Module:
Biological Foundations of Mental Health

Week 5
Reward, emotion & action

Topic 3
The reward system of the brain

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Lecture transcript

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In this lecture, I will describe the reward system of the brain. But before I go into details about the reward pathway, let us define the notions of reward and positive reinforcement.

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Humans, as well as other organisms, engage spontaneously in behaviours that are rewarding. And they do so because the pleasurable feelings that are associated with the reward provide positive reinforcement, which means that the behaviour is repeated. So we can say that a reward is an appetitive stimulus, that when given to a human or another animal, alters its behaviour by producing positive reinforcement.

Now rewards can be classified into two categories-- natural rewards and artificial rewards, such as drugs of abuse.

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Examples of natural rewards include food, water, sex, and nurturing. All of these reinforce behaviours that are necessary for our survival.

With such a role of the reward pathway in motivation and reinforcement, it is important to note that this hedonic system can be deregulated in people suffering from various psychiatric orders, for example, people suffering from eating and affecting disorders, and hedonia-- that is, a lack of pleasure-- or dysphoria, a negative affect-- and also in people abusing drugs. I will show examples of this later in the lecture. And there is a pathway in the brain that is responsible for our responses to rewards, which you can see in the next slide.

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Responses to rewards are mediated primarily by the ascending mesolimbic dopamine pathway, that plays a primary role in the reward system. The mesolimbic dopamine pathway connects the ventral tegmental area, VTA, one of the principal dopamine-producing areas in the brain, with the nucleus accumbens. That is an area found in the ventral striatum, that is strongly associated with motivation and reward.

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Another major dopamine pathway, the mesocortical pathway, travels from the VTA to the prefrontal cortex, and is also considered part of the reward system.

So the reward system is generally considered to be made up of the main dopamine pathways of the brain, and especially of the mesolimbic pathway, and also formed by structures like the VTA in the nucleus accumbens, which are connected by these dopamine pathways.

As the structures that are associated with the reward system are found along the major dopamine pathways in the brain, it is not surprising that the brain responds by increasing the release of a neurotransmitter, dopamine, when it is exposed to a rewarding stimulus. So because this pathway is a key detector of a rewarding stimulus, it is an important determinant of motivation and incentive drive. So in simplistic terms, activation of this pathway tells the individuals to repeat what it did to get that reward.

Not surprisingly, it is a very old pathway from an evolutionary point of view. For example, the use of dopamine neurons to mediate behavioural responses to natural rewards is seen in worms and flies which have evolved one to two billion years ago.

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But how was this brain reward pathway discovered? Its discovery came from pioneering experiences by two scientists, James Olds and Peter Milner, who performed intracranial self-simulation experiments in rats, in 1954. These experiments consisted in implanting electrodes in the brains of rats and allowing the animals to self-stimulate by pressing a lever that delivered a mild burst of electrical current to stimulate the neurons.

What they discovered is that electrical stimulation in certain parts of the brain, particularly in the septal area, which lies close to the nucleus accumbens, would produce the strongest effects, making rats to self-stimulate repeatedly. Olds and Milner's experiments were significant, because they appeared to verify the existence of brain structures that were responsible for rewarding experiences. Because if the rats pressed the lever repeatedly to receive stimulation to these areas, it suggested that the experience was rewarding.

Various rewards sites have been identified in the brain since these initial experiments. And it was discovered that some of the most sensitive areas are situated along the length of the medial forebrain bundle. That is a large collection of nerve fibres that travels between the VTA and the lateral hypothalamus, and towards the nucleus accumbens.

Some areas of a medial forebrain bundle were found to be so sensitive, that rats would choose receiving stimulation to them over food or sex. Eventually, it was recognised that dopamine neurons are activated during this type of rewarding brain stimulation, and researchers found that they could cause rats to stop press a lever by administering a dopamine antagonist, that is a drug that blocks the effect of dopamine. In other words, without the activity of dopamine, the rats were less likely to find brain stimulation reinforcing, and so they stopped pressing the lever altogether.

Now it is important to notice that like with self-stimulation, the reward pathway is strongly activated by drugs of abuse, who all induce release of dopamine at dopamine terminals, including the nucleus accumbens.

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The drugs induced the release of dopamine in the nucleus accumbens was demonstrated with experiments in which a small microdialysis probe was implanted into the brains of freely moving rats. And this allowed to measure the amount of dopamine that is released into the extrasynaptic space.

You can see on this figure, that injection of rats with drugs such as ethanol and morphine, resulted in strong release of dopamine in the nucleus accumbens, and also, but to a lesser extent, to some release in the dorsal caudate nucleus. That is a part of the dorsal striatum.

You can also note that both the magnitude that is the amount of dopamine released and the duration of the effect increase with the dose of the drug. Although it is not shown on this figure, most drugs abused by humans, which include opiates, ethanol, nicotine, amphetamine, and cocaine, can activate the reward pathway by inducing the release of dopamine in the nucleus accumbens, and have the same dose dependent effect.

The very strong effect of drugs on dopamine release explains why drugs are more addictive than natural rewards. When some drugs are taken, they can release 2 to 10 times the amount of dopamine than natural rewards do. This can occur almost immediately, when drugs are smoked or injected. And the effects can last much longer than those produced by natural rewards.

The resulting effects on the brain's reward pathway dwarf those produced by natural rewards, and the effect of such a powerful reward strongly motivates people to take drugs again and again. Moreover, this deregulated dopamine release affects all the brain circuits, alerting all the brain regions of novel rewarding experience, and recruiting other neurotransmitter systems.

But how does simulation of the brain's reward circuits can teach one to keep taking drugs? Our brains are wired to ensure that we will repeat life sustaining activities by associating those activities with pleasure or reward. So whenever the reward circuit is activated, the brain notes that something important is happening that needs to be remembered, and teaches us to do it again and again and again without thinking about it.

Because drugs of abuse stimulate the same circuit, we learn to abuse drugs in the same way, and this is why scientists sometimes say that drug abuse is something we learn to do very, very well.

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But what if the reward pathway becomes persistently activated? Such persistent activation of the reward pathway occurs in the case of chronic drug abusers or even in individuals consuming unusually large quantity of food. To answer this question, scientists have quantified dopamine neurotransmission in the brains of addicted or obese individuals, using positron emission tomography-- PET.

They have found that compared to non-addicted or non-obese control subjects, individuals that were addicted or obese had reduced levels of dopamine D2 and D3 receptors in their striatum. This reduction of dopamine D2 and D3 receptors in the striatum is evidenced by the decreased intensity of the red signal in this figure.

This shows that new adaptations occur in the brain following over activation with a reward pathway, and that the brain adjusts to the overwhelming surges in dopamine and other neurotransmitters by producing less dopamine, or by reducing the number of receptors that can receive signals.

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So what could be the consequences of such neural adaptations? A current hypothesis is that dopamine's impact on the reward circuit could become abnormally low, considerably reducing that person's ability to experience any pleasure. This would then explain why the chronic drug abuser eventually feels flat, depressed, and unable to enjoy things that previously brought pleasure. So such drug abusers need to take drugs just to try and bring their dopamine function back up to normal. This could also explain why tolerance develop, requiring large amounts of the drug to create the dopamine high.

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All reinforcing drugs induce the release of dopamine in the nucleus accumbens, but they use distinct mechanisms to do so. But before looking at how drugs interfere with the mesolimbic reward pathway, let us analyse the major types of neurons that are part of this pathway.

We have already seen that dopamine neurons in the ventral tegmental area project to the nucleus accumbens where they release dopamine when activated. What is also important is to know that VTA neurons are under the inhibitory control of local GABAergic interneurons. So activation of those GABAergic VTA neurons would prevent release of dopamine in the nucleus accumbens by inhibiting VTA dopamine neurons.

So how do different drugs act? They control the activity of these neural mechanisms by various means. For example, nicotine activates VTA dopamine cells directly by banding to nicotinic acetylcholine receptors that are expressed on their surface, which causes dopamine to be released in the nucleus accumbens.

Psychomotor stimulants like cocaine and amphetamine, increase the concentration of dopamine in the synaptic cleft in the nucleus accumbens, through direct actions on dopamine transporters at dopamine terminals.

The rewarding properties of opiates are mediated by their binding to mu-opioid receptors that are found in two locations in the brain reward circuits. Mu-opioid receptors are expressed on the GABAergic VTA interneurons, and opioids accurately inhibit these interneurons, causing disinhibition of the dopamine VTA neurons, and consequently release of dopamine in the nucleus accumbens and other terminal fields.

Mu-opioid receptors are also expressed on the nucleus accumbens and on dorsal striatal neurons. Opiates can stimulate these receptors directly, and therefore, produce reward in a dopamine independent manner.

As for alcohol, it facilitates the release of dopamine in the nucleus accumbens by indirectly activating dopamine neurons. Alcohol inhibits GABAergic VTA interneurons by binding to gamma aminobutyric acid A receptors on those neurons, and by facilitating the release of opioid peptides in the VTA. In addition, alcohol-induced release of opioid peptides in the nucleus accumbens could also produce reward in a dopamine independent manner.

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We have, so far, detailed the fundamental role of dopamine and the mesolimbic dopamine system in reward. But it is important to note that since the earliest research on the reward system, our perspective on dopamine's role in reward has changed slightly. At one time, dopamine was considered to be the neurotransmitter responsible for causing the experience of pleasure. But it is now thought to be involved in aspects of reward other than the direct experience of pleasure. Likewise, the mesolimbic dopamine system clearly plays an important role in reward, but that role may not be as hedonic as previously thought.

This slide shows experimental examples suggesting that dopamine is not a hedonic signal, which means not a pleasure signal, but a signal for motivated behaviour.

A more current view, either dopamine does not cause hedonic reactions or pleasure, but rather more specifically increases the motivation components of reward, such as incentive salients, producing wanting or seeking without causing liking or show hedonic impact. Another major alternative hypothesis is that dopamine causes learning about rewards.

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Not only does the reward system involve more than dopamine, but brain circuitries other than the mesolimbic dopamine pathway are critically involved in mediating the effects of reinforcement. One has to remember that the mesolimbic pathway does not act in isolation, but is part of a series of integrated circuits which involve several other key brain regions-- at the centre of this network, the cortical basal ganglia circuit.

This circuit involves cortical areas, such as the orbital frontal cortex and the interior cingulate cortex, that work in concert with basal ganglia structures like the ventral striatum, the ventral pallidum, and the mid-brain dopamine neurons, to execute motivated, well-planned behaviours. For example, the ventral striatum receives major cortical input for the orbital frontal cortex and the interior single cortex, and substantial dopaminergic input from the ventral tegmental area and the substantia nigra.

On the other hand, the ventral striatum sends projections through the ventral tegmental area and substantia nigra, and to the ventral pallidum, which in turn, via the medial dorsal nucleus of the thalamus, project back to the prefrontal cortex.

Other circuits work in tandem with elements of the reward system to develop appropriate goal-directed actions, which relies on the combined interplay of sensory inputs, emotional informations, and memories of prior outcomes. For example, a reward pathway tells the memory centres in the brain, which involve the hippocampus and the amygdala, to pay particular attention to all features of this rewarding experience so that it can be repeated in the future.

In this respect, the amygdala, which is particularly important for conditioned forms of learning, interacts with the VTA nucleus accumbens pathway to determine the rewarding or aversive value of an environmental stimulus. By doing so, it helps an organism establish associations between environmental cues and whether or not that particular experience was rewarding or aversive-- for example, remembering what was associated with finding food or fleeing a predator.

On the other hand, the hippocampus is critical for declarative memory-- the memory of persons, places, or things. Along with the amygdala, it establishes memories of drug experiences, for example, which are important mediators of relapse.

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Various behavioural mechanisms of reward can be measured nowadays thanks to advances in neuroimaging technologies. For example, a functional neuroimaging task called the monitory incentive delay task, or MID task, can be used to measure brain activation patterns that are associated with specific aspects of reward in humans. In this test, subject lay under an MRI scanner that will cause brain activation patterns, while they play repeated trials in which they win or lose money, or any equivalent incentive, depending on their ability to pay attention and react quickly.

This task is the reaction time task, which means that it tests how quickly the subject can react and pull the trigger to hit a target that only appears for a short time on the screen. If the subject can hit the target, they will score points. Subject can tell where the target will appear and how many points it can win by the symbol they see on the screen before each trial. For example, a circle with three lines, as in this picture, means 10 points. Responding too early or too late will result in a loss.

The subjects receive one incentive-- money or equivalent-- for points to enhance motivation during the task. Patterns of brain activity are recorded when a reward is anticipated, that is, after the cue is given, but before the subject hits the target, or when receiving the outcome. In this task, regions of the reward system, such as the nucleus accumbens, are activated when a reward is anticipated.

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We use the MID task to study the reward system in our group. One of our aims is to understand how deficits in reward processing is implicated in mental disorders, such as attention deficit hyperactivity disorder, ADHD, and addictions.

First, we have analysed a large sample of 13-year-old adolescents, trying to define clusters of brain activation patterns in their whole brain, while they anticipated a reward in the MID task. In this way, we found that not only structure that are associated with the reward pathway were activated during a reward anticipation in this task, but several of the clusters were also identified. You can see on this figure the location of these clusters.

One cluster consisted of the caudate, putamen, and nucleus accumbens, that all form part of the striatum. And this is a cluster that we named the Reward Cluster.

Another cluster that we labelled the Attention Cluster, included areas of the occipital cortex involved in early visual processing.

Third cluster, the Response Preparation Cluster, including cortical somatosensory and motor areas.

We then explored the relation of these ephemeral clusters with behavioural outcomes that are relevant for ADHD and addictive behaviours. We observed that a low activation in the reward cluster is associated with high ADHD related hyperactivity in boys. On the other hand, the Attention Cluster and the Response Preparation cluster, showed significant negative association with lifetime alcohol consumption.

Overall, our results indicate that specific reward-related brain processes relate to distinct and clinically relevant behaviours. They also indicate that functional collections related to reward anticipation, such as reward processing, attention processing, and response preparation, are differentially associated with adolescent ADHD symptoms and alcohol consumption.

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In summary, we have seen that the reward system refers to a group of structures that is involved in mediating rewarding experiences. But while it is evident that the mesolimbic dopamine pathway is implicated in pleasurable and potentially addictive behaviours, the substrates of pleasure are not confined to this system.

We have also seen that dopamine is not the only neurotransmitter involved. In fact, we have seen that the actual network dedicated to creating the feelings we associate with rewarding or aversive experiences is more complex.

Finally, I have shown you that current research using neuroimaging approaches aims at better understanding the distinct contribution of components of the reward system in psychiatric disorders, such as drug addiction, ADHD, and depression.

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