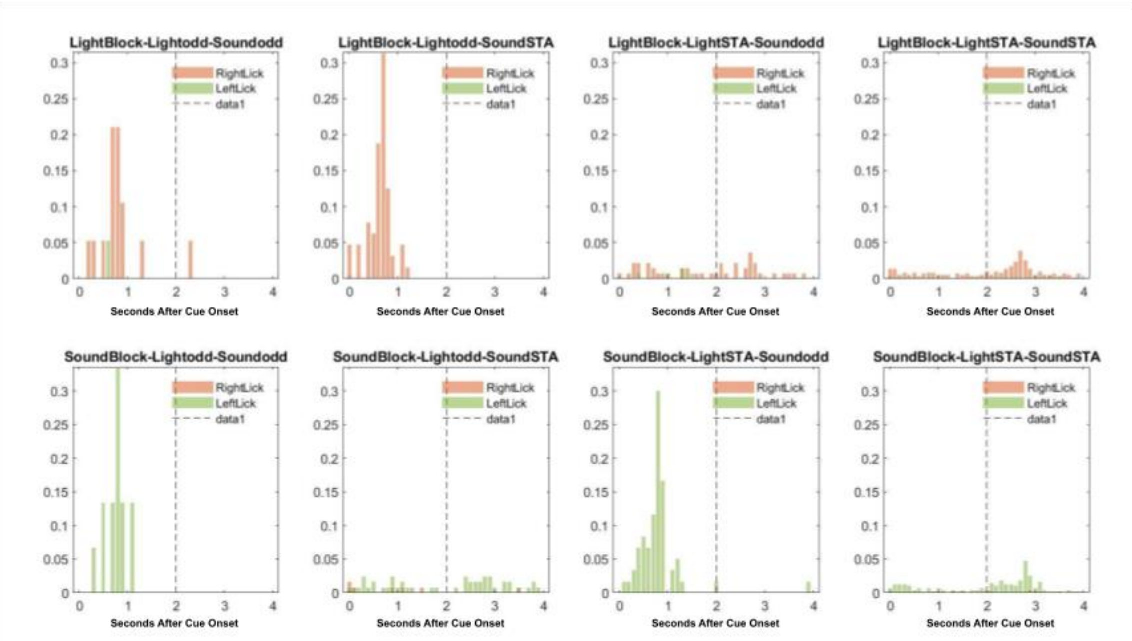


Figure 11: Histogram of the response time of the first lick from cue onset. The behavior on light and sound blocks are separated (light block on the first row, Sound block on the second row). The response to cue types are then separated to show the response time of the rat to Oddball light and Oddball sound cues, or Oddball light and standard sound cues, etc.

5. after training, the rat may swiftly shift its attention as shown by licking Side Transition During Modality Transition in day 4-10 of step 4:

The two reward port design of this task allows us to see how the rat transitions between different reward ports as the rat transitions between different modalities of attention. If the rat has learned to associate the right reward port with the light modality and the left reward port with auditory modality, then the transition in the licking side would indicate an awareness of change in target modality. By setting right licks as 1 and left licks as -1 and averaging the total left and right licks through multiple sessions, we can see each lick's general licking side preference in relation to block transition. From Figure 12, it can be seen that the rat is able to transition licking side preference in both types of transitions with around just 3 licks

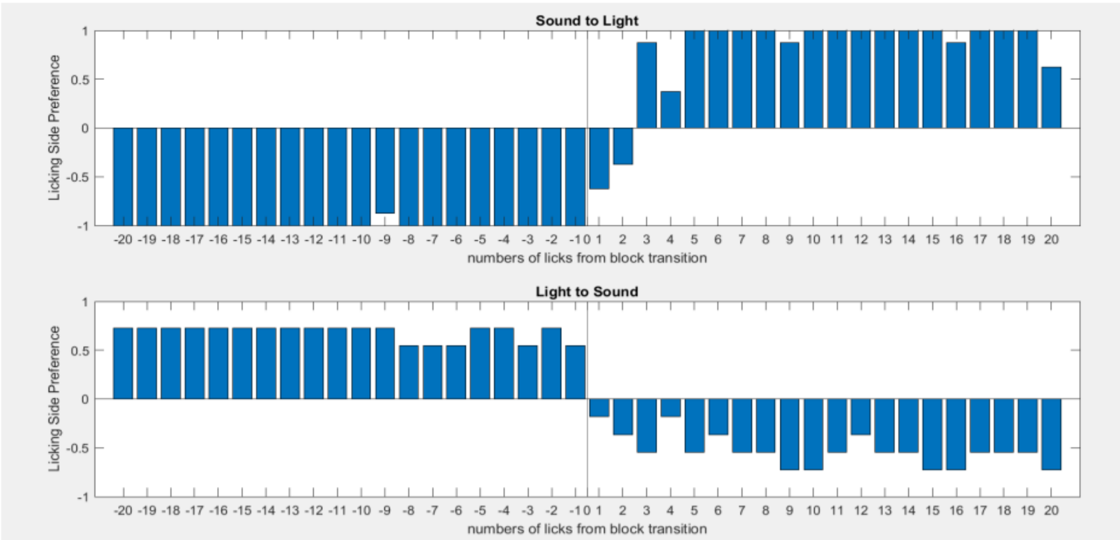


Figure 12: Licking side preference in the 20 licks before and after block transition. We define licking preference as the weighted average of licking right reward port and licking left reward port with licking right set as 1 and licking left set as -1. Thus, -1 means 100% lick rate to the sound block while +1 means 100% lick rate to the light block and 0 means that the rat is licking right half the time and licking left the other half.

6. The rat showed a faster attention shift from light to sound than sound to light

Through the oddball structure of this task design, we are able to infer the attended modality of the rat through the type of cue to which the rat decided to lick. If the rat licks in response to light-Oddball, sound-Standard, we will define the rat as licking to the light modality. To examine how the attended modality transitions as the target modality shifts, I pulled the 20 licks before and after block transition from day 22 to 28. Then if the lick is licking towards the light modality, I would set the value of that lick as 1. If the lick is licking towards the sound modality, I would set the value of that lick as -1. Then by summing the values of every 20th lick before sound to light block transition, I would be able to get a value of the average preference to light or sound modality on the 20th lick before transition. Dividing that number by the total number of transition points between day 22 and 28 would give a value between -1 and 1 which indicates average preference for light or sound modality. From Figure 13, we can see a clear drop in performance after block transition in both types of transition. In Sound to Light Block transition, the attended modality preference changes immediately more toward attending light modality compared to the preference for sound modality just prior to transition. In Light to Sound Block transitions, the rat can also be seen to immediately shift attended modality preference toward sound modality.

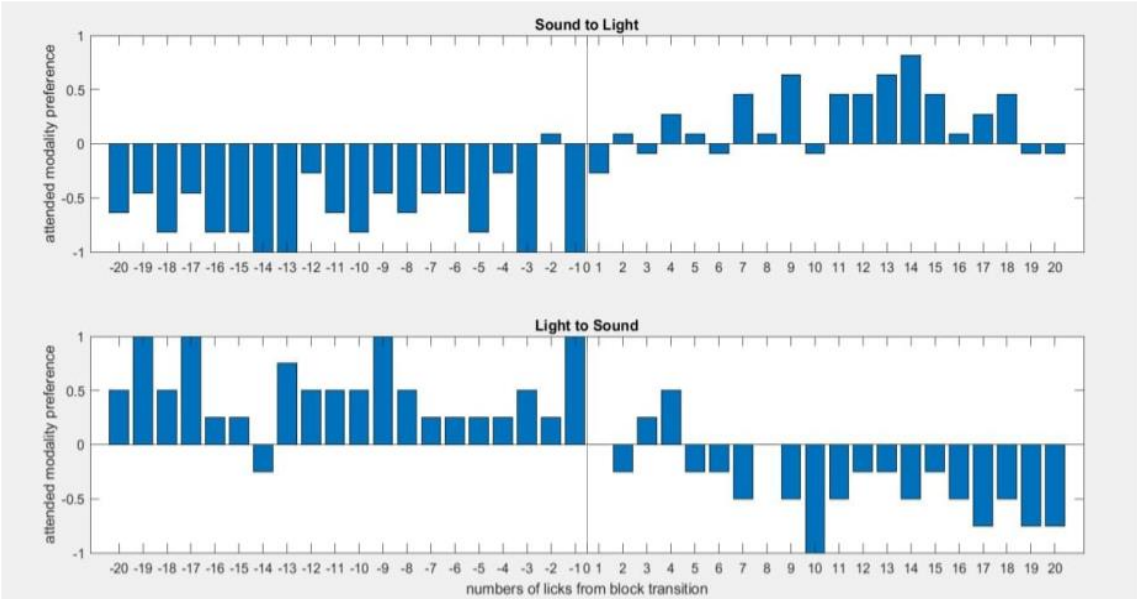


Figure 13: The modality the rat licks to in the 20 licks before and after block transition. We define attended modality preference as the weighted average of licking to light modality and licking to sound modality with licking to light set as 1 and licking to sound set as -1. Thus, -1 means 100% lick rate to the sound block while +1 means 100% lick rate to the light block and 0 means that the rat is licking right half the time and licking left the other half.

（二） Discussion

1. Benefit of two reward port task

We modified a uniport cross-modal oddball Go/No GO task (Figure 3) to one where the rat needs to lick right to light, and lick left to sound which rather than making the task more challenging to train due to added complexity of having to switch between licking left or right, it made the task easier to train. We theorized that this is due to 2 main factors.

(1) Two reward ports allow the rat to have one distinct response to auditory and one distinct response to visual cue which makes it easier for the rat to exhibit executive inhibition of its reaction to the irrelevant modality. In support of this, we can see that the rat changes its licking side faster than the attended modality (Figure 12, Figure 13). Thus, the licking side might serve to aid the rat in switching the attended modality. Furthermore, in this task, we did not require the rat to return to the fixation port between trials which allows the rat to stay on the side paired with the relevant modality block. Thus, the rat can use certain behavioral habits to remember the lick side and through that, help remember the current task target modality.

(2) The two-reward port design also allows us to add hint light. The hint light is a light above the reward port of the side that the rat should lick. The hint light much more definitively informs the rat of which side to lick and allows it to associate it to one modality. This increased understanding of the task rules would allow the rat to form the behavior response quicker and more strongly. The hint light also helps the rat remember the behavioral response which would be extremely helpful to the rat especially closer to the start of training. Overall, the implementation of hint light solves the problem of the difficulty in rat understanding of target modality of uni-port oddball task (Figure 3)

2. Possible Modification to task cue frequency

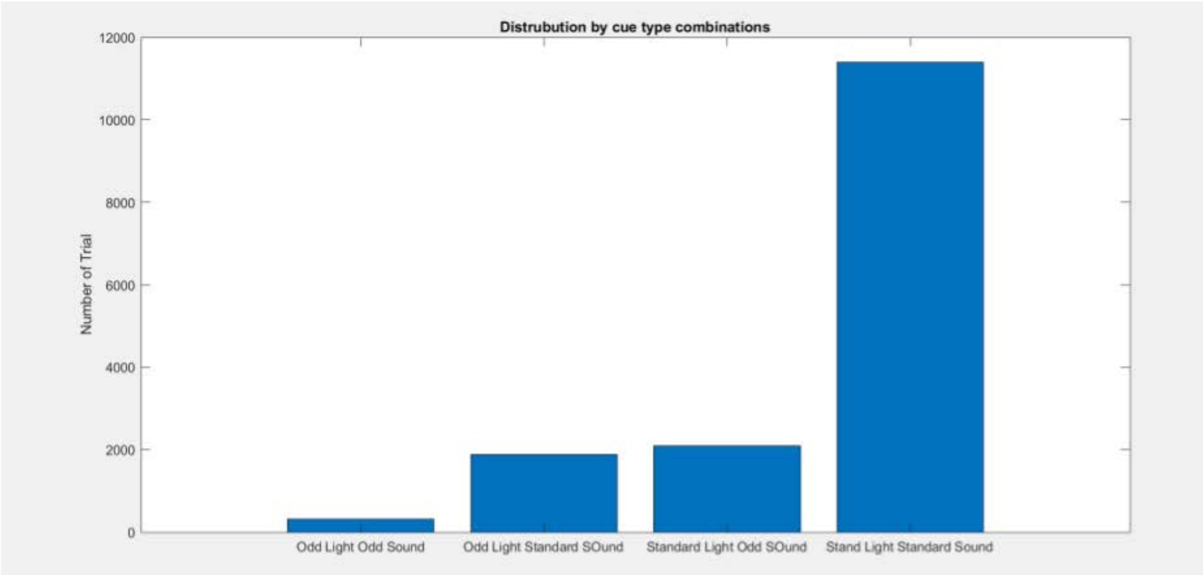


Figure 14: Bar graph of the total number of total trials by cue combination

In this task, the Light modality cues and Sound modality cues were programmed independently of each other in this task. Standard cues are normally supposed to be more common in a oddball task paradigm so the Odd-Light Standard-Sound and Standard-Light Odd-Sound cue combination ratio to the standard-light standard-Sound combination is reasonable but the low number of Odd-Light, Odd-Sound pair make it challenging to make any statement on the effect of congruent (Odd-Light Odd-Sound) vs incongruent (Odd-Light Standard-Sound or Standard-Light Odd-Sound) trials. A possible improvement to this training might be to fix the ratio of cues during one session. By treating each light and sound cues as one unit (rather than light and sound cues as independent), it would be possible to make the probability of the congruent Odd-Light Odd-Sound combination as like the incongruent Odd Standard combination. Doing so would eliminate possible biases against Oddball light Oddball sound cue pairs.

3. **Within a modality block we observed that the rat occasionally will spontaneously switch licking side**

The rat is seen to spontaneously change its attended modality and then switch the licking side to that of the modality it switched its attention to. This spontaneous change in licking side occurs i of any change in task condition and of the rat's own decision. This suggests that the rat forgot the relevant modality or maybe it's evaluation for the relevant modality changed somehow.

四、結論與應用

(一) Conclusion

In this project, we developed a novel cross-modal selective attention task that explicitly revealed the attended modality of the rat. Through stepwise training, the rat is able to learn to switch target sensory modality and perform oddball tasks with a 80% hit rate. We demonstrate that the rat shows different behavioral response to the same sensory stimuli under different context and demonstrate that the response window was reasonable. We then showed that the rat demonstrates rapid cross modal attention switching. This novel behavior task thus solves the issue of ambiguity of attended modality in subjects of previous cross-modal attention tasks and can allow further neurophysiological study of the mechanisms of crossmodal attention.

(二) Application

With a behavioral task set up, we can begin to ask questions of the neurocircuitry behind these attention shifts. We can ask when this filter is set up, where it is set up? To what extent does the filter suppress processing of unattended stimuli? Using EEG as a measurement of the sensory processing, we should observe completely different result in the sensory cortexes depending on the answer.

五、、參考文獻

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1. The descriptions of methods and experimental protocols need to be stated in more details.
2. This study focus on developing a new behavioral paradigm for cross-modal selective attention, however, there is few discussions on the underlying neuronal circuitry involving in this attention shift.
3. Only one rat was included in this study. The sample size needs to increase.
4. 本研究嘗試建立新的 cross-modal selective attention paradigm，內容詳盡說明 cross-modality 的優勢，資料也很漂亮，可充分反映老鼠的行為是否被建立。但數據僅源自一隻大鼠，並且不確定其嘗試過程，多少隻大鼠才有一隻可以成功，這是可惜的地方。