The Role of D1 Receptor Medium Spiny Neuron Pathway in Video Gaming Addiction Relapse

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Abstract: Video game addiction has gained increasing amount of attention as the problem keeps prevailing, especially among adolescents. Inspired by mechanism of cocaine induced substance addiction (D1R-MSN direct pathway) and a potential treatment protocol proposed in previous literature, experiments are done in 40 human subjects to test the mechanism of video game addiction relapse and craving. The results show that low frequency deep brain stimulation of 12 Hz combined with an infusion of drug SCH23390 (D1 receptor antagonist) causes an increase in self-control time, indicating a reversal effect of video game addiction relapse and craving. The same combination of treatment is shown to reduce firing frequency of video game cue induced D1R-MSNs, providing neuroscientific basis for the mechanism of the addiction and the treatment. The combination also proves the role of synaptic change in D1R-MSNs direct pathway in the cause of video game addiction relapse and craving. The mGluR1 dependent long-term depression (LTD) reducing total glutamate release and surface expression of AMPA receptors might be the mechanism behind the treatment.

1 INTRODUCTION

Addiction is the inability to quit using a substance or taking part in a behavior, regardless of the harm they might bring. Common types of addictions include cocaine addiction, gambling addiction, heroin addiction etc (Medical News Today, 2021). The mechanism of addiction is complex and involves multiple brain areas. Nucleus Accumbens (NAc) has been proven to play an important role in the addiction (Scofield et Al, 2016). According to the type of dopamine receptors that the neuron express, medium spiny neurons (MSN) are divided into two classes: D1 receptor MSNs and D2 receptor MSNs (Reinius et al, 2015). D1R-MSNs mainly build up the direct pathway. In the pathway, Nucleus Accumbens receives input from prefrontal cortex, then project to SN and VTA, which in turn project to thalamus and to the cortex to direct behavior. Activation and potentiation of these D1R-MSNs ultimately disinhibit the thalamus projection to the motor cortex and enhances movement and execution of movements (Smith, Lobo, Spencer, Kalivas 2013). The direct pathway is also found to be related to craving behavior (Scofield et Al, 2016). D1 receptors are shown to be responsible for LTP mechanism which increases the strength of potentiation between the connection of cortex neurons and MSN (Smith, Lobo, Spencer, Kalivas 2013).

Few papers have regarded the role of NAc in behavioral addiction such as video game addiction, but studies on cocaine have revealed an important role of NAc in drug relapse and craving behavior. It has been shown that cocaine selectively potentiates cortical afferents onto D1 MSNs (Creed, Lüscher 2013). It is a mechanism that is possibly triggered by the activation of ERK kinase by D1 receptor binding with dopamine. The activation of ERK kinase is correlated with the insertion of AMPA receptor and locomotor sensitization (Pascoli, Turiault, Lüscher 2012). Since the dopaminergic neurons are also glutamate releasing, the drug cue causing a firing of these cotransimission neurons will release Glutamate as well (Broussard 2012), stimulating D1R MSN for drug seeking behavior. A protocol proposed that gives D1 receptor antagonist SCH23390 and low frequency deep brain electrical stimulation of 10-15Hz to the Nucleus Accumbens Shell area can reverse the enhanced motor behavior caused by a LTP that is caused by repeated exposure of cocaine (Creed, Pascoli, Lüscher 2015).

In recent years, gaming addiction, sometimes referred to as Internet and video gaming addiction

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(IGVD) or Internet gaming addiction (IGD), has garnered attention. According to GAS scale of criteria for gaming addiction, relapse is among the 7 criteria, suggesting a potential similarity with some of the substance addiction like the cocaine addiction as mentioned before (Lemmens, Valkenburg, Peter 2009). Besides, previous papers have shown that NAc is increasingly active in the subjects with internet or gaming addiction (Kuss, Griffiths 2012), and it has been reported to be activated in cue-induced gaming urge (Ko et al 2009). Considering the similarity in nucleus activity and symptoms, we hypothesize that the D1R MSN pathway also plays a role in video gaming addiction and its relapse behavior. The goal is to use the protocol from Creed et al paper on humans and test whether the treatment causes both electrophysiological and behavioral changes that are aligned with a reversed effect of video game addiction.

2 MATERIALS AND METHODS

2.1 Subjects

All the 40 participants have gone through the Game Addiction Scale (GAS), validated to be a standard measure of gaming addiction. According to the modification done by (Khazaal et al, 2018), we adjust the questionnaire to fit internet gaming and video gaming investigation. We include questions like “Do you play video games on the Internet or off line to escape from real life situations?” Each question begins with “During the last 6 months, how often do you…”, and the answer is given in a 1-5 point scale (Khazaal et al, 2018).

Each question is in accordance to the seven criteria of addiction: salience, tolerance, mood modification, relapse, withdrawal, conflict and problems. With the point of scale, 40 subjects with similar high score of severe addiction problem is chosen for better control.

2.2 Electrode Implantation

In this experiment, multi-electrode array (MEA) consisting of 64 platinum microelectrode is implanted into the human brain Nucleus Accumbens Shell area to perform both functions of recording and deep brain stimulating (DBS). This requires an MR imaging on a 1.5 T scanner to identify brain area (Horn et al, 2017). During the implantation of the electrode, the patients are generally under anesthesia but were awake when electrode testing is performed (Horn et al, 2017). The participants are given the video game cues (their favorite video game according to the questionnaire presented on the TV screen in front when doing surgery), and the signals of action potential rate is recorded. The electrodes are planted at the spot where the rate is the highest. The rate can be visualized by oscilloscope that is connected to the array and heard by the loudspeaker connected. (Carter, Shieh 2015).

In this way, the specific D1R-MSNs that are responsive to video game cues are detected. They are thus prepared to be recorded and stimulated by electrodes of MEA. The electrode used are also modified with drug infusion capability (Vanegas et al 2019), which will be used later to inject SCH23390, the D1 receptor antagonist (Faedda, Kula, Baldessarini 1989).

2.3 Self-control Tasks

The participants with the electrodes implanted will undergo several blocks of treatments and tasks. It is shown in an abbreviated scheme in fig.1. The self-control task aims to gather data of whether certain patterns of treatments can reverse the behavioral aspects of video game addiction: relapse and craving. The participants are placed in a vacant room with only one TV screen and a joystick connected, through which they can play the games they are addicted to. However, they are asked to control their impulse as long as possible. We are thus recording the self-control time before and after giving certain patterns of treatments. Electrophysiology data regarding D1R-MSN activity are also recorded in the process.

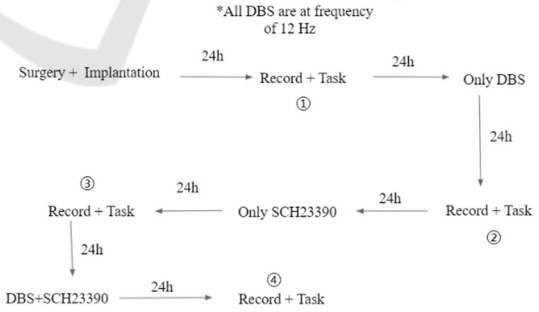

Figure 1> Experiment procedure and scheme.

An interval of 24 hours is given between each task and treatment. It aims to give adaptation time to participants. More importantly, it aims to test the long-term effect of the treatment. In similar experiments executed on rats, the protocol that successfully reverse the effect of addiction in the long term shows consistency in the data after 24 hours.

Considering ethical issue and the tediousness of the experiment, we set no longer interval than 24 hours which could have been a better measurement for long term effect.

The same patch of 40 subjects goes through 4 treatment and task blocks in sequence. Considering the uneasiness when it comes to the approval of human participants, the different combinations of treatments are done on the same person. However, adjustments can be done if any preceding tasks evoke a long-term effect in data. For instance, if significant difference is found in both behavioral and electrophysiological data in the second task, the preceding treatment (only DBS) will switch position with the following treatment (only SCH23390). Besides that, SCH23390 is a short-lived drug with elimination time of around 25 minutes (Faedda, Kula, Baldessarini 1989), and the DBS stimulation is only 12 Hz for 10 minutes. Thus, the treatments themselves, if not evoking a chemical change, will not have impact on the following treatment.

2.4 Electrophysiology Recording

Using Multielectrode assay, we can gather the signals of the potential around the recording probe. The raw signal will need to be processed in a sequence of steps for analysis. First, by applying a band pass filter with a typical narrow band of 300-3000Hz, the noises are largely filtered out, leaving only the information of action potential of all the recorded neurons (Obien, Deligkaris, Bullmann, Bakkum, Frey 2015).

The next step would be to detect time of spikes using amplitude thresholding. Finally, each neuron recorded has a particular firing pattern and shape, so we can sort all the spikes into different individual neurons. This will require some sophisticated technology like PCA and wavelet transformation (Obien, Deligkaris, Bullmann, Bakkum, Frey 2015).

With the spike pattern of both individual neurons and the aggregate of all neurons, we can count the spikes and reckon the spike rate. It is calculated by the number of spikes divided by the same time interval (Gerstner, Kistler, Naud, Paninski 2014). It can act an indicator of synaptic strength.

3 RESULTS

3.1 Behavioral

In testing the reversal effect of three different treatments (only DBS, only SCH23390, DBS + SCH23390), we used self-control time as a benchmark. In the first task where no treatment is given, we expect a low self-control time, which we proposed as about 30 minutes. In the ideal situation, the second and third task will yield similar results, with no significant increase in self-control time. It is only in the last treatment that a significant increase in self-control time is recorded, indicating a successful impact of the final treatment on video game addiction relapse in most subjects. The pattern can be visualized in Fig.2 with the estimated and expected data shown in Table 1.

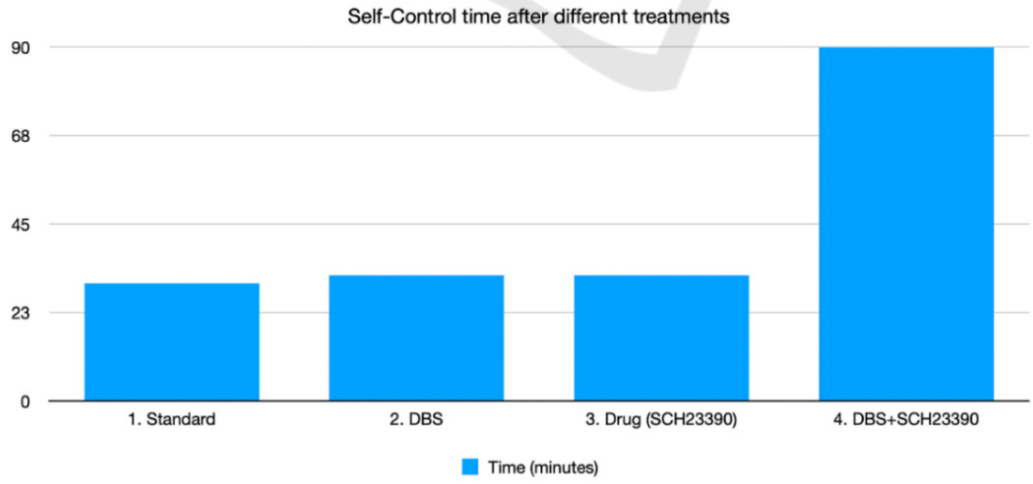

Figure 2: Self-control time after different treatment.

Table 1: Estimated time difference.

Experiment set up	Time (minutes)
1. Standard	**30**
2. DBS	**32**
3. Drug (SCH23390)	**32**
4. DBS+SCH23390	**90**

If the result is not as expected, a significant increase in self-control time would be observed in either second or third task. If the effect is long term, the rest of the task is likely to be affected and show same pattern of increase in self-control time.

3.2 Electrophysiology

In determining the effect of different treatment on the D1R-MSNs, we gathered data regarding spike frequencies for individual neurons (gone through spike sorting) and the whole patch of neurons (before spike sorting). A higher spike frequency indicates a stronger synaptic connection. We expect the spike frequency to be high in the first task when no treatment is given, which explains the corresponding low self-control time, since the impulse is generated through frequent firing of neurons that builds up the direct pathway that contribute to craving and relapsing. We also expect the firing pattern to be similar in both second and third task, indicating an ineffectiveness of treatment on the long-term synaptic structure of D1R-MSNs. It is only in the final treatment that is reported to induce LTD (Creed, Pascoli, Lüscher 2015) can lower the firing frequency in the recording after 24 hours. This can explain the corresponding increased self-controlled time. The pattern is shown in Fig.3 with the estimated data in Table 2.

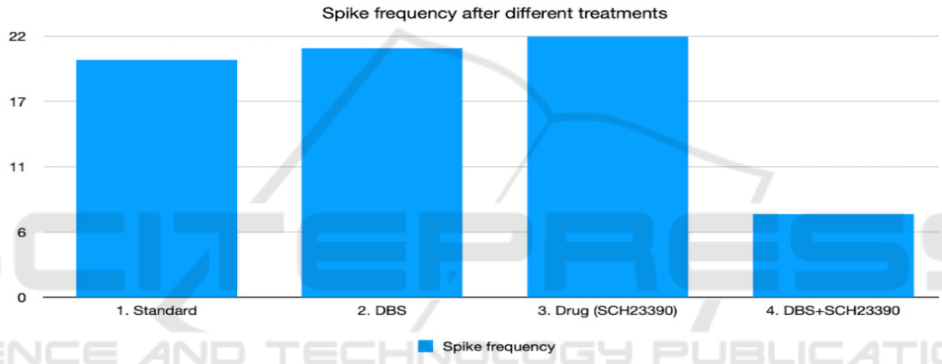

Figure 3: Spike frequency (Hz) after different treatments.

Table 2. Estimated spike frequency data.

Experiment set up	Spike frequency
1. Standard	**20**
2. DBS	**21**
3. Drug (SCH23390)	**22**
4. DBS+SCH23390	**7**

If the results go unexpected, a decrease in spike frequency is likely going to be recorded in either second or third task and is likely to last for the following tasks. If either situation occurs, it would invalidate our hypothesis to certain extent. If DBS alone can cause a long-term effect, we cannot prove how without D1 receptor antagonist, LTP induced by D1 receptor is offset. If SCH23390 alone can cause a long-term effect, we cannot prove how the short-lived drug can have an impact alone on the long-term structure of the synapse. Only together with low frequency DBS that can induce LTD, and SCH23390 that can prevent the effect of LTP, can we explain the mechanism of video game addiction relapse and craving, and the mechanism of how to solve it.

4 DISCUSSION

The reversal effect that only occurs when low frequency DBS and SCH23390 is given together is likely caused by a specific type of LTD: mGluR1-dependent LTD. It is reported that frequency of 10-15 Hz stimulation is associated with mGluR1-dependent LTD (Creed, Pascoli, Lüscher 2015). There are two pathways of mGluR-dependent LTD. The first pathway: Low frequency electrical stimulation excites the afferent cortex neuron and promotes the release of enough Glutamate neurotransmitter from pre synaptic region to the synaptic cleft for mGluR receptor to accept. Group 1 mGluR receptor generates endocannabinoids by activation of phospholipase C, which generates diacylglycerol, which in turn in the

end revert by the lipid precurson to endocannabinoids (Wilson & Nicoll 2002). The DBS also likely causes a post synaptic excitability, opening the L-type voltage-gated calcium channels, which positively modulate the mobilization of the endocannabinoids (Lüscher, Huber 2010).

Endocannabinoids are released by exocytosis back to reach to the presynaptic membrane and more specifically, the CB1 receptor on it. The CB1 receptor in turn inhibit the Calcium channel, which is important for the release of neurotransmitter (Lüscher, Huber 2010). A long-term decrease in EPSC recorded in the post synaptic region is expected.

Another pathway shows that Stimulation of Group I mGluR activates phospholipase C (PLC), inositol triphosphate (IP3) pathway to release Ca2+ from intracellular stores and protein kinase C (PKC). PKCα phosphorylates ser880 of GluA2 to trigger endocytosis of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) and reduce the level of surface expression (Kang, Kaang 2016). Both pathways act to decrease the amplitude of currents passing to post synaptic region (Scheyer, Christian, Wolf, Tseng 2018). In either way, it can help explain our data that there is a decrease in the spike counts, since weaker currents passing through the AMPA receptors is less likely to induce a negative 55mV potential that results in an action potential.

5 CONCLUSIONS AND FUTURE DIRECTION

The expected results indicate the availability of treatment protocol of 12Hz low frequency Deep Brain Stimulation combined with infusion of SCH23390 D1 receptor antagonist targeting Nucleus Accumbens shell area in relieving symptoms of video game addiction relapse and craving. It is visualized by a decrease in self-control time in video game addicts when asked to control impulses. The electrophysiology results also prove the role of D1R-MSNs and the mechanism of video game addiction as well as the mechanism of LTD in solving the problem.

Internet gaming and video game addiction is a problem that is exclusively investigated in human. However, there is problem in figuring out mechanism if human are used as subjects. It is hard to isolate the effect of D1R-MSNs in the addiction (what we tested in this paper is a reverse way of thinking that proves the significance by blocking the effect), and it is unethical to develop a video game addiction in human from zero to test the effect. In vitro studies have been done in epilepsy patients(Jones 2016). Similar studies can be done in the future from patients suffering from comorbidity in different types of addictions. In vitro investigation will be more precise and controllable.

The technology currently applicable on human is still immature. Some technology that is current under development will help constitute a more complete experiment. MIT researchers are currently developing an Ultrathin needle that will allow more specific targeting of infusion into the brain (Trafton 2018). SEEG is a technology that is currently used to more precisely spot the sources of epilepsy (Isnard et al 2018). Similar approach might be used in video game addiction cause source in the future. These technologies can provide an even more accurate and controlled environment for studying the video game addiction.

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