Afferent GPi and Efferent from RMTg to VTA of LHb for Reward Omission

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Abstract: Reward omission is an essential part in reinforcement learning that has not been fully appreciated, as most of the studies have been focused on the positive reward prediction error (RPE). Therefore, this thesis investigates into the globus pallidus internal segment (GPi), an important afferent of the lateral habenula (LHb), that is responsible for reward omission coding. First, destroying the GPi enables us to find out whether it is the only input for reward omission into the LHb, which is the main area for negative RPE. Then, it will be determined whether Gamma-aminobutyric acid (GABAergic) neurons also involve in the omission signal transmission besides glutamatergic neurons by optogenetically inhibiting GPi glutamatergic neurons. Furthermore, a comparison between the efferent GABAergic neurons of the LHb in the rostromedial tegmental nucleus (RMTg) and the ventral tegmental area (VTA) will be made.

1 INTRODUCTION

Numerous researches have already been done on the investigation of understanding how brain neurons code for RPE, which simply means the discrepancy between expected and actual rewards signaled by the dopamine (DA) neurons in the VTA (Schultz, Dayan, Montague 1997). Also according to Schultz et al. (Schultz, Dayan, Montague 1997, Schultz, Apicella, Ljungberg 1993), when actual reward is greater than expected, DA neurons will be activated (positive RPE), while they will be depressed if reward is less than the predicted reward (negative RPE). Despite the fact that the entire neural circuit for RPE is still unclear, there have been a myriad of researches into the circuitry involved in positive RPE (Keiflin, Janak 2015), and even punishment prediction (Mattfeld, Gluck, Stark 2011). However, as the other type of negative prediction error besides punishment prediction, the reward omission seems to be neglected by many. Reward omission can be understood as unexpected reduction in actual reward. This is crucial for survival, since it also shows the ability to update the reinforcement learning behavior to adapt to changes in the environment (Bromberg-Martin, Matsumoto, Hong, Hikosaka 2010).

Previous researches (Stamatakis, Van Swieten, Basiri, Blair, Kantak, Stuber 2016, Lecca et al 2017, Tooley et al 2018, Li, Pullmann, Jhou 2019) have shown that ventral pallidum (VP), hypothalamus (HT), and the GPi all project to the LHb, which is the major region for the coding of reward omission (Matsumoto, Hikosaka, 2007, Tian, Uchida 2015). Furthermore, the VP (Tooley et al 2018) and the HT (Stamatakis, Van Swieten, Basiri, Blair, Kantak, Stuber 2016, Lecca et al 2017) are both proved to be responsible for the punishment prediction, while the GPi is not (Lazaridis et al 2019). However, in the Lazaridis paper (Lazaridis et al 2019), the GPi, co-releasing glutamatergic/GABAergic neurons, is said not to encode negative value or develop a prediction signal for any negative events. However, actually this outcome is one-sided because he only mentioned the aversion, leaving out omission entirely. As a result, it is certain that the GPi codes for reward omission (Hong, Hikosaka 2008), as many other research articles have also come to the same positive conclusion. What we do not know yet is whether the GPi is the only input to the LHb for omission, or the VP and the HT are also involved, apart from their roles for punishment prediction.

Moreover, Shabel et al. (Shabel et al. 2012) identified that both the excitatory glutamatergic neurons and inhibitory GABAergic neurons from the

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GPi send projections to the LHb. Actually, in 2008, neurons in the GPi had already been classified into two types, the positive type and the negative type, by Hong and Hikosaka (Hong, Hikosaka 2008). The negative type, which will be activated when no reward is presented, shows extremely similar firing pattern to neurons in the LHb. As a result, presumably it is the GPi glutamatergic neurons, that mainly, if not entirely because of the coexisting GABAergic neurons, send signals to its downstream LHb when reward is omitted.

Apart from the afferent of the LHb, there have been large amount of studies about its efferent. It has been proved the RMTg, the immediate downstream of the LHb, responsible for negative RPE (Jhou et al 2009), is mediated by the LHb glutamate neurotransmitters during negative RPE (Graziane, Neumann, Dong 2018). After that, the VTA-projecting GABAergic neurons from the RMTg will send inhibitory inputs (Eshe et al 2015) directly to depress the DA neurons (Tian, Uchida 2015). While other pathways from the LHb to the VTA DA neurons including dorsal raphe nucleus etc. have also been mentioned in Tian and Uchida paper (Tian, Uchida 2015), my focus is the GABAergic projection from the RMTg to the VTA, making a comparison with the GABAergic neurons in the VTA. Because the RMTg is a small area close to the VTA, not many people regard its GABAergic neurons as a distinct region from the VTA GABAergic neurons. Nevertheless, one of the differences between their functions can be revealed by the coding of reward omission. As mentioned above, the RMTg will be activated during negative RPE (Graziane, Neumann, Dong 2018), while the GABAergic neurons in the VTA show no significant modulation by reward omission (Cohen et al 2012). Therefore, understanding the circuitry will give a brighter view of how RPE is regulated in the main region VTA and others, hence increasing our understanding about the complicated brain works, as well as learning behavior.

The thesis will look deeply into the neural circuit of omission, mainly the GPi input to the LHb to determine whether it is the only input to the LHb for reward omission, as well as what kind of neurotransmitters are involved in the signaling process. Additionally, the efferent pathway of the LHb from the RMTg to the VTA during reward omission will also be examined to provide a comparison between the GABAergic neurons in the RMTg and the VTA.

2 RESULTS

2.1 Positive Results

2.1.1 GPi is the Only Input into the LHb Coding for Reward Omission

To determine the significance of GPi in reward omission response, the GPi will be destroyed by passing electricity through. Then, mice of the lesion and control group that have already learnt the association between the odour cue and water reward will again be presented with the same odour cue, but without the following water as reward (Figure 1A). During this reward omission period, extracellular recording of firing patterns will be taken at the LHb and will be sorted afterwards (Figure 1B).

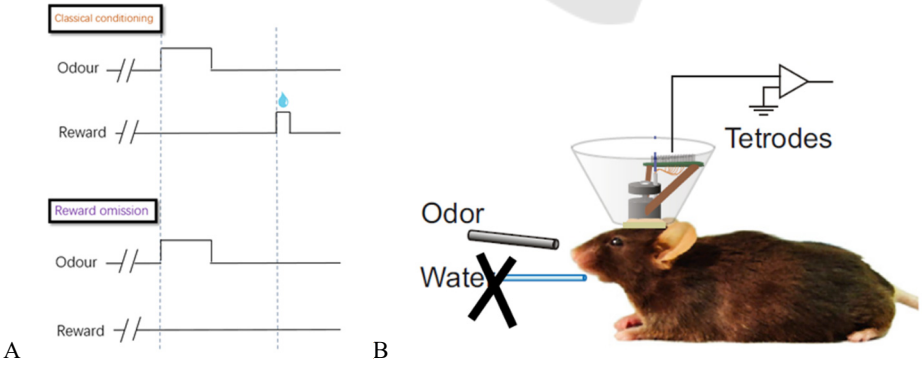


Figure 1: Basic experimental procedure for the GPi lesion experiment. (A) Mice will first be trained to associate the odour cue with the following water reward through a classical conditioning task. Then, during the experimental period, only the odour cue will be delivered, while the actual result will be omitted. (B) Extracellular recording of the LHb will be made during reward omission.

As shown in Figure 2, the population spike of neurons in the LHb of the control and lesion group of mice responds differently to reward omission. Normally, the excitatory glutamatergic neurons will transmit the excitation elicited by the omitted reward to the LHb, where the neurons will be also be activated (Hong, Hikosaka 2013), as shown by the control group (Figure 2A). However, on the contrary, neurons in the LHb show no activity during reward omission in the lesion group (Figure 2B), indicating that they do not receive any signals for coding reward omission.

The entirely disappeared response in the LHb reveals that destroying the GPi has a complete effect on reward omission coding, i.e. none of the other neurons that project into the LHb send omission signals. Hence, it can be concluded that the GPi is the only input into the LHb coding for reward omission.

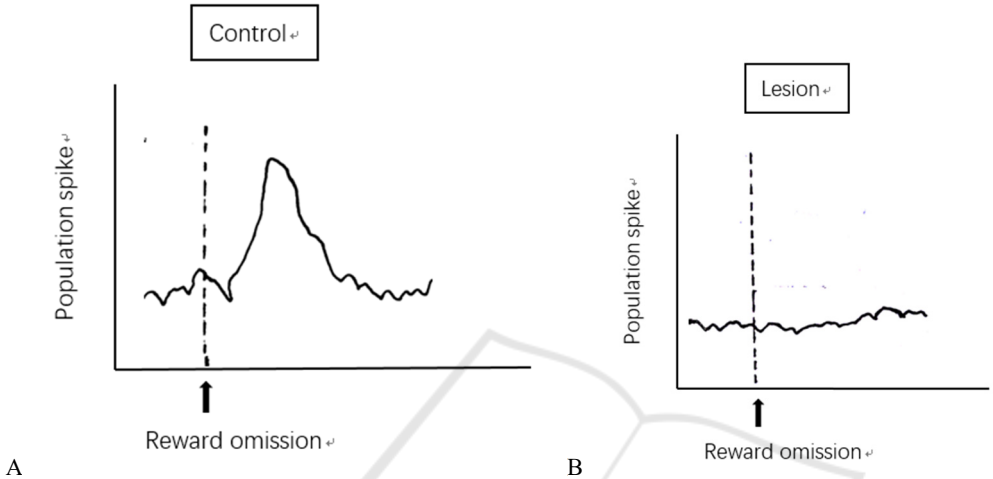


Figure 2: Expected result from the control group and the GPi lesion group of reward omission. (A) Unaffected population spikes at the LHb during reward omission is recorded. (B) No firing of excitation is detected when no reward is presented to the group of mice with lesioned GPi.

This result is anticipated according to the major role of the GPi for reward omission (Matsumoto, Hikosaka, 2007, Tian, Uchida 2015), and of the VP and the HT for punishment prediction (Stamatakis, Van Swieten, Basiri, Blair, Kantak, Stuber 2016, Lecca et al 2017, Tooley et al 2018), which are distinct and different. Therefore, it is not expected that one brain region is responsible for more than one coding process to ensure effectiveness and accuracy.

2.1.2 Neuron-type Determination in the GPi for Reward Omission Coding

As mentioned above, the excitatory glutamatergic neurons are estimated to be the only neuronal type responsible for reward omission (Hong, Hikosaka 2008). To verify the correctness of this hypothesis, we would like to let only the GABAergic neurons in the GPi work when reward is omitted, while inhibiting the glutamatergic ones. Then whether neural activities will be detected can confirm whether the GABAergic neurons are also involved in the reward omission coding.

In this neuron-type determination experiment, virus and the Cre-loxP system will be included for the inhibition of neurons. Halorhodopsin (HR), a light-gated anion channel, will specifically be expressed in glutamatergic neurons (see Method). Then the reward omission task (Figure 1A) will be performed again after inhibiting the glutamatergic neurons in the GPi via optogenetics, and neural activities at the LHb will be recorded during omission (Figure 3).

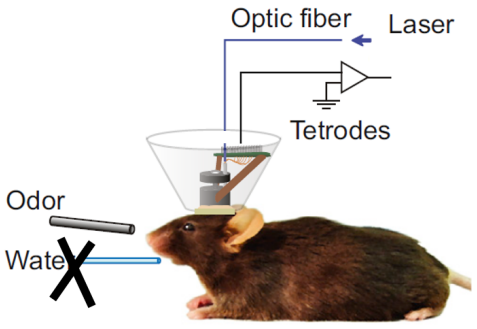
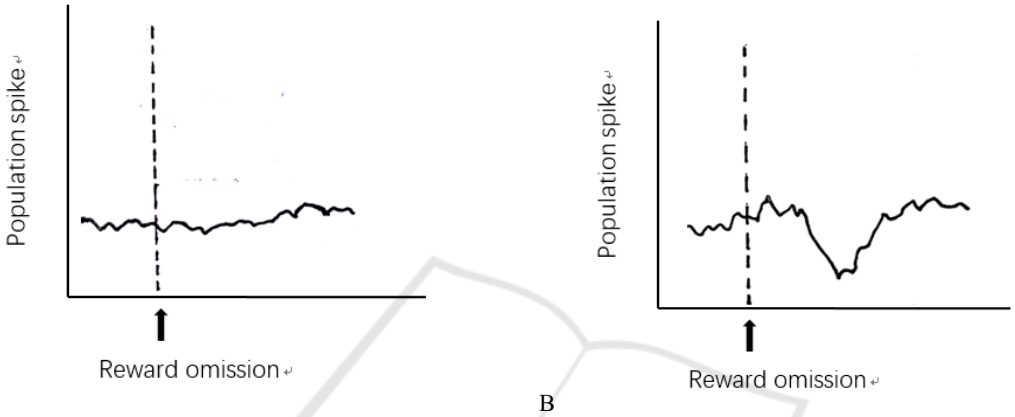


Figure 3: Laser shone through the optic fibre for optogenetically inhibit the GPi glutamatergic neurons, and tetrodes for detecting neural activity at the LHb.

Only Glutamatergic Neurons in the Gpi Respond to Reward Omission. If no neural activity is detected at the LHb (Figure 4A), then it is clear that the GABAergic neurons do not respond to reward omission signals. This will lead to further consideration of what is the purpose of the GPi GABAergic neurons. It may suggest another circuit including various downstream of the GPi, which certainly needs plenty of researches into this field, because it is unlikely that one distinctive type of neuron is present in brain without any actual purpose.

Both Glutamatergic Neurons and Gabaergic Neurons in the Gpi Respond to Reward Omission. The other possible outcome is that depression is recorded at the LHb because of the only activation of GABAergic neurons (Figure 4B). This indicates that the GABAergic neurons will also respond to reward omission. Therefore, the interpretation of this phenomenon may be the counterbalance of the co-releasing neurotransmitters to prevent the neurons being too activated.



A B

Figure 4: Neural activities detected at the LHb. (A) Only glutamatergic neurons code for reward omission in the GPi, deduced by undetected neural activity induced by GABAergic neurons. (B) Both glutamatergic neurons and GABAergic neurons code for reward omission in the GPi, deduced by a depression response of GABAergic neurons when reward is omitted.

2.2 Negative Results

2.2.1 GPi is Not the Only Input into the LHb Coding for Reward Omission

Using the same method described, the result may also be that still there are action potentials at the LHb, which means the GPi is not the only upstream of the LHb responsible for reward omission, and other regions like the VP and the HT may also play a nonnegligible part. Hence researches into the VP and the HT regarding reward omission require to be done.

However, this outcome means a limitation for the experiment that determines the neuron types in the GPi. If it is true that other regions are also involved in reward omission response, this means that even inhibiting glutamatergic neurons in the GPi will not get the expected recording, since other regions will also be activated during reward omission. Therefore, the neural activities in the LHb that are singly induced by the GABAergic neurons in the GPi cannot be detected, because of the interference from neurons of other brain regions. It is also not practical to destroy both the VP and the HT, because it almost means destroying the entire system, which may lead to the dysfunction of other brain works, such as learning behavior and memory.

2.3 Difference in Functions of the Gabaergic Neurons in the RMTg and the VTA Regarding Reward Omission

One aspect to distinguish the RMTg GABAergic neurons from the VTA GABAergic neurons is their different responses to reward omission signals. To test excitations induced by omission signals from the LHb, extracellular recording at the RMTg is done during this period. As for detecting neurons in the VTA, H129-ΔTK-tdT will be used to anterogradely label the VTA neurons from the RMTg, and the DA neurons in the VTA will be fluorescently labeled by AAV carrying Green Fluorescent Protein (GFP) (see Method).

By comparing the overlapping of the tdTomato-labeled neurons and the GFP-labeled neurons, it is expected that they are exactly the same, according the Cohen et al. (Cohen et al 2012) that only DA neurons

in the VTA respond to actual reward omission. The consistency shows that no other neurotransmitter apart from DA is responsible for reward omission in the VTA. In the meantime, excitation of GABAergic neurons in the RMTg should be recorded (Graziane, Neumann, Dong 2018). Therefore, one of the differences between the RMTg GABAergic neurons and the VTA GABAergic neurons is that the former codes for reward omission while the latter does not. Hence it will be incorrect if one confuses the two together.

However, if the labeling does not overlap with each other entirely, one proper interpretation may be that the VTA-projecting GABAergic neurons in the RMTg are also involved in other brain activities like punishment prediction. As a result, a more considerate design of experiment to test this hypothesis should be conducted in the future.

3 DISCUSSION

Because of the lack of investigation of reward omission from previous researches, the thesis explained some designed experiments regarding GPi in reward omission coding and explained the functional difference between GABAergic neurons in the RMTg and the VTA.

The 'blocking' experiment will be used, i.e. destroying the GPi to see whether there are still responses in the LHb. If yes, then the GPi is not the only input into the LHb coding for reward omission. Hence further researches should look into the VP and the HT to test their functions and responses in reward omission, but not only limited to the punishment related signals (Stamatakis, Van Swieten, Basiri, Blair, Kantak, Stuber 2016, Lecca et al 2017, Tooley et al 2018). Brain regions coding for reward omission should not be neglected, because this is an irreplaceable part of reinforcement learning.

If no, it can be concluded that the GPi fully influences the activity of the LHb neurons in reward omission. Only if the GPi has been proved to be the only input into the LHb activated by reward omission signals, then the optogenetics can be used to inhibit the GPi glutamatergic neurons and record firing patterns at the LHb to see whether GABAergic neurons in the GPi also code for omission (Hong, Hikosaka 2008, Hong, Hikosaka 2013). Some reconsideration about how to determine the involved neurons if the GPi is not the only source should be put into the limitation. In addition, the results will elicit more questions, for example, the role of GABAergic neurons. Do they really help code for omission just to ensure the neurons do not get too activated? Since they cannot exist without any purpose, is it possible that they lead to a whole new pathway into the VTA? These are presently only guesses without evidence.

As for the efferent of the LHb, although the RMTg is closely linked to the VTA, the function of its GABAergic neurons should not be confused with those in the VTA. One of the differences elaborated here is the difference in coding for reward omission. Certainly more considerate experiments should be done to reveal their functional differences, since this interpretation only partially considered the omission response based on previous researches.

Large areas in reinforcement learning, including reward omission coding, remains unexplored. Therefore, hypotheses are expected to be made and tested, and hopefully this thesis will be of some help.

4 METHODS

4.1 Animal

20 adult male mice will be used for the GPi lesion experiment, 10 of which are used as lesion group, and the rest are used as control group, containing 5 of sham-lesion and 5 of no operation. The mice belong to the sham-lesion and no operation group show no difference in responding behavior at postsurgical tests, so they will be regarded as the same in the experiments. Mice in the lesion group and sham-lesion group will be verified by histology.

For the neurotransmitter-determination experiment, 10 adult male transgenic mice with SLC17A6-Cre will be used.

For the GABAergic-neuron comparison experiment, 10 adult male transgenic mice with DAT-Cre will be used.

All animals were singly housed on a 12-hour dark/12-hour light cycle.

4.2 Surgery

Electrolytic lesions will be made using a stainless-steel electrode. The head plate that will be attached to the skull are going to be used as the anode. After 10 days of training on the conditioned task, the 20 normal mice will be chosen randomly to become either lesion group or control group. Electricity will be delivered to destroy the GPi (from bregma: -0.7mm posterior, 1.8mm lateral, 3.95 mm depth) in the lesion group, while the sham-surgery group will have no current delivered. During surgery, mice will be anesthetized and placed in a stereotaxic frame. For the best result

of the surgery, monitoring the mice's breathing rate and maintaining the temperature of the mice are necessary. Additionally, after recovery, all the mice that go through the surgery will be presented with the odour cue that they learnt in the association task before. If the licking frequencies of mice remain high, then they are ready for the experiment since their memory has been tested unharmed by the surgery.

As for transgenic SLC17A6-Cre mice group, the optic fibre will be implanted, together with the electrode for the mimic stimulations, into the GPi, so that light can be shone through to activate the HR.

4.3 Viral Injection

During the same surgery, adeno-associated virus (AAV), carrying the transcription stop gene flanked by double loxP sites with the same orientation and a following HR, will be injected into the GPi region of the transgenic SLC17A6-Cre mice.

The same method should be used to inject AAV, carrying the transcription stop gene flanked by double loxP sites with the same orientation and a following GFP, into the VTA (from bregma, AP: −2.9 to −3.1 mm; ML: +0.35 mm; DV: −4.65 mm) of the transgenic DAT-Cre mice.

Meanwhile, H129-ΔTK-tdT will be injected into the RMTg (coordinate relative to bregma: AP −6.8 mm; ML ± 0.3 mm; DV −8.4 mm) for anterograde monosynaptic tracing (Zeng et al 2017).

The expression of AAV in specific neurons is highly selective and efficient, and both the HR and the GFP expression is uniform across specifically targeted neurons. The amount of virus injected should be accurately controlled, so that the virus cannot diffuse into nearby brain regions.

4.4 Behavior Task

Before the surgery, all mice will be trained in a classical conditioning task. The task will be a head-fixation one, so the animals will be head-restrained using a head plate and habituated for 15 minutes for 1-2 days before training. Each behavioral trial begins with an odour cue (CS) for 1 second, followed by a 1-second delay and a drop of water as the reward (US). After training, mice will perform the licking behavior during the delay between the cue and reward, indicating that they have learned the association between the odour and water. When the lick rates constantly reaches a standard frequency, the surgeries can be conducted.

After the surgery and recovery (about 10 days), mice will be water-deprived for the experiments. The body weight was maintained above 85% of their full body weight. Licks were detected by breaks of an infrared beam placed in front of the water tube.

4.5 Electrophysiology

After 10 days of resting, the recording tetrode will be implanted to the normal and the transgenic SLC17A6-Cre mice through the craniotomy above the LHb to a depth of 1.8mm below bregma. For the transgenic DAT-Cre mice, the recording tetrode should be implanted to the RMTg (coordinate the same as above). All electrode wires are connected to an electrode interface board for relaying electrophysiological signals to the data system. For the extracellular recording, spikes will be sorted via specific softwares for analysis.

4.6 Histology

After the experiments, 2 mice from the lesion group and 2 from the sham-surgery group will be sacrificed. Their brains will be examined for the extent of lesion by histology. Basically, coronal brain slices will be made, and the area influenced will be recorded.

5 CONCLUSION

By observing the afferent and efferent circuitry of the LHb, we hope to gain a better understanding about the mechanism coding for reward omission. It is identified whether the GPi is the only input coding for reward omission, and whether its GABAergic neurons, apart from the glutamatergic neurons, are also involved in omission signal transmission. Additionally, to help distinguish the difference between the GABAergic neurons in the RMTg and the VTA, their functional difference regarding reward omission response was presented.

However, it is certain that more considerate and further researches should be done to investigate into the field of RPE, including reward omission. As there are still many unidentified parts and new questions elicited by the experiments in this thesis, which were mentioned above, improvements and more profound considerations are expected to be made.

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