Study on Interaction of Dopamine Reward Prediction Error Pathway and VTA-CA1 Novelty Pathway in VTA Region

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Abstract: The function of dopamine neurons (DA) and the dopaminergic pathways in the brain have been studied for scientists for years. However, people still have questions about how these neural pathways interact with each other, building "bridges" between different regions of the brain. This paper investigates the mechanism of dopamine reward prediction error pathway and VTA-hippocampus novelty pathway in VTA Region, and hypothesized that there may exist some interactions between the RPE pathway and VTA- hippocampus novelty pathway in the VTA. Behavioral experiments are designed to further investigate the dopamine activity on VTA and hippocampus when the two pathways work together. The experiments will compare the DA firing in transgenic mice's VTA and CA1 regions in the hippocampus when prediction error happens in novel environments and familiar environments. The results are predicted to show that novelty loop and RPE loop might interact with each other.

1 INTRODUCTION

Dopamine (DA) is a crucial neurotransmitter in the brain, and the midbrain DA neurons are well known not only for regulating emotion, its important function also include controlling voluntary movement, creating associations with rewarding stimuli, attending to salient environmental stimuli, motivating behavior, and maintenance of working memory (Bissonette, Roesch 2016). The newest review in 2021, *Dopamine, Prediction Error and Beyond* (Diederen, Fletcher 2021) provided an overview of the functions of of dopaminergic pathways in reward learning and evidences that suggest a crucial role for dopamine in predicting not only reward, but also general future outcomes.

1.1 Dopaminergic Reward Prediction Error

Studies have found that there are four functionally distinct DA projections in the brain (Diederen, Fletcher 2021), and most of DA neurons are centered in two small nuclei in VTA and substantia nigra (with other two subnucleus (Nair-Roberts, Chatelain-Badie, Benson, White-Cooper, Bolam, Ungless 2008); One of the pathway called mesolimbic pathway, primarily facilitates reward prediction error (RPE) signals and transmits DA from VTA to the nucleus accumbens (NA) in the ventral striatum (Diederen, Fletcher 2021), and another pathway, mesocortical pathway, also connect VTA with a few other regions, including prefrontal cortex (Watabe-Uchida, Eshel, Uchida 2017).

The importance of DA in signaling reward prediction error (RPE) has well been proved (Schultz, Wolfram 2016). Before the conditioned stimulus training, when no reward was predicted, DA fired after receiving a reward; when the reward was predicted, DA fired when the predictive stimulus occurred; when the predicted reward didn't occur, however, DA were silenced. Related experiments have been done in monkeys and rodents, and datas have shown that when the animal adapts its behavior to new situations, the responses of DA neurons may be particularly important when they are learning (Schultz, Wolfram 2016, Schultz, et al 1993).

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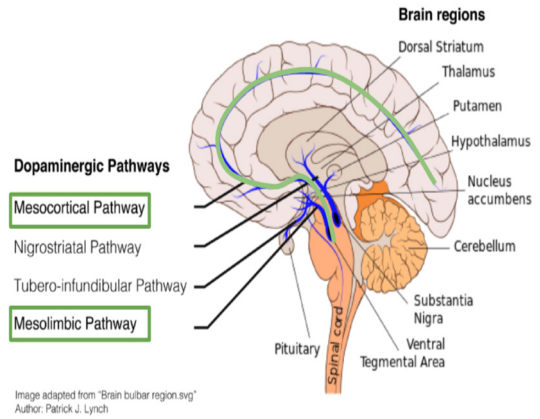

Figure 1: The dopamine reward prediction error pathways are highlighted with green. Image adapted from Diederen KMJ, Fletcher PC. Dopamine, Prediction Error and Beyond. Neuroscientist. 2021 Feb;27(1):30-46. doi: 10.1177/1073858420907591. Epub 2020 Apr 26. PMID: 32338128; PMCID: PMC7804370. Originally adapted from Patric J. Lynch, "Brain bulbar region.svg".

1.2 VTA-CA1 Novelty Pathway

Although researchers have found the major four dopaminergic pathways in the brain (García-García, Zeighami, Dagher 2017), other studies have found that there exists another functionally important loop between the hippocampus and the VTA. Scientists have found that the exposure to novel stimuli can evoke investigatory activity and increase NA dopamine in freely moving rats, and the unilateral perfusion of the ionotropic glutamate receptor antagonists kynurenic acid in the ipsilateral but not the contralateral VTA would block novelty-evoked elevations in NA dopamine (Legault, Wise 2001). The loop was further explained by Lisman JE and Grace AA in 2005 (Lisman, Grace 2005) that there are two pathways in the VTA- Hippocampus loop serving different functions. The down-ward loop carries novelty signals from the hippocampus to the VTA where it stimulates the novelty dependent firing of these cells; in the up-ward arm, the DA that is released enhances LTP in CA1 (Lisman, Grace 2005).

Herein, based on the observations above, a hypothesis is made: there may exist some interactions between the RPE pathway and VTA- hippocampus novelty pathway in the VTA.

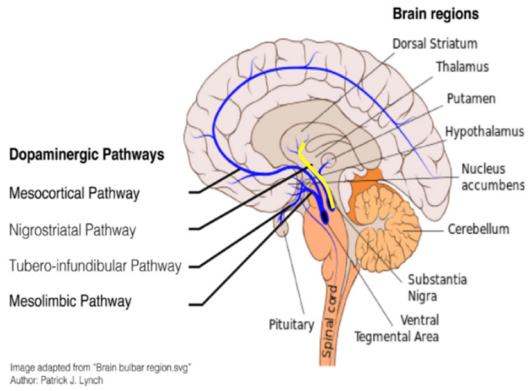

Figure 2: The VTA-CA1 novelty pathways are highlighted with yellow. Image adapted from Diederen KMJ, Fletcher PC. Dopamine, Prediction Error and Beyond. Neuroscientist. 2021 Feb;27(1):30-46. doi: 10.1177/1073858420907591. Epub 2020 Apr 26. PMID: 32338128; PMCID: PMC7804370. Originally adapted from Patric J. Lynch, "Brain bulbar region.svg".

2 EXPERIMENTAL APPROACH

2.1 Subject

Eighteen transgenic mice in which the mRNA encoding the CRE enzyme is made only in dopaminergic neurons (hereafter referred as CRE mice.)

In order to achieve this, the promoter of the Tyrosine Hydroxylase is going to be placed at the 5' end of the DNA coding region of CRE enzyme and inserted onto the mice chromosomes in the transgenic mice.

2.2 Apparatus

Two square cheese board mazes (One painted yellow and one painted blue.) The surface of the apparatus stands 70 cm above the floor, 77.5 cm x 77.5 cm, 3 cm in thickness. A hundred and forty-four food wells (2.5 cm in diameter, 1.5 cm in depth) are drilled into the surface of the maze in evenly spaced parallel rows and columns 2.5 cm apart (10 cm from the edges.) A start box (20 cm in length, 15 cm in width, 20cm in height) is placed on the maze surface, centers perpendicular to the rows of food wells, with the posterior edge of the box placed along the edge of the apparatus. There are 3 pieces of walls around the cheese board mazes (30 cm in height) and are painted the corresponding color of the cheese board. Figure. 1 shows the sketched design of the apparatus.

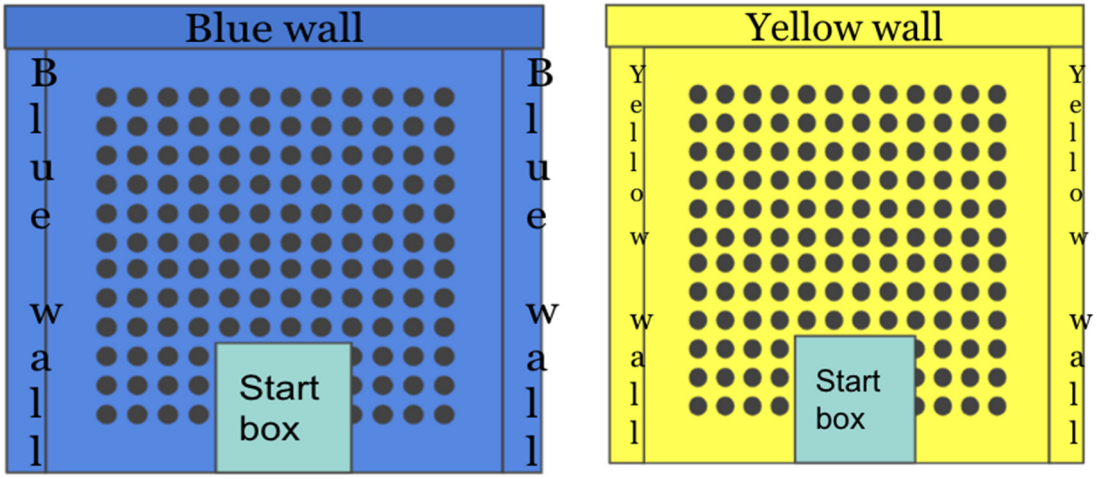

Figure 3: Cheese board mazes. Reproduced from (Gilbert, Kesner 2002). Gilbert, P. E., & Kesner, R. P. (2002). Role of rodent hippocampus in paired-associate learning involving associations between a stimulus and a spatial location. Behavioral Neuroscience, 116(1), 63–71. doi:10.1037/0735-7044.116.1.63.

2.3 Experimental Grouping

The 18 CRE mice will be randomly divided into 3 groups, 6 mice for each, marked as control group, Group A, and Group B. The control group will not receive any surgery other than inserting electrodes into VTA and CA1 regions. Group A and Group B will receive the surgery described in the following paragraph.

2.4 Surgery

The surgery is designed to control the silencing of dopaminergic neurons in the VTA-Hippocampus novelty pathway. ArchT, a high-light sensitivity optical neural silencer, found by scientists in FCK-ArchT-GFP lentivirus (Han, Xue et al 2011) is going to be injected to CA1 regions of the mice in order to achieve this goal. Since the mRNA encoding the CRE enzyme is made only in dopaminergic neurons in the subject, the ArchT gene can only be expressed in DA neurons in the VTA-hippocampus pathway.

CRE mice in Group A and Group B will take the surgery. The surgical procedure for virus injection is adapted from Han, Xue et al., 2011 (Han, Xue et al 2011). Under isoflurane anesthesia, 1 µl FCK-ArchT-GFP lentivirus is going to be injected through a craniotomy made in the mouse skull, into the CA1 region in the hippocampus. Virus will be injected at a rate of 0.1 µl/min for a total of 10 min after which the injector is left in place for an additional 10 min to allow for viral diffusion from the tip. Then, an unilateral optical fiber will be implanted into the brain, 0.9mm below the brain surface about the injection site. Two small screws will be anchored at the anterior and posterior edges of the surgical site and will be bound with dental glue to secure the implant in place (Iaccarino, Singer, Martorell, Rudenko, Gao, Gillingham, Mathys, Seo, Kritskiy, Abdurrob, Adaikkan, Canter, Rueda, Brown, Boyden, Tsai 2018). Finally, implant electrodes to detect the neural activity in CA1 and VTA. After all surgical procedures, each mouse will be given a 2 weeks recovery before being tested.

To verify the novelty evoked dopamine firing in CA1, the mice will be put on the yellow cheese board apparatus and record the DA firing after the recovery before training. Because it is a novel environment for the mice, theoretically there will be dopamine firing in CA1 in the mice's brain.

2.5 Training

The reward learning is necessary before the PE experiment, and the training can also make the mice get familiar with the yellow cheeseboard apparatus. The conditional training procedure is partially adapted from Gilbert and Kesner, 2002 (Gilbert, Kesner 2002). The graphical representation of the first week and second week training apparatus is shown in Figure 4 and Figure 5. During the first week of training, each mouse will be given 1 hour per day to explore the test apparatus (yellow cheese board maze only) individually. While the mouse is exploring, 10 pieces of Froot Loop cereal will be spread out across the surface of the yellow cheese board. The door to the start box will be open and each mouse can freely enter the cheese board from the

interior of the box. For the 2nd week of training, a single, neutral object will be introduced into the cheese board. It will be placed at the very center of the cheese board. The object will be used to shape each mouse to displace an object to receive a food reward. Once a mouse consistently displaces the object to receive a food reward, it is ready for the behavioral experiment later.

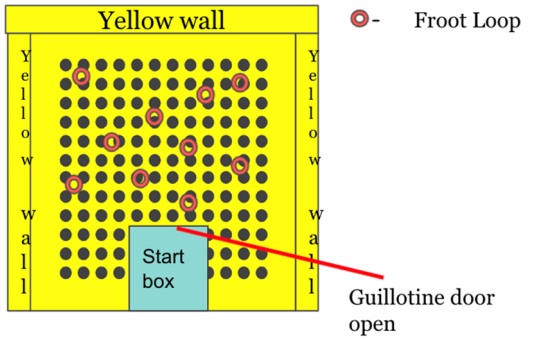

Figure 4: A graphical representation of the first week training apparatus.

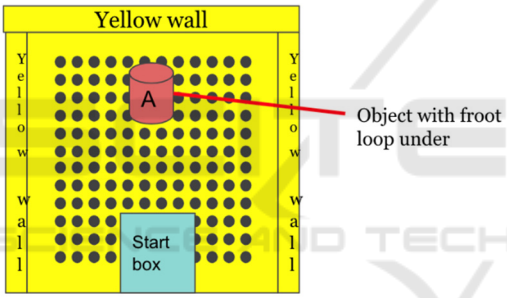

Figure 5: A graphical representation of the second week training apparatus.

2.6 Behavioral Experiment 1

Blue cheese board will be used in this experiment, as a novel environment.

For the CRE mice in Group B, their dopamine firing in VTA and CA1 will be tested as each of them enters the apparatus from the start box.

For the CRE mice in the control group and Group A, each of them will go through the following PE experiment. A single, neutral object (same as which in the training) will be introduced into the very center of the testing apparatus. A froot loop will be placed in the food well under the object, and the mouse will be placed in the start box. The dopamine firing in the VTA and CA1 region will be recorded once the mouse exits the start box. Once the mouse displaces the object and gets the food reward, it will be moved into the start box again. The object will be replaced at the center, and the froot loop under the object will be removed this time. Let the mouse restart, and record its DA firing in VTA and CA1 once it exits the start box.

2.7 Behavioral Experiment 2

Yellow cheese board apparatus will be used in this experiment. For the CRE mice in Group A and Group B, their VTA-Hippocampus novelty pathway will be silenced using an optogenetic method.

2.7.1 Optical Stimulation Procedure

The optical stimulation procedure is well described in (Iaccarino, Singer, Martorell, Rudenko, Gao, Gillingham, Mathys, Seo, Kritskiy, Abdurrob, Adaikkan, Canter, Rueda, Brown, Boyden, Tsai 2018). A 200 mW, 4,793nm DPSS laser will be connected to a patch cord with a fibre channel/physical contact connector at each end. During the experiment, 1mW (measured from the end of the fibre) of optical stimulation will be delivered for 1h.

In order to verify the effect of the optogenetic method of silencing of DA neurons in CA1, each mice will be given an optical stimulation for an hour on the optical implantation site. Then, they will be introduced to a novel environment, and record their dopamine firing in CA1. If there's no potentiation recorded in CA1, then the VTA-Hippocampus novelty pathway is silenced.

After the VTA-Hippocampus novelty pathway is completely silenced, the control group, Group A, and Group B will go through the same procedure described in the PE experiment in Behavior Experiment 1.

3 ANALYSIS AND PREDICTED OUTCOME

Based on my hypothesis that there may exist some interactions between the RPE pathway and VTA-hippocampus novelty pathway in the VTA, combined with the background knowledge of PE and the two pathways, I made the following analysis and inference.

1. In the Behavioral Experiment 1, since the blue cheese board apparatus is a novel environment for the mice, there will be a large number of novelty-evoked dopamine firing in the CA1 region in all three groups of CRE mice as they enter the apparatus. In the Behavioral Experiment 2, however, there will be no

novelty-evoked dopamine firing in CA1 for Group A and Group B since the VTA-Hippocampus novelty loop has been silenced. Since the mice have been trained in the yellow cheese board before, it is a less novel environment for the mice. Therefore, there will be less novelty-evoke dopamine firing for the control group in the Behavioral Experiment 2 than in the Behavioral Experiment 1.

2. In the Behavioral Experiment 1, the novelty-evoked dopamine firing might change the reward prediction error dopamine responses in VTA. By comparing the dopamine firing data of Group A in Behavioral Experiment 1 and 2, the interaction of dopaminergic RPE pathway and VTA-hippocampus novelty pathway can be specified.

3. It is possible that the novelty-evoked DA release in CRE mice in Behavioral Experiment 1 goes through the up-ward arm of VTA-hippocampus loop (Lisman, Grace 2005) enhances LTP in CA1, and the interaction between the dopaminergic RPE pathway and VTA-hippocampus pathway sends RPE signal to the hippocampus, hence reinforcing the RPE learning.

4 CONCLUSIONS

A method determining the connection between the dopamine reward prediction error pathway and the VTA-CA1 novelty pathway by simulating the experiment of prediction error with and without novelty was established in this research. It can help us further explore the interaction between different regions of the brain, including the interaction between VTA and hippocampus-CA1, PFC and VTA. If the hypothesis is true, then we might inferred that people can use novel environment to reinforce RPE learning, that is, making learning more productive.

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