

Nerves, and fibers, and slowly built-up cells
The neurobiological basis behind 'wanting', 'liking' and compulsion

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Besides, Dorian, don't deceive yourself. Life is not governed by will or intention. *Life is a question of nerves, and fibres, and slowly built-up cells in which thought hides itself and passion has its dreams.* You may fancy yourself safe and think yourself strong. But a chance tone of colour in a room or a morning sky, a particular perfume that you had once loved and that brings subtle memories with it, a line from a forgotten poem that you had come across again, a cadence from a piece of music that you had ceased to play I tell you, Dorian, that it is on things like these that our lives depend.

- Oscar Wilde 1891

Table of Contents

Introduction	4
Behavior	5
Addiction.....	5
<i>Liking</i>	6
<i>Wanting</i>	9
<i>Compulsion</i>	10
Obsessive-compulsive disorder.....	11
Conclusion.....	12
Imaging the brain	14
Brain regions involved in liking.....	14
<i>Liking and emotion</i>	14
<i>Striatum</i>	15
Brain regions involved in wanting.....	15
<i>The nucleus accumbens and ventral pallidum</i>	16
<i>Reward prediction and the dorsal / ventral striatum distinction</i>	16
Brain regions involved in compulsion	17
Brain regions in addiction and OCD.....	17
Conclusion.....	19
Subsets of the brain	20
Intracranial self administration.....	20
The ventral striatum.....	21
<i>The VTA-accumbens pathway in reward prediction</i>	21
<i>The ventral striatum in addiction</i>	22
Ventral Pallidum.....	23
Dorsal striatum	23
<i>Habit formation</i>	23
<i>In addiction</i>	24
<i>In compulsive spectrum disorders</i>	24
Other systems associated with addiction and OCD	25
<i>Executive control by the OFC and ACC</i>	26
Conclusion.....	26
Nerves, fibers, and slowly built-up cells	28
Dopamine vs. opioids	28
Dopamine.....	29
<i>Dopamine in anhedonia</i>	30
<i>Two types of wanting</i>	31
<i>Dopamine in reward learning</i>	33
<i>Dopamine in automated behavior and compulsion</i>	34
Adenosine and the A2A Receptor	34
Conclusion.....	35
Zooming out	36
Insight and Willpower	37
Conclusion	38
Acknowledgements	41
References	41

Introduction

This thesis will deal with ‘wanting’, ‘liking’ and compulsion and the role they play in addiction and OCD. In this thesis we’ll be ‘zooming-in’ on the problem, starting with a description of the behavior followed by several chapters focusing on the specific brain regions involved and finally a discussion of the relevant neurotransmitters. To do this we will be discussing addiction and obsessive compulsive disorders (OCD). These are examples of disorders in which ‘wanting’, ‘liking’ and compulsion have been implicated. We’ll then look at imaging studies and other experiments that have identified the brain regions involved in the behavior that we are interested in. To really try to understand the neural substrate of ‘wanting’, ‘liking’ and compulsion the specific cells and mechanisms will have to be explored, this will be done in chapters three and four. These two chapters, the key chapters of this thesis, will deal with the core of the problem: the exact cells and mechanisms that produce ‘wanting’, ‘liking’ and compulsion. In the words of Oscar Wilde we will be investigating: *‘(the) nerves, and fibres, and slowly built-up cells in which thought hides itself and passion has its dreams’*.

The main question and sub question that have been used as the basis of this thesis are:

What is the neurobiological difference between ‘wanting’, ‘liking’ and compulsion?

Sub questions are:

Is there a common mechanism behind obsessive-compulsive disorder and addiction?

Can ‘wanting’ and ‘liking’ be dissociated: is it possible to want something while not liking or vice versa?

How relevant is the known basis for these behaviors found in animals for humans, can we not consciously ‘override’ these systems?

This last question that may have seemed straightforward to Oscar Wilde (“life is not governed by will or intention”) but not everybody is ready to accept this. A situation that can have a serious influence on the way we deal with and treat addicted patients.

Behavior

Discussing 'wanting', 'liking' and compulsion isn't just a 'fuzzy' subject for neuroscientists to have philosophical discussions about during fancy dinner parties. There is a significant clinical relevance to studying these concepts. If we can show that 'wanting', 'liking' and compulsion are mediated by specific regions in our brain we can start treating disorders in which 'wanting', 'liking' and compulsion are implicated as true diseases. It is important to realize that mental diseases such as addiction and OCD can be traced back to a malfunctioning brain (an organ) in much the same way as heart disease to a malfunctioning heart (also an organ). Addiction and OCD should not be stigmatized as 'lack of volition', but as disorders of the systems that cause volition.

To cover the behavioral aspects of 'wanting, 'liking' and compulsion two disorders in which these concepts have been implicated, i.e. addiction and OCD, will now be discussed. This chapter will deal with question one and two of our research sub-questions: Is there a common mechanism behind obsessive-compulsive disorder and addiction? And: Can 'wanting' and 'liking' be dissociated: is it possible to want something while not liking it?

Addiction

In this thesis addiction is taken to refer to what in the DSM-IV is called 'substance abuse' (DSM-IV, Koob 1997). The symptoms of drug addiction, as they are defined in the DSM-IV, have been interpreted as follows (Koob 2009):

- A compulsion to seek and take the drug
- Loss of control in limiting intake
- Emergence of a negative emotional state

In this thesis three main theories about drug addiction will be briefly discussed. These theories are not at all mutually exclusive. In all of these theories it is assumed that drug taking starts out at a conscious voluntary behavior (it is liked) that transforms into a compulsive (destructive) disorder. The theories differ however on the underlying mechanism that may involve either: automated behavior, devaluation of the drug or sensitization for drug cues.

Drug use as an automated process – A large amount of the actions daily performed by humans consists of automated behavior. Think of driving a car, or playing the piano. These are actions that we can perform almost without being aware of it. Automated behavior acts as a computer program with the following hard-wired rules: stimulus -> response. It is effortless, fast and performed without conscious awareness of control. In normal life, this is not a problem, in fact: we depend on it. It would be impossible to drive a car if every individual motor action, like changing gear or steering, would require conscious (non-automated) behavior. The same goes for playing the piano. Now according to Stephen Tiffany automated behavior may play an important role in addiction (Tiffany 1990). Think of a situation in which a cigarette is handed a smoker trying to quit, the taking (accepting) and lighting of the cigarette can be an automated process whereas abstaining from smoking will involve a conscious (effortful) process. In fact, most people will argue that the first behavior is more

likely to be automated and *not* performing a preprogrammed (automated) behavior is actually a task that requires consciousness and effort.

Another important aspect of this theory is the fact that the function stimulus - response does not incorporate value. Otherwise stated: this behavior will persist after devaluation of the reward, an important aspect of drug addiction.

It is important to realize that automated behavior, under normal circumstances, can be controlled by conscious action. Only when this is no longer possible (this is a malfunction in the system caused by the drug) do we speak of involuntary (compulsive) drug taking or drug addiction. We lose control when we are unable to inhibit our impulses, a process (involving the frontal cortex) extensively described in the drug-addiction literature (For instance: Jentsch 1999, Groman 2009).

Hedonic allostasis – A very prominent theory on addiction comes from George Koob (Koob 1997, 2004) Koob supposes that to the hedonic aspects of drug taking there is an opposing effect. The body (always in search for homeostasis) resets its reward thresholds after (chronic) drug use. This (the lowering of the hedonic set point) is called hedonic allostasis. Allostasis differs from homeostasis in that a given set point is not maintained but changes. In practice drug use will result in a negative emotional state in which the abuse itself is maintained by negative reinforcement: drugs are taken to inhibit withdrawal. The not taking of a drug will result in the build-up of increased stress, which is only relieved by the taking of the drug. The drug taking itself does no longer need to be pleasurable (Koob 2005).

Incentive sensitization – This theory makes a dissociation between ‘liking’ and ‘wanting’ (Berridge 2007). According to Berridge and Robinson drug dependence is mediated by sensitization of the neural substrate of incentive salience. This means a significant increase in ‘wanting’ the drug following a drug-associated stimulus (like an injection syringe or a Pavlovian associated stimulus light in an animal model.). ‘Liking’ (or reward) mediate initial drug use but not the drug dependence as confirmed by addicts who claim that they no longer like the drug but still use it.

This chapter will deal with addiction as a process starting out with ‘liking’ followed by ‘wanting’ and resulting in compulsive behavior. All four theories just mentioned, attribute some importance to ‘liking’, ‘wanting’ and compulsion as they do to ‘reinforcement’ (discussed under ‘liking’), ‘incentive salience’ (discussed under ‘wanting’) and ‘habits’ (discussed under compulsion).

Liking

Drug use in the beginning must be done voluntarily (in humans) so it figures that the drug must be ‘liked’ at first (Koob 2009). Although we can think of exceptions: teenagers may start abusing alcohol under peer pressure, not because they like it. In the case of cocaine use it has been shown that there is a correlation between positive effects of initial use and the tendency to use again (Davidson 1993).

Is 'liking' a conscious concept? - At first sight it is; people will described 'liking' as the conscious awareness of hedonic feelings. But conscious perception may not be a prerequisite of 'liking'. When people are presented with subliminal images (which they do not consciously perceive) of happy vs. angry faces this influences their appreciation and consumption of a beverage (Winkielman 2005). It is important to realize that the subjects in the study of Winkielman were unaware of the effect of the subliminal stimulus they had received. Thus, a happy face put the participants in a higher 'liking' state without them being consciously aware of it.

Expression of 'liking' - There are many similarities in the expression of 'liking' in both humans and other animals. In Jerusalem, Steiner has extensively studied 'liking' expressions in newborn humans and primates (Steiner 2001). His data combined with data from Grill and Norgen (Grill 1978) gives us several examples of evolutionary consistent behavior regarding 'liking' and 'disliking'. When human newborns, primates, monkeys and even rats are presented with a sweet taste (for instance a sucrose solution) this elicits typical positive affective behavior: tongue protrusions, hand licking, and others. A bitter taste, quinine for instance, results in negative affective reactions: gapes and headshakes (Berridge 2000, 2008). Not all animals express the same expressions of 'liking' and 'disliking', but there is great overlap. Humans however, are the only animals that express the true Duchenne smile¹ (Steiner 2001).

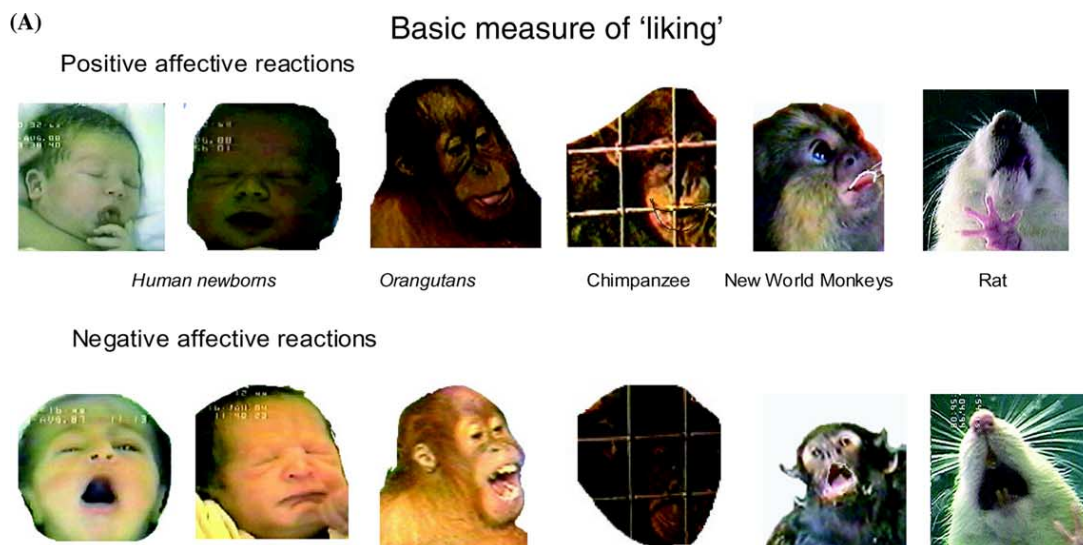


Figure 1: Positive and negative affective behavior consistent in human newborns, primates, monkeys and rats. Positive affective behavior ('liking') includes tongue protrusions and lib smacking whereas negative affective behavior ('disliking') includes gaping and grimaces.

Although there are slight variations between different species, 'liking' and 'disliking' behavior is easily recognizable by a casual observer, as can be seen in figure 1 and a motion picture on the website of the lab of Kent Berridge. This shows the face validity of the model, one of the three basic premises for a good

¹ The Duchenne smile is characterized by contraction of the muscles around the eye resulting in 'crow's feet'. Supposedly humans are unable to voluntarily produce a Duchenne smile without genuine pleasure.

animal model. Predictive validity is given by the similarities in response to a sweet or a bitter taste in humans and other animals. The construct validity of this model will be dealt with in chapter three and four of this thesis.

The identification of specific 'liking' and 'disliking' behavior is important because this behavior is quantifiable (i.e. it is possible to count how much tongue protrusions an animal makes following a stimulus.) and therefore forms the basis of a lot of animal research in this field. In humans, another method to assess 'liking' or 'appreciation' would be to simply ask the participant, but this question alone will force the participant to consciously assess his feelings, biasing the results. Apart from that, adult humans may give 'socially acceptable' answers. Research has been done to see if adult humans still express the same characteristic behavior as newborn infants. The problem is that although adult humans do express this behavior, they have a very strong conscious control over it. It has been shown that facial expression following odor presentation is more related to the experimental situation (whether or not the subject is aware he or she is observed) than to the liking or disliking of an odor (Gilbert 1987).

The role of 'liking' in addiction – As mentioned before, initial drug use is usually voluntary in humans. This assumes that the drug must be liked by the subject to continue drug use. However, liking does not seem to have too much to do with addiction- unlike initial drug taking. Drug addicts persist in drug seeking behavior when the drug itself is no longer liked (Berridge 1995).

Subjective responses to drug use can be assessed using the 'Addiction Research Center Inventory' (ARCI). This is a questionnaire of about 550 questions that has been shown to be precise and useful in the past (Haertzen 1963). Specific parts of the ARCI deal with euphoria and other subjective feelings following drug use; these have been used to investigate the role of 'liking' (and 'wanting') in addiction. It has for instance been shown that although 'liking' a drug is associated with further use, addicts report that drug 'wanting' plays a much bigger role (Lambert 2006). As described below: an increasing amount of research points toward a major role in the addiction process for wanting and especially compulsion as opposed to liking.

Reward ('liking') in reinforcement – A reinforcer is an event that increases the likelihood of a specific behavior that preceded it. The presentation of sucrose will for instance increase lever pressing by an animal, if it has learned that these lever presses result in a sucrose treat. This sucrose treat is a positive reinforcer, examples of negative reinforcers are withdrawal symptoms. A negative reinforcer causes continuation of the behavior by *not* appearing. The word sucrose "treat" implies reward and thus 'liking' (a reward is supposed to be rewarding, thus liked). Berridge does not make a very clear distinction between reinforcement and reward. Other scientists however do make this distinction. Everitt and Robbins (Robbins 2007), for instance, claim that there is a distinct difference between reward or subjective (hedonic) feelings and reinforcement. Reinforcement, they claim, can be traced back to specific brain regions whereas the substrate for reward would be very hard to identify because it is related to so many different aspects of the stimulus. There are many distinct ways in which a stimulus can be pleasing and these are mediated by five different senses. Similar

distinctions between reinforcement and subjective liking were found in a study by Lamb et al. (Lamb 1991), discussed in the next paragraph.

Wanting

'Liking' and 'wanting' are to a great extent "entangled". At first sight, it seems logical that we want what we like and if we like something better, we'll want it more. However, it's just not that simple: several experiments have shown that it is possible to like something while not wanting it and the other way around.

'Wanting' as a neuroscientific concept refers to the (implicit) drive that an animal (humans included) has to obtain a reward. It is relatively easy to measure. If we teach an animal that work (for instance: the pushing of a lever) will result in reward we can measure how much work (lever presses) the animal is willing to do for the reward, thus how much the reward is wanted.

Wanting can be unconscious. – Lamb et al. (1991) used a setup in which five male participants were given the opportunity to work (lever press) for different doses of morphine and a saline control. The participants did not know what they would receive, but they did understand that the drug and concentration they received on the first day of the week would not be changed throughout the week. As expected, a high dose of morphine had a strong reinforcing effect on lever pressing: participants were willing to press more than four times per second for over ten minutes. When the subjects received a placebo they did (apart from during the first day of the week) not press the lever. The remarkable finding in this study was that the participants vigorously pressed the lever in an 'all or none' fashion even for a very low dose of morphine. Analysis of the subjective effects of the drug using ARCI showed that the subjects were not consciously aware of any effect of the low dose of morphine. This experiment is important because it shows that even humans can work for something without consciously perceiving it as pleasurable.

Wanting can be discerned from liking – Several researchers have tried to disentangle wanting and liking in both humans and animals. In humans, the possibility to 'just ask them' remains open, but there are some difficulties to this. When asked, people may not be able to distinguish 'wanting' and 'liking' themselves and give the wrong answer. Also (as mentioned before) when participants are forced to consciously be aware of 'wanting' and 'liking' this awareness itself will make a difference to their answer, as they will incorporate social acceptability and other criteria in their answer. The only correct way to measure 'wanting' and 'liking' in humans is to measure it without the participants being explicitly aware of this. This was, for instance, done by Finlayson et al. (Finlayson 2007), who devised a method to distinguish 'wanting' and 'liking' for different types of food.

In this study, hungry participants were presented with high quality photos of different types of food. They were then asked about hedonic feelings evoked by surrounding this food ('liking') using the questions: "how pleasant would it be to experience a mouth full of this food now?" This is a questionable measure of 'liking', the participants did not experience the taste of the food so what was measured might actually be 'wanting' the food or the 'liking' the picture. Finlayson et al. did, however, devise a nice way to measure 'wanting'. They used

a 'forced choice paradigm', in which participants were forced to choose between two types of food which one they would like to eat the most now (Finlayson not using the word 'want' on purpose). After presenting all the different types of food in different pairs, using this paradigm it was possible to assess 'wanting' scores for the different types of food relative to each other.

By testing the participants for both 'liking' and 'wanting' in a hungry state and in a satiated state (using a commercially available pizza) Finlayson showed that 'wanting' and 'liking' are differently affected by satiety. Savory foods were wanted less and liked more in the satiated state compared to the hungry state whereas sweet foods were wanted more but liked less in the satiated state. These results may have been influenced by the test meal that was used to create a satiated state (the pizza) but they do show a relatively successful attempt to separately measure food 'liking' and 'wanting'. These results also show that 'wanting' and 'liking' can be differently affected.

Incentive salience – This refers to the fact that rewards and reward-associated stimuli are appetitive stimuli that attract attention and become wanted (Berridge 2007). In other words, to an animal that really *wants* something these stimuli will 'pop out' of the environment. Suppose that a certain stimulus is always paired with a reward, such as a light signal preceding a treat in a Pavlovian context or drug paraphernalia to a drug addict. These stimuli will evoke feelings of 'wanting' more and more and will take up larger and larger portions of the subject's attention. As an example: drug addicts devote disproportionately large amounts of their attention to objects that remind them of their favorite drug, creating a severe feeling of 'wanting' (craving). This 'increased sensitivity' to the drug cue is what keeps these addicts vulnerable to relapse.

Wanting in addiction, incentive sensitization – The incentive sensitization theory by Robinson and Berridge (1993) states that after repeated drug use patients become addicted as a result of sensitized 'wanting' but not 'liking'. Patients may not experience increased hedonic feelings but changes in their mesolimbic system (discussed in chapter three and four) will cause them to be more sensitive for drugs and drug-associated cues (incentive salience). Even when the patient has been abstinent for a while, he remains highly sensitive for these cues, creating vulnerability for relapse. The theory would explain the behavior of drug addicts in an elegant fashion and sensitization does certainly play a role in drug addiction, but the molecular and behavioral evidence stating that it is the major cause of drug addiction is rather scarce (as explained in chapter 4).

Compulsion

Compulsion, relating to addiction, refers to the continuation of an action regardless of aversive effects or devaluation of the reward. Compulsion in OCD also refers to the continuation of an action after devaluation (It used to be useful, but has lost its function after unnecessary repetition.). There are models that measure continuation of an action after devaluation, although they are usually used in their relationship to 'habit', which is related to, but not the same as, compulsion. Most of these models involve indeed devaluation of the reward (Faure 2005, Yin 2005). Models more specific to compulsory behavior in drug

addiction look at behavior following the appearance of aversive stimuli during reward seeking (Vanderschuren 2004). These are of course associated with the definition of substance abuse: the continuation of drug-seeking regardless of devaluation of the reward or aversive effects.

Measuring compulsion - A often cited paradigm to show compulsive drug-seeking in animals was developed by Vanderschuren and Everitt in 2004 (Vanderschuren 2004). They showed that rats would refrain from drug seeking if they are exposed to a previously conditioned aversive stimuli: a cue predicting a foot shock. However, after prolonged cocaine exposure (comparable to drug addicts) the cue was no longer able to inhibit drug seeking. This is a clear example of continuation of drug seeking regardless of aversive stimuli, an important aspect of compulsion. It is important to realize that the compulsive drug-seeking was caused by the effects of chronic drug taking, thus distinguishing occasional recreational drug use and real addiction. Also: according to Vanderschuren and Everitt, a natural reinforcer (sucrose) is unable to produce the same effect, again indicating the unique property of drugs of abuse to create compulsive behavior.

Compulsion and habit formation – Habits make life easier. As discussed before: we wouldn't be able to drive a car or hit a tennis ball over the net if it weren't for automated behavior. Habits refer to sequences of automated behavior of the stimulus -> response form. Habits are formed when behavior that may initially be performed to obtain a reward (action -> outcome mediated), is trained to be performed as a fixed sequence of actions, no longer sensitive to the outcome (Graybiel 2000, 2008). This definition of habits suggests that they somewhat related to compulsive behavior; especially the insensitivity for the current value of the reward is striking. It has been suggested that habits play an intermediate role when drug use becomes compulsive (Everitt 2005).

Compulsion in drug addiction – As pointed out by Vanderschuren and Everitt (Vanderschuren 2005) “Not the mere procurement and use of drugs, but the fact that patterns of seeking and taking become compulsive after prolonged drug use is a defining characteristic of drug addiction.” Thus: there is no addiction without compulsivity. ‘Liking’ and ‘wanting’ may play a role in the initial drug taking and in occasional recreational use of drugs; true addiction is associated with compulsive (involuntary) drug intake. Whether or not the compulsive drug-taking is caused by automated (habit) behavior (Tiffany 1990) in combination with loss of inhibitory control (Jentsch 1999), increased sensitivity to drugs and drug-predictive cues (Robinson 1993) or hedonic allostasis (Koob 2005) remains debatable, but most scientists will agree that addiction is not caused by lack of willpower, but is a destructive compulsive mental illness. In fact, there are many links with compulsive disorders such as OCD, as will be discussed in the remainder of this chapter.

Obsessive-compulsive disorder

Many people claim or appear to have some kind of obsessive or compulsive behavior. An often-used example involves little children who will only step on the edges of tiles. But many adults do have some kind of obsessive / compulsive behavior, including ‘checking’ behavior: “did I really lock the door?” Only when

these behaviors start influencing daily life and when they become a serious threat to normal functioning can we speak of obsessive-compulsive disorder (OCD).

OCD is a highly prevalent anxiety disorder. As the name implies, it is characterized by both obsessions and compulsions. Obsessions are recurrent thoughts that the patient unsuccessfully tries to avoid. Compulsions are unwanted behaviors that the patients feel compelled to perform. Often compulsions are a response to an obsession: "Did I lock the door?" followed by : checking if the door is locked.

There are other OC-spectrum disorders including Tourette's syndrome. The high co-occurrence between Tourette's syndrome and OCD and the fact that these disorders have a similar phenotype suggests that they may have a similar neural background (Graybiel 2000).

The semantic similarity between addiction and compulsive disorders is easily made. Addicts are "obsessed" with the drugs and drug seeking behavior is "compulsive". As discussed before, compulsion is an integral aspect of addiction, whether or not the same neural substrates underlay compulsion in both addiction and OCD is one of the main questions of this thesis.

As to the behavioral aspect: an important similarity regarding compulsive behavior in these two disorders is that in both cases the patients are usually aware of their disorder. They (unsuccessfully) try not to engage in compulsive behavior and the outcome of the behavior (reward) is no longer of interest.

Conclusion

In this chapter a short introduction to both addiction and obsessive compulsive disorder has been given. One of the main questions of this thesis is whether or not these disorders are actually similar in a neuroscientific sense. So far we have only analyzed behavioral aspects of these disorders, but there seem to be many similarities. Although they do not agree on the underlying mechanisms, all theories on drug addiction state that drug use becomes compulsive. This compulsion may be mediated by several different mechanisms as is true for obsessive compulsive disorder.

As to the second sub-question of this thesis: there is some evidence to suggest that it is possible to want something without liking it or the other way around. This evidence is debatable, however. In fact: most instances in which something is wanted while it is not liked may actually represent the beginning of automated behavior, habits or even compulsion. Think of drug addicts (like the ones participating in the study of Lamb et al. (1991), previously discussed) who pursue drugs while no longer liking them. They may explain their behavior as 'wanting to take drugs' but we would probably explain their actions as compulsive. Robinson and Berridge, in their incentive sensitization theory, hypothesize that dissociated and heavily increased 'wanting' is what causes compulsive drug seeking in addicts.

A different example is animals liking food but not being willing to work for it, as demonstrated by Salamone et al. who showed that rats become highly sensitive

to high fixed ratios (having to do a lot of work for food) after dopamine depletion, but still 'like' to eat (Salamone 2001). This may be interpreted as dissociation of 'wanting' and 'liking'. Perhaps it can be stated that liking something but not being willing to work for it is the opposite of compulsion. This is something that will be explored in the following chapters of this thesis.

Imaging the brain

With the invention of PET, SPECT and fMRI, modern neuroscientists now have the possibility to actually 'look into the human brain' to reveal the neural substrate of a typical behavior. Especially fMRI has given the field of cognitive neuroscience a tremendous impulse. It is important to realize that fMRI measures an indirect signal: the BOLD (blood oxygen level dependent) signal. Although active neurons are bound to need more oxygen, this technique remains an indirect measurement of neuron activity.

Since we have discussed 'wanting', 'liking' and compulsive behavior in the last chapter, we are now going to 'zoom in' to the neural substrate of these phenomena. The first step is the identification of specific brain regions for which several imaging studies will be discussed. After the identification of important brain regions the function of these regions will be discussed in more detail in chapter three.

Brain regions involved in liking

To identify the regions that underlie our feelings of 'liking', fMRI has been used. The experiment that seems obvious is the following: put a subject in the scanner, make him or her 'like' something, use a neutral control and compare brain activation in these two situations ('liking' VS control). Unfortunately, it's not that simple. Liking is very difficult to pinpoint to a specific brain region, because of its multidimensional nature (think about the liking / reinforcement distinction). Also there is a difference in measuring 'liking' and the conscious awareness of 'liking', thus when participants are asked to evaluate whether or not they 'like' something, results obtained in an imaging experiment may actually represent the process of consciously evaluating and not 'pure liking'.

Taking into consideration the difficulties of this research several researchers have tried to pinpoint the brain regions involved in 'liking' using an innovative approach. Simply comparing the effects of a not-liked versus a like stimulus is not sufficient. The different stimuli will differ from each other in multiple aspects creating experimental variability. Small et al. circumvented this variability by administering the same stimulus (chocolate) in different states: eager to eat chocolate vs. satiated after intake of large amounts of chocolate (Small 2001). Comparing the effects of the same stimuli when it was experienced as pleasant ('liked') versus when it was no longer experienced as pleasant (not-'liked') they were able to associate several brain regions with pleasantness. These regions have been associated with 'liking' in several studies and are discussed below.

Liking and emotion

According to the study by Small et al., the orbital frontal cortex (OFC) can be functionally divided in two sub regions. The lateral OFC responds to punishment (disliking) whereas the medial OFC responded less when the chocolate was experienced as unpleasant (after satiety) and thus seems to respond to 'liking'. Similar results were obtained by bananas and banana odor (O'Doherty 2000). The OFC is involved in taste (flavor) processing (Small 2007). This suggests that the identification (salt, sour) of a stimulus and its appreciation can be mediated by the same brain region. The OFC has also been shown to respond to pleasant

touch (Francis 1999) and nice music (Blood 1999). Rolls et al. have shown that a specific sub-region of the OFC reacts to pleasant somatosensory (touch) stimuli (Rolls 1999).

The subcallosal region is found to be associated with 'liking' or 'pleasantness' in several studies. It has been shown to react to pleasant taste (Small 2001). Both Brown and Blood (Brown 2004, Blood 1999) found a strong association between activity in the subcallosal region and pleasant music. Royet did not find this association with music but did show an association between pleasant / unpleasant olfactory and visual stimuli and the subcallosal region (Royet 2000). The subcallosal region plays a prominent role in studies investigating emotion. In a meta-analysis it was shown to be especially involved in sadness (Phan 2002). This is not so contradictory as might seem. Studies investigating 'sadness' often use sad music or sad pictures, which at the same time may be considered beautiful. Participants when asked to rate sadness may incorporate feelings of melancholia or nostalgia evoked by the music or visual stimulus and thus rate something 'very sad' while they still appreciate the stimulus very much.

Like the subcallosal region the Insula is very much of interest for people who study emotion. Phan et al. showed in a meta-analysis that the Insula can be associated with a wide range of emotional states, especially if the subjects are asked to recall such a state from their past (Phan 2002). The insula was associated with the appreciated taste of chocolate by Small et al. (Small 2001). Brown found an association between 'liked' music and activation in the Insula (Brown 2004) but this was not confirmed in a study looking into the effects of happy vs. sad music by Mitterschiffthaler et al. (Mitterschiffthaler 2007). The insula plays a key-role in the work of Antoine Becharra this will be elaborated upon in the last chapter of this thesis.

Several other regions that are associated with emotion are likely to play a role in subjective appreciation of stimuli. These include the the Amygdala (Zald 1998), the parahippocampal gyrus (Blood 1999) and the anterior cingulate cortex (Brown 2004).

Striatum

The striatum, consisting of a dorsal and ventral part, has been implicated in 'liking' or pleasantness in several imaging studies (e.g. Mitterschiffthaler 2007). Other (non-imaging) approaches have also implicated this brain region especially with 'wanting', but also with 'liking'. Whether or not the striatum plays an important role in 'liking' or just in reinforcement remains debated, some scientist argue that manipulations of the striatum can results in increased 'liking' of a stimulus (Kelley 2002, Peciña 2008) but their evidence for this statement is debated as discussed in chapter four.

Studies implicating the *dorsal* striatum in 'liking' are sparse, although there are some examples, including a study by Small et al. (Small 2003). That showed a correlation in dorsal striatum activity with pleasantness ratings of a meal.

Brain regions involved in wanting

The easiest approach to measure wanting is to expose subjects to pictures of things they want versus pictures of things they do not want. This approach has in

fact been explored by many research groups with varying results. The problem is that participants may actually 'like' the pictures themselves or may not understand the questions they are asked refer specifically to 'wanting' not to 'liking'. Many such studies have shown great overlap between regions involved in 'liking' and 'wanting'. As an example: studies investigating the neural basis of craving (for chocolate, cocaine and marijuana) have repeatedly shown a correlation with the insula, the subcallosal region and the OFC (Rolls 2007, Filbey 2009, Kilts 2001).

The nucleus accumbens and ventral pallidum

As described in the first chapter, wanting can be measured best when the subjects are unaware of this. It is possible to evoke unconscious wanting using subliminal images of motivational stimuli. In humans, useful motivational stimuli include monetary rewards. This principle was used by Pessiglione et al. in an elegant study to measure brain activity associated with wanting (Pessiglione 2007).

In this study, participants were exposed to subliminal images of either a penny or a pound (a significant difference in value). This image represented the amount of money the participants could win by exerting force on a handgrip. Even if the participants did not consciously perceive the stimulus (penny or pound) their motivation to exert force was still increased when they had been exposed to a pound. This increased motivation correlated with increased activity in the ventral pallidum, a major destination for projections from the nucleus accumbens.

The nucleus accumbens seems to emerge often in studies investigating 'wanting'. Studies in which participants are exposed to pictures of things they want almost never fail to report a correlation with activity in the nucleus accumbens (Kilts 2001, Volkow 2009, Filbey 2009 but see Pelchat 2004). Many imaging studies have indeed associated both the accumbens and the ventral pallidum with 'wanting' or 'craving' for natural rewards and drugs of abuse, respectively (Rolls 2007, Kilts 2001, Franklin 2007), but not necessarily with 'wanting' in experienced drug users (Childress 2008, Filbey 2009).

Reward prediction and the dorsal / ventral striatum distinction

Reward prediction is a very important concept when we talk about 'wanting' or motivation in general. It seems natural that we 'want' things to which we attribute a high value. Thus, there is a direct link between 'wanting' and reward prediction. This corresponds to the function of the ventral striatum, which has also been associated with reward prediction (Berns 2001).

O'Doherty et al. link the function of the ventral striatum as a 'reward predictor' or 'critic' to the function of the dorsal striatum as an 'actor' (O'Doherty 2004). When participants are exposed to a stimulus that will be followed by a reward (pavlovian conditioning) they learn to predict the reward value on the basis of the stimulus. The difference with *operant* conditioning is that participants are actually asked to base a decision (pursue or not pursue the reward) based on the stimulus. In an ingenious study O'Doherty et al. showed that the ventral striatum is involved in both ways of conditioning, reflecting the necessary reward

prediction. The dorsal striatum however was specifically involved in operant conditioning relating to the aspect that an action must be performed on the basis of the predicted reward.

This corresponds to the actor – critic model, a model originating from computational neuroscience. In this model an ‘actor’ performs a response to a stimulus on the basis of a reward prediction. The ‘critic’ uses the value of the reward, in its relation to the predicted reward (prediction error), to update the reward prediction signal for future use. The dorsal striatum is indeed involved in stimulus – response reactions, linking it to compulsion as discussed later on in this chapter. The ventral striatum has been linked to reward prediction and prediction error in several studies, especially by Wolfram Schultz (Schultz 1997), this will be explored in chapter four.

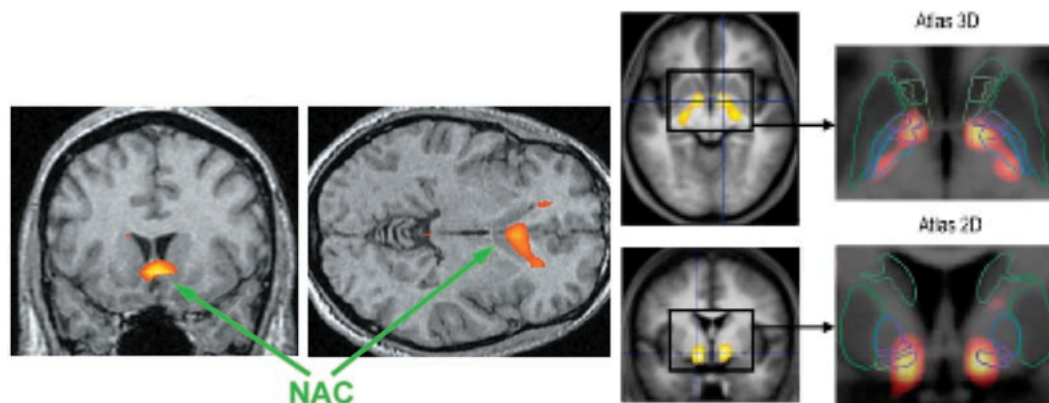


Figure 2, LEFT: Berns et al. (2001) show that the nucleus accumbens (main part of the ventral striatum) is active following an unpredicted reward. RIGHT: Pessiglione (2007) correlated increased activity in the ventral pallidum (blue) below the ventral and dorsal striatum (green) with increased motivation to obtain a reward.

Brain regions involved in compulsion

The main brain regions especially associated with OCD are: the basal ganglia, the anterior cingulate cortex, the orbitofrontal cortex and the thalamus (Rauch 1998, Huey 2009, Friendlander 2006). Note that most of these regions have been shown to be implicated in both ‘liking’ and ‘wanting’. Within the basal ganglia especially the caudate nucleus (part of the dorsal striatum) has been implicated in automated signal – response behavior (Graybiel 2000).

As mentioned before, the OFC plays a role in the recognition of rewarding stimuli (liking), but has also been associated with ‘wanting’. The basal ganglia, including the ventral and the dorsal striatum, have been associated with ‘wanting’, but also with automated behavior, such as playing the piano or riding a bicycle. This indicates an important link between automated behavior, habits and compulsive behavior. Many researchers point towards the important role that automated behavior plays in compulsion (for instance in OCD) in the form of ‘fixed action patterns’ (FABs) (Graybiel 2008) or ‘structured event complexes’ (SECs) (Huey 2009).

Brain regions in addiction and OCD

It is no surprise that the striatum has often been associated with addiction. Although the ventral striatum has traditionally been the focus of addiction

research, more and more data points to a role for the dorsal striatum after prolonged drug intake. A very elegant example of this is a study by Porrino et al. who show changes in glucose metabolism in monkeys after initial or chronic (3.3 months) cocaine intake (Porrino 2004a, 2004b). A clear demonstration of how drug related changes in the striatum move from the ventral, limbic ('wanting') striatum to the sensorimotor ('automated, habitual') dorsal striatum.

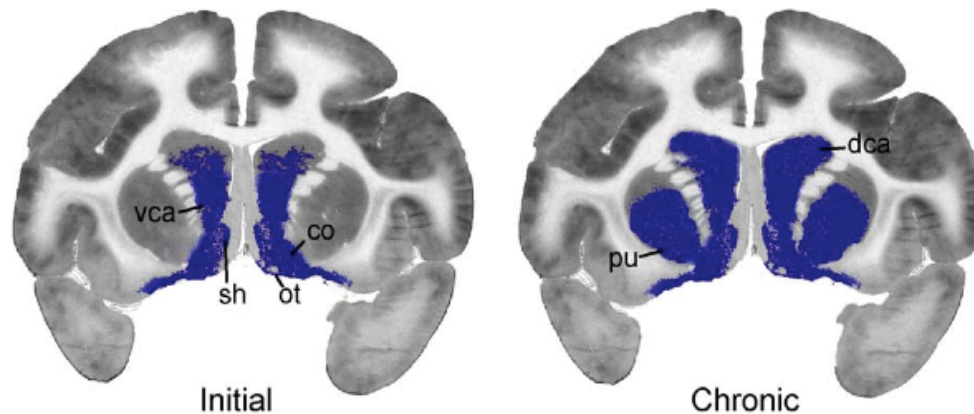


Figure 3 Porrino (2004) using The [C_{14}]Deoxyglucose method to measure glucose metabolism showed decreased glucose metabolism of the lateral dorsal striatum after chronic drug use (right) but not after an initial cocaine injection (left).

Most of the regions discussed before to be related to 'wanting' and 'liking' have been found to have altered activity in addicted individuals. The ventral striatum, orbitofrontal cortex and the anterior cingulate cortex have been found to be altered in substance abuse (Breiter 1997), cigarette craving in smokers (Franklin 2007) and even in gaming addiction (Chih-Hung Ko 2009).

Imaging studies in OCD patients usually involve the comparison between patients and controls performing implicit learning tasks, delayed reward tasks or other tasks with which OCD patients commonly have problems. The overlap with brain regions involved addiction and OCD is striking. The orbitofrontal cortex, anterior cingulate cortex and basal ganglia have been associated with OCD in imaging experiments (Remijnse 2006, van den Heuvel 2005, Peterson 1998). Patients with lesions in the striatum and the pallidum have shown OCD-like symptoms (Laplane 1989). Based on imaging experiments, cortico – striatal dysfunction has been supposed to be the foundation of OCD (Graybiel 2000, Rauch 1998).

Cortico–striatal function refers to the control that the prefrontal cortex has over the striatum. Apparently, within the prefrontal cortex, especially the orbitofrontal cortex is responsible for interpreting data about rewards (the outcome of actions) and via its connections to the striatum maintains action–outcome based behavior (Torregrossa 2008). In, what is probably the most famous lesion study ever published, a patient named Phineas Gage had his OFC (and a large portion of the rest of the prefrontal cortex) removed in an accident. This caused behavioral changes resulting in 'impulsive' behavior (Harlow 1868, republished 1993). In fact (as just mentioned), the OFC is found to be altered in both addiction and OCD, relating to the role that impulsive, stimulus-response mediated, behavior plays in these disorders (Jentsch 1999, 2008, Groman 2009).

Some even claim that basal OFC metabolism can be a predictor for responsiveness to treatment in OCD patients (Brody 1998).

Conclusion

A hypothesis seems to emerge here. Liking, as in the subjective evaluation of stimuli, is a very broad concept that touches upon multiple aspects of neuroscience, including taste perception and emotions. In order for a stimulus to be liked, several aspects have to be taken into consideration.

- The identification of the stimuli. This may be loud, soft, sour, salt etc. Regions that are involved in the identification of stimuli do seem to play a role in the subjective evaluation of these stimuli.
- Emotional aspects of the stimuli. This is reflected in the activity of the subcallosal area and the insula, but also the amygdala (Castriota-Scanderbeg 2005).
- A 'liked' stimulus may or may not be reinforcing. This is probably where the (ventral) striatum comes in. More evidence for this will be discussed further on in this thesis.

Wanting, shares many regions, including the OFC with 'liking', but is especially correlated with activity in the dorsal and ventral striatum. Imaging studies have shown that the striatum may be responsible for calculating the value of a predicted reward and thus may be deciding how much a reward should be 'wanted'. It is likely that the ventral striatum plays a role in the updating of a reward prediction based on experiences, while the dorsal striatum uses this prediction to perform an action in response to a stimulus.

It's difficult to pinpoint a specific brain region responsible for compulsion, but there are regions involved in habitual and automated behavior, such as parts of the basal ganglia including the (lateral) dorsal striatum. A core aspect of compulsion may be this automated (stimulus - response) behavior in combination with failed inhibition (impulsivity) by the prefrontal cortex. This is not only a major overlap between OCD and addiction but also explains co morbidity with impulsivity-related disorders such as attention-deficit hyperactivity disorder (ADHD) and addiction (Potenza 2009).

Subsets of the brain

In the first two chapters the difficulties in distinguishing 'liking', 'wanting' and compulsion were introduced and a number of specific regions were discussed. In this chapter, we will take a closer look at these systems and their involvement in addiction and compulsive disorders.

Intracranial self administration

1954 was a very important year for this field of neuroscience. In that year Olds and Milner published their (now famous) self stimulation experiments (Olds 1954). Using intracranial electrodes, they identified regions in which an electrical stimulation has a reinforcing effect, causing the rat to vigorously respond for stimulation. They also identified regions of which animals will try to avoid stimulation and neutral regions. Now, some 56 years later, thanks to intracranial self-stimulation, lesion and pharmacological experiments, many brain regions responsible for 'wanting', 'liking' and compulsion have been identified.

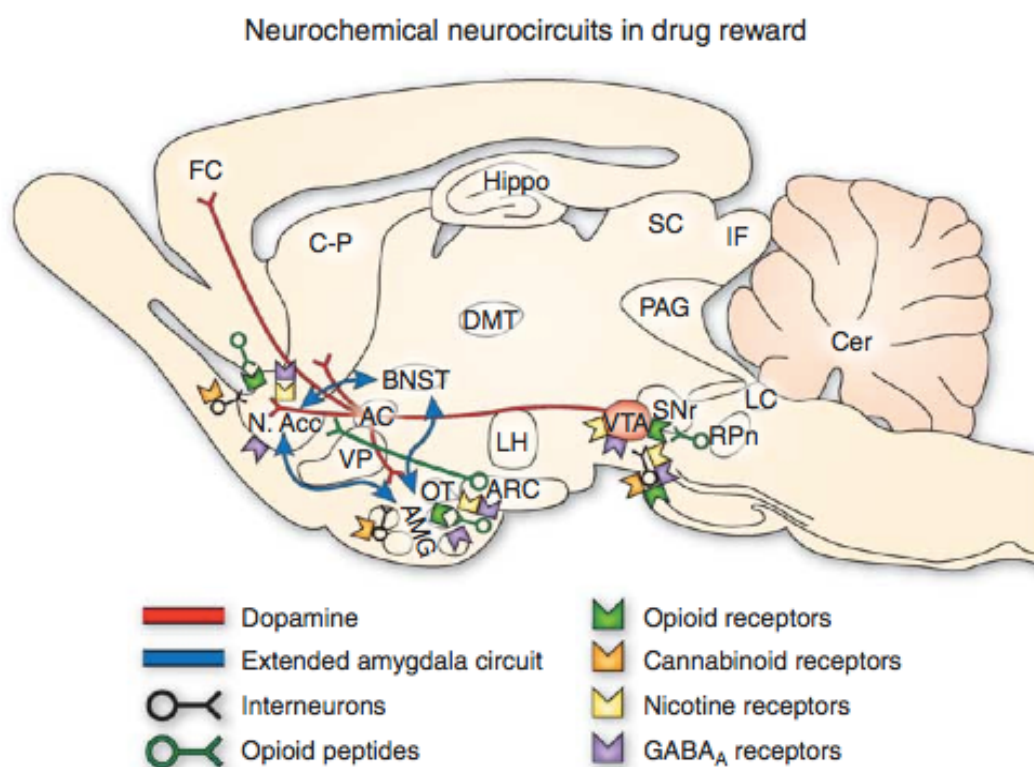


Figure 4: From Koob, Volkow 2009 and Koob 2005. This image shows the primary brain regions that are involved in the immediate rewarding effects of drugs. It is after decades of research that we are now able to show that different addictions are actually mediated by the same brain regions. FC = Frontal cortex, C-P = caudate putamen, N.Acc = nucleus accumbens, VP = ventral pallidum, AC = anterior commissure, AMG = amygdala, OT = olfactory tract, BNST = bed nucleus of the stria terminalis, ARC = arcuate nucleus.

Figure 4 shows an overview of the most important brain regions discussed in this thesis and the connections between them. This figure was taken from an article by George Koob and Nora Volkow, two leading scientists in the field of drug addiction (Koob 2005, 2009). In this figure, several regions that have been

implicated in drug addiction can be seen. The nucleus accumbens for instance, that (as described before) plays a key role in many different drug addictions. Both cocaine and amphetamine can influence nucleus accumbens activity directly and the nucleus accumbens can also be influenced by opioids. This can be either via the opioid receptors on the accumbens itself or via the VTA, which contains opioid receptors and projects to the accumbens. Apart from this, cannabinoid and nicotine receptors are shown, next to GABA_A receptors that play a role in alcohol consumption.

In this picture, not too much attention is paid to the dorsal striatum (Caudate putamen or C-P) and its innervation from the substantia nigra. Indeed, the dorsal striatum may not be directly influenced by drugs of abuse, but after the reward is recognized and learned in the system depicted here, reward seeking becomes more and more automated and finally compulsive mediated by the dorsal striatum. This will be explained further in the following paragraphs.

Apart from being involved in drug addiction, these structures have a normal role in our behavior and the processing and anticipation of natural rewards. That is: they are all of significant importance for 'wanting', 'liking' and compulsion.

The ventral striatum

The VTA – accumbens pathway is one of the most studied pathways in this field. The VTA is the origin of dopamine-containing neurons that project to the nucleus accumbens. It is clear that within the ventral striatum especially the nucleus accumbens plays a very important role in both 'wanting' and 'liking' rewards. Lesion studies have shown that the nucleus accumbens plays a major role in sucrose preference (Martínez-Hernández 2006) and conditioned place preference. Manipulations in the accumbens can influence both 'wanting' and 'liking' (Faure 2010, Kelley 2002, Peciña 2000, 2008 Salamone 2009). Activity in the nucleus accumbens has been associated with behavior in anticipation of a palatable meal (Mendoza 2005), feeding (Pritchett 2010) and exertion of effort (Mingote 2008).

The VTA-accumbens pathway in reward prediction

As indicated in chapter two, this pathway plays an important role in reward prediction. This has been confirmed in several behavioral experiments. A very nice one came from Yun et al. (2004). They injected a GABA_B agonist (baclofen) into the VTA and showed that this has an important effect on animal behavior following a reward-predictor. Normal rats, after training, responded to a discriminative stimulus (DS) by performing a nose poke to obtain a sucrose reward. When VTA function was impaired following a baclofen injection, the rats responded correctly to a DS (reward predictor) in far less occasions. As seen in figure 5, there is even a dose-dependent effect. The authors then went on to show that a dopamine receptor antagonist in the nucleus accumbens has a similar effect. They then used in-vivo electrophysiology to confirm the connection between these two effects by showing that inhibition of the VTA can actually attenuate accumbal neuronal firing. They showed this in a subgroup of nucleus accumbens neurons that, under normal circumstances, fired right after the discriminative stimuli. This research, taken together with the imaging studies described in chapter two, provides strong evidence that the connection between

the VTA and the nucleus accumbens plays a significant role in reward prediction. In fact: this pathway has been shown to both in humans and in rodents code for a predicted reward, not only in the case of drugs, but also for natural reinforcers like sucrose. Thus, when following the basic rationale that a higher predicted reward will result in increased 'wanting', we can not underestimate the importance of this pathway in 'wanting' behavior.

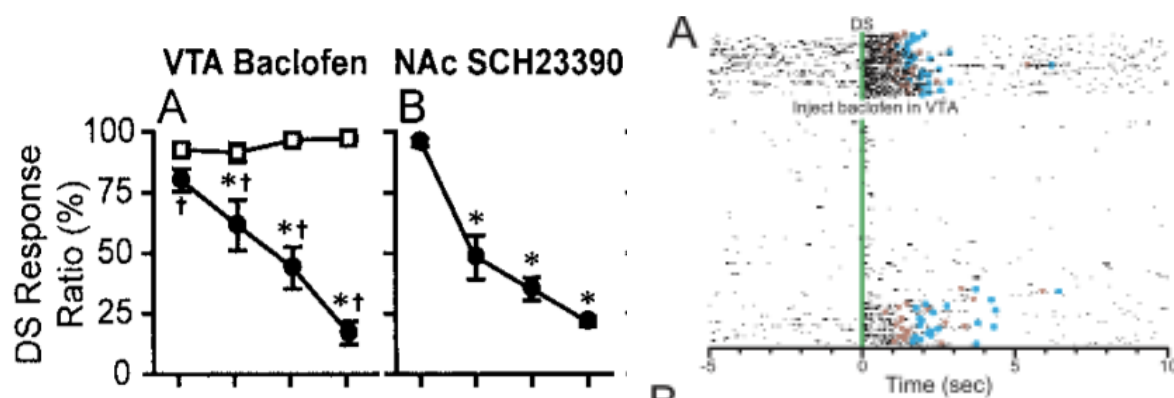


Figure 5 both from Yun et al. (2004). LEFT: behavioral responses to a discriminative stimulus (DS). Both a GABA-B receptor agonist (Baclofen) in the VTA and a D1-receptor antagonist in the accumbens inhibit operant responding to a discriminative stimulus. Normal responding is indicated by the white rectangles on the left. RIGHT: Electrophysiology experiment measuring neuronal firing in the core of the nucleus accumbens following a DS. Black dots represent neuronal firing, orange and blue rectangles represent operant behavior (nose poking) and entry of the reward receptacle respectively. Injections of baclofen into the VTA inhibit both neuronal firing and operant behavior. Even during recovery, the latency of entry into the reward receptacle remains increased.

The ventral striatum in addiction

It is important to realize that the thesis defended here is not that an addiction is just an increased form of wanting. Addiction is a disease influencing the systems that underlie 'wanting', 'liking' and compulsion. A good example of this can be found in the VTA - Ventral striatum pathway. Here we find an important difference in the underlying factors that cause the pathologic behavior in addiction and wanting of a natural reinforcer. Chen et al. (2008) found that although self-administration of both natural reward (sucrose, food) and cocaine increases activity in the VTA, only cocaine creates long lasting effects and synaptic plasticity changes. This gives some insight in how drugs cause disease by 'hijacking' our conventional reward system.

Since the ventral striatum is of importance for both 'wanting' and 'liking', it is very likely that it influences the intake of natural reward and / or drugs of abuse. Indeed, infusions of opioid-receptor agonist into the ventral striatum have resulted in increased intake of palatable food, normal chow, sucrose solution and ethanol (Zhang 2002, Kelley 2002). This would suggest that opioid activity in this region may 'sensitize' the system for further rewards.

Although research seems to focus on the biggest part of the ventral striatum: the accumbens, the olfactory tubercle is also likely to play a role in 'wanting' and addiction. Ikemoto showed that the ventralmost part of the striatum, the olfactory tubercle, is especially sensitive to cocaine self-administration (Ikemoto 2003). Cocaine was self-administered marginally in the accumbens shell but,

self-administration into the accumbens core and the dorsal striatum was negligible compared to self-administration into the olfactory tubercle. In this research the olfactory tubercle was also shown to be important for conditioned place preference for cocaine.

Obviously, the ventral striatum mediates the rewarding aspect of the drug, corresponding to the initial phase of addiction in which the drug is still 'liked' and 'wanted'. But even in experienced drug users the nucleus accumbens mediates craving (Volkow 2009). Changes in 'wanting' do play a role in addiction, as stated by Berridge & Robinson who presume that increased sensitivity to drug cues causes more 'wanting' of the drug (Berridge 1995, 1998). They fail, however, to fully explain addiction. Drug treatment does indeed create sensitization for drug related cues, but also increases motivation for natural rewards (Mendez 2009). Human drug addicts, however, go great lengths to obtain drugs *at the expense* of natural rewards such as food, sex and social contact.

Ventral Pallidum

The ventral pallidum (VP), which is a major output structure of the accumbens plays an important role in motivation and / or reward. Indeed, it has been shown that animals readily self-stimulate this region (Panagis 1995). The VP has been implicated in disorders of motivation (Napier 2010) and lately, in vivo electrophysiology experiments have shown a correlation between neural activity in the VP and cocaine seeking behavior (Root 2010). It has been shown that both lesions of the ventral pallidum and its afferent the medial dorsal thalamus attenuate conditioned place preference (McAlonan 1993). This supports the importance of the VTA, accumbens, VP, thalamus network in reward recognition and possibly reward learning.

Dorsal striatum

In the last chapter the crude distinction was made between 'wanting' mediated by the ventral striatum and automated behavior (habits, compulsion) mediated by the dorsal striatum. Although this distinction may be oversimplified and some imaging studies proposing different results were discussed, it does seem to be more or less valid.

The dorsal striatum, which is innervated by dopamine neurons from the substantia nigra, has been described as being of major importance for automated behavior such as cycling or gearing using a manual transmission. It also plays an important function in the later phase of drug abuse. The involvement of the dorsal striatum in stimulus – response actions also points to an important overlap between OCD and addiction, which are both characterized by stimulus – response actions instead of action – outcome mediated behavior.

Habit formation

The data linking the dorsal striatum to stimulus – response behavior is overwhelming. An example of a recent experiment linking the dorsal striatum (especially the lateral part) with this behavior comes from an electrophysiology experiment by Kimchi et al (Kimchi 2009). In this experiment neurons in the dorsal striatum of rats were monitored while they learned an operant task. It

turns out that the amount of dorsal striatal neurons responding to the task increased while the task is learned. Also, certain aspects of the task became insensitive to reward devaluation (habitual) early on in the learning process. Not only is there a relation between the dorsal striatum and habit formation, it is required for habit formation. This has been shown in devaluation studies, and example of which is study by Yin et al. (2004). In this study animals are trained to obtain a sucrose reward by pressing a lever. When the sucrose reward is devaluated using taste aversion (pairing the sucrose reward with a lithium chloride injection, which makes the animal feel sick) the rats will stop consuming sucrose. But when they are placed back into the operant chamber for an extinction trial (in which no sucrose is delivered) normal rats will start to press for sucrose. Lever pressing has become habitual in these rats. They respond to the stimulus (the lever) with an action (lever pressing) regardless of the outcome (feeling sick). Rats with lesions in the dorsolateral striatum however no longer press for sucrose after it has been devalued, there behavior is still action – outcome based. Again, the effect seems to be stronger in the lateral part compared to the medial part of the dorsal striatum. In fact, in a related paper Yin et al (2005) show that lesions of the dorsal*medial* striatum inhibit outcome based behavior and stimulate stimulus – response type behavior.

In addition

Although the ventral striatum plays an important role in the initial ‘wanting’ of drugs, it is likely that the actual addiction is maintained by automated behavior mediated by the dorsal striatum. This can be seen in animals that have been trained to exert effort (lever press) to obtain an intravenous injection of cocaine paired with a stimulus light. This light can then become reinforcing in itself (conditioned reinforcer), causing animals to vigorously lever-press when they are exposed to just the light. This process (in pre-trained rats) can be attenuated by dopamine antagonists in the *dorsal* striatum (Vanderschuren 2005).

The theory of addiction as a process developing from the ventral striatum to the dorsal striatum is very elegant, and the resemblance with the situation of drug use transforming from liked to wanted to compulsive behavior is striking. What is even more important is that a system that could mediate this process has actually been identified. A series of fiber tracing experiments has shown how reciprocal connections between the ventral midbrain and the striatum create a system along which information can ‘spiral’ from the ventral (limbic) to the dorsal (motoric) striatum (Haber 2000). Neurons from the striatum do not only receive input from the VTA and the substantia nigra, they also send afferents back. These neurons terminate in their own region in the midbrain (which is organized along a similar gradient as the striatum). However, the receiving regions in the midbrain overlap in such a way that some information from (for instance) the accumbens shell end up in a region associated with the accumbens core. The dopamine neurons from this region will then, via GABAergic interneurons, be disinhibited and be more likely to fire, stimulating the accumbens core and restarting the cycle.

In compulsive spectrum disorders

With its function in habit formation and stimulus-response guided behavior, the dorsal striatum seems a prime candidate to be malfunctioning in OCD. As seen in

chapter two, the dorsal striatum has indeed been implicated in OCD. Behavioral experiments have also indicated an important role for (especially the lateral) dorsal striatum in compulsive behavior. However, it is difficult to establish if the role of the dorsal striatum in OCD is similar to its role in addiction. This is (among other reasons) due to the lack of good animal models for OCD or other compulsive spectrum disorders.

The current model for OCD implicates the striatum as a whole in so-called cortico-striatal-pallidal-thalamal-cortico loops (Menzies 2008). The function and exact composition of these loops is not completely agreed upon, but it is known that they play an important role in the mediation of automated behavior. Especially the connections from the OFC to the striatum and on to the thalamus have been suggested to play an important role in OCD (Graybiel 2000, 2008).

Animals with lesions in the dorsal striatum may exhibit compulsive symptoms and there is evidence to suggest that this region plays a big role in compulsion. Humans with lesions in the striatum can display OCD-like behavior (Laplane 1989) and deep brain stimulation in the caudate nucleus seems to be beneficial to OCD patients (Aouizerate 2009). These studies, combined with the imaging studies described in chapter two, implicate the dorsal striatum in OCD, but it is difficult to explain what exactly is happening in OCD patients inside this brain region.

Other systems associated with addiction and OCD

The striatum being the integrating center of the limbic system has been the focus of addiction research and together with the OFC stands high on the list of favorite brain regions for OCD scientists. As mentioned in the last chapter, however, there are other areas that should also be discussed. These include the amygdala, hippocampus and the anterior cingulate cortex. An overview of these areas is presented in figure 6 which (in this case) was taken from work of Barry Everitt and Trevor Robbins, but appears often in similar forms in the scientific literature in the addiction field.

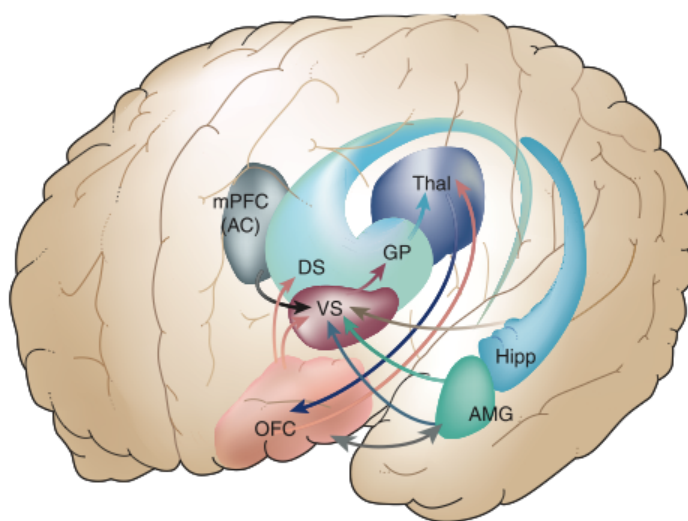


Figure 6 (Everitt & Robbins 2006) The brain regions so far identified to be involved in drug addiction (and OCD). AC = anterior cingulate, DS = dorsal striatum, VS = ventral striatum, GP = globus pallidus, Thal = thalamus, Hipp = hippocampus, AMG = amygdala, OFC = orbital frontal cortex.

The role of the ventral striatum with its input from the VTA, prefrontal cortex, amygdala and its output to the thalamus via the ventral pallidum, was previously discussed. This circuit is responsible for outcome-based behavior. A lot of these areas were also identified in chapter two in relation to both 'wanting' and 'liking'. This suits with their role in outcome-based behavior such as sucrose preference and conditioned place preference in animals and the initial stages of drug addiction in humans. The dorsal striatum, which also projects to the thalamus but via the internal and external segment of the globus pallidus, however, has been implicated in automated, habitual and even compulsive stimulus – response type behavior and thus the final phase of drug addiction. The difference between the first (limbic) and the second (motor) circuit can be seen more clearly in figure 7. Another set of regions shown in these illustrations and their role for 'wanting', 'liking' and compulsion should be discussed in more detail.

Executive control by the OFC and ACC

Under normal circumstances, humans and other animals are able to control their urges and cravings. An example of this is when we refuse a short-term small reward to get a larger award at a later point in time. This can be tested in both humans and animals and turns out to be under prefrontal control (Page 2009, Burke 2008). A way to look at it is to suppose that these brain areas have executive control over the basal ganglia inhibiting inappropriate (and / or automated) behavior and making sure that behavior remains action – outcome based or becomes automated after training when this is more relevant (in the case of playing tennis for instance). Indeed, manipulations of (especially) the OFC result in impulsive and even compulsive behavior (Latagliata 2010). This shows the link between compulsive and impulsive behavior: both have to do with the incapability to control urges or impulses. Overlap between impulsivity and sensitivity to drug addiction has indeed been shown in animal models (Belin 2008,) and in the human population (Potenza 2009). The frontal cortex is connected to the striatum via the cortico-striatal circuits (Lehéricy 2004) and these circuits have received increasingly more attention in the field of both addiction and compulsive-spectrum disorders.

Conclusion

In this chapter the most prominent brain regions in the field of addiction and OCD were analyzed with respect to their role in 'wanting', 'liking' and compulsion. As discussed in chapter 1, it has been suggested that addiction transforms from voluntary ('liked' and 'wanted') behavior into compulsive inflexible drug seeking. A similar transition from involvement of the ventral striatum to involvement of the dorsal striatum can be seen in animal models for drug addiction. Indeed, a rough distinction can be made between brain regions associated with action – outcome behavior, 'wanting' and 'liking' and brain regions associated with automated behavior, habit formation and compulsion. These areas are summarized in figure 7 that shows the regions from the former group in yellow and the later group in gray.

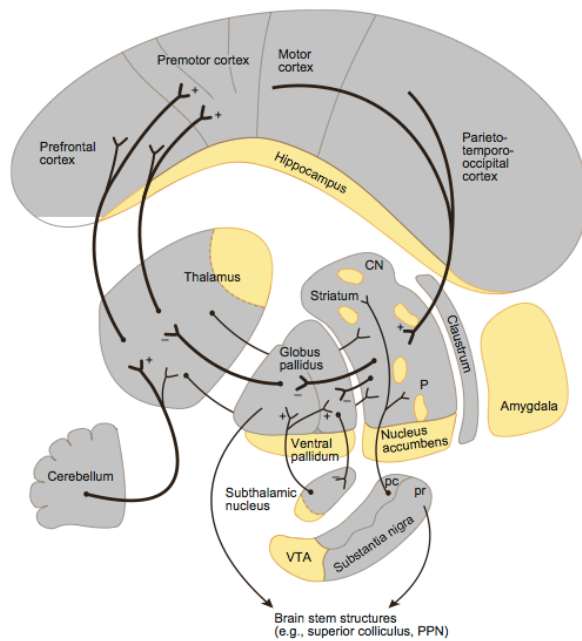


Figure 7 (Graybiel 2008). The regions of the motor (gray) and limbic (yellow) circuits, organized in a peculiar form, to emphasize the cortico- striatal- pallidal- thalamico- cortico 'loop', clearly seen in this picture.

Addiction and OCD are not only caused by the basal ganglia gone astray. A very important role has been assigned to the OFC and the anterior cingulate cortex. These brain regions are (under normal circumstances) capable of inhibiting automated behavior performed by the striatum. Interactions between the cortex, the accumbens, the amygdala and the hippocampus in fact mediate action - outcome behavior, and lesions in these regions can result in impulsive, stimulus response behavior. As can be seen in rats who express impulsive behavior after hippocampus lesions (Cheung 2005) or humans acting impulsive in the Iowa Gambling test after ventralmedial prefrontal cortex damage (Becharra 2005).

Nerves, fibers, and slowly built-up cells

In the first three chapters the difficulties in distinguishing 'liking', 'wanting' and compulsion have been introduced. Although specific brain regions have been associated with 'wanting' and 'liking', it remains difficult to distinguish these two concepts. In this chapter a series of experiments will be discussed that targeted the specific cells that underlie 'wanting' and 'liking'.

Dopamine vs. opioids

It has been suggested before that both opioids and dopamine play an important role in 'wanting' and 'liking'. In the last chapter it was made clear that practically all drugs of abuse influence dopamine and/or opioid systems resulting in reinforcement, compulsion and preoccupation (Koob 2009). It has been stated that dopamine and opioid have dissociable functions in which dopamine mediates 'wanting' and opioids mediate 'liking' (Flavia Barbano 2007, Berridge 2007). Berridge et al. showed that dopamine depletion causes a decrease in 'wanting' (of food) but not in 'liking'. This was demonstrated by destroying dopaminergic fibers using 6-OHDA and then measuring behavioral responses. Wanting can be assessed by measuring the willingness of an animal to perform effort to obtain a reward. Liking is identified by facial expressions and other typical behavior as discussed in chapter one. It seems 6-OHDA mediated dopamine depletions do not attenuate sucrose preference. The animals are still able to express 'liking' behavior when sucrose is administered and they express 'disliking' behavior when they receive quinine (a bitter substance used in the production of tonic) (Berridge 1998). These and other experiments showed that dopamine is not required for the 'liking' of natural reward: as stated by Barbano & Cador: dopamine lacks involvement in food palatability evaluation (Barbano 2006, 2007).

Opioids, on the other hand, have convincingly been shown to mediate the hedonic qualities of food. They mediate food intake only in sated rats (when the food is not taken because it is needed, but because it is liked) (Barbano 2007). And even in humans an opioid antagonist (naltrexone) can decrease the perceived palatability of food (Yeomans 1997, 2002).

As to the function of opioids, this seems to be related to the area in which they are released. Within the brain, so-called 'hedonic hotspots' within the nucleus accumbens, ventral pallidum and parabrachial nucleus have been identified in which opioid infusions significantly increased 'liking' responses of an animal (Peciña 2000, 2008). Some scientists go as far as to state that these 'hotspots' are the only brain structure *causally* involved in 'liking' (Kringelbach 2009, 2010). According to them, all other brain structures relating to 'liking' (as identified in chapter two) may *code* the 'liking' signal and play a role in the conscious perceiving of 'liking', but are not *necessary* for 'liking' it itself. In support of this: patients who lack those frontal regions such as the OFC are still able to express 'liking', appreciation and joy. Again, this comes down to a semantic problem, how do we define 'liking' as opposed to 'reward' and 'reinforcing'? Then there is the question of the validity of the model itself: Berridge et al. do not present

thorough evidence that the facial 'liking' expressions are synonymous to the experience of 'appreciation' in humans.

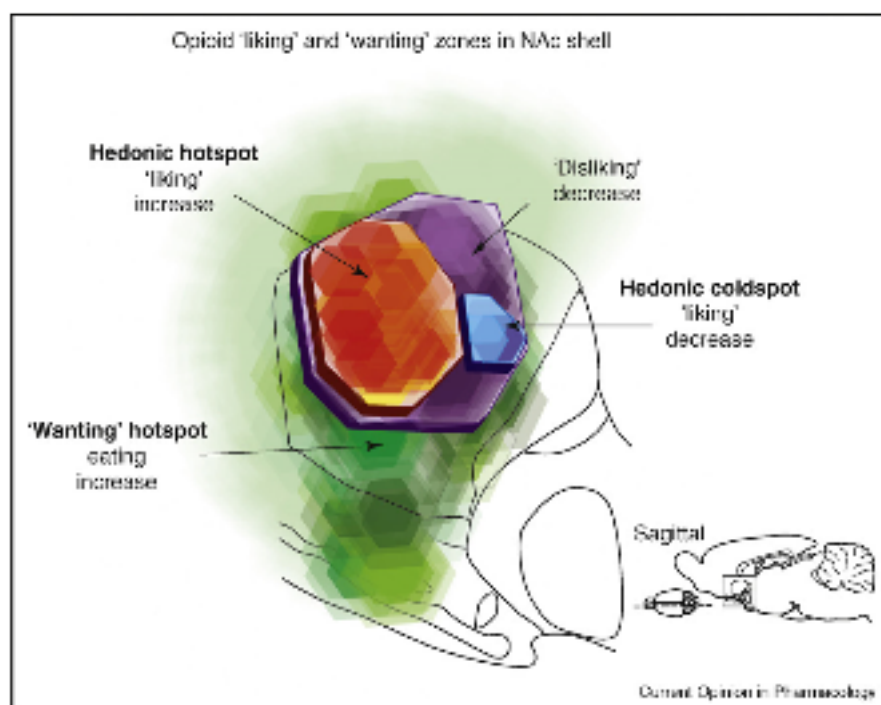


Figure 8, Peciña 2000: Opioid infusions in the nucleus accumbens shell produce different effects in different locations. An infusion may result in 'liking increase', 'disliking decrease', 'liking decrease' or a 'wanting increase'. Apparently the nucleus accumbens is not a homogenous structure as the same substance has different effects in different sub-regions.

The sharp distinction between the function of dopamine and opioids does not go uncontested. Especially the role of dopamine has been criticized. Dopamine has been proposed to mediate: reward, reward learning, incentive salience and attention. These theories do not all exclude each other and some of them are further described below. There is also some criticism as to the function of opioids (especially μ -opioids). μ -opioid receptor knockout mice have been shown to display diminished food anticipation (Kas 2004) and there is some data indicating that within specific brain regions opioids may stimulate 'wanting' (Peciña 2008).

Dopamine

Concerning addiction, dopamine is one of the most important and most discussed neurotransmitters. It seems clear that dopamine has something to do with reward, but opinions differ on its exact function.

Dopamine is not an excitatory, like glutamate, or an inhibitory, like GABA, neurotransmitter. It is a modulatory neurotransmitter, a very important aspect of dopamine as this enables its heterogeneous function.

One of the first identified functions of dopamine is the mediation of motor behavior. This function, primarily mediated by dopaminergic neurons from the substantia nigra (close to the VTA) to the dorsal striatum, is impaired in disorders related to movement initiation such as Parkinson. This role of dopamine is not specifically addressed in this thesis. Rather the role of dopamine

in the mesolimbic and the mesocortical system is described. It seems that dopamine's role in 'wanting' and 'liking' is mediated in these two systems. The nigrostriatal pathway however does seem to play a role when behavior becomes habitual. This points at the close link between the motor behavior and habits. Both relate to the execution of automated programs, we don't consciously think about every individual movement when we hit a ball, we just initiate an automatic motor program in response to a stimulus (the ball when we intent to hit it.).

Dopamine in anhedonia

Following up on the self-stimulation experiments of Olds and Milner (Olds 1954) people began searching for the neuronal mechanisms and the neurotransmitters that mediated the vigorous self stimulation of so called 'pleasure centers' (Olds 1958). Actually, Olds himself together with Travis showed that a dopamine receptor antagonist (Chlorpromazine) could attenuate electrical self stimulation (Olds 1960). Dopamine was shown to be very relevant to the motivational aspects of a reward, such as an electrical stimulation. Roy Wise postulated a hypothesis on the mechanisms behind the influence of dopamine on motivation (Wise 1978).

According to Wise, a dopamine antagonist does not attenuate the motivation and animal expresses to obtain a reward by impairing basic motor behavior initiation. This could have been expected based on the known role of dopamine in the nigrostriatal pathway. Wise believed (but not necessarily still does (Wise 2004, 2008)) that dopamine mediates the hedonic value of a reward and that a dopamine antagonist devaluates reward. He bases this conclusion on the fact that animals perform less lever presses to obtain a reward under dopamine blockade, together with data in human subjects showing that euphoria-inducing drugs, like amphetamines, also increase extracellular dopamine and that neuroleptics produce anhedonia.

The anhedonia hypothesis does not go uncontested. Although it is clear that dopamine can mediate motivation, the fact that it does so by mediating reward value has been heavily criticized. As described before, Berridge et al. claim that dopamine depletion does not attenuated facial liking expressions. Wise responded by claiming that facial liking is just a basic response corresponding to the valence of a substance "more a part of swallowing than of smiling" (Wise 2008). This however was disproven by Berridge et al. who showed that the same substance (water with a high salt concentration) can evoke different facial expressions under different circumstances: normal animals dislike high salt water, but salt-deprived animals show facial liking expressions (Tindell 2006).

One of the best arguments in favor of the anhedonia hypothesis comes from an experiment by McFarland and Ettenberg (1995, 1998). In this experiment, it was found that haloperidol (a dopamine receptor antagonist) does not have an effect on the amount of time that rats require to cross a runway to obtain a heroin reward. The next day however, when the rats are allowed to run for a heroin reward without any pretreatment, it seems that the haloperidol rats take longer to cross the runway. This caused McFarland and Ettenberg (and Wise) to conclude that a dopamine antagonist does not attenuate the direct motivation

(wanting) of an animal, but in fact devaluates the reward (heroin) itself. The animals experienced heroin under the influence of haloperidol on the first day; that caused the reward to be devalued; in turn, this caused the decreased motivation the next day (when the animals remembered the devalued reward). The important difference with the studies of Berridge and others is the timing. According to McFarland and Ettenberg, the results obtained by Berridge may be caused by devaluing of the reward because the animal receives the reward several times during the paradigm while under 6-OHDA mediated dopamine depletion. This does not correspond to the fact that the animals still express facial liking however.

It is interesting to note that the theory of McFarland and Ettenberg implies a role for dopamine in reward learning. Roy Wise is also convinced that dopamine plays a role in reward learning (Wise 2004). There are some indications that dopamine plays a role in reward learning, they are discussed further on in this chapter.

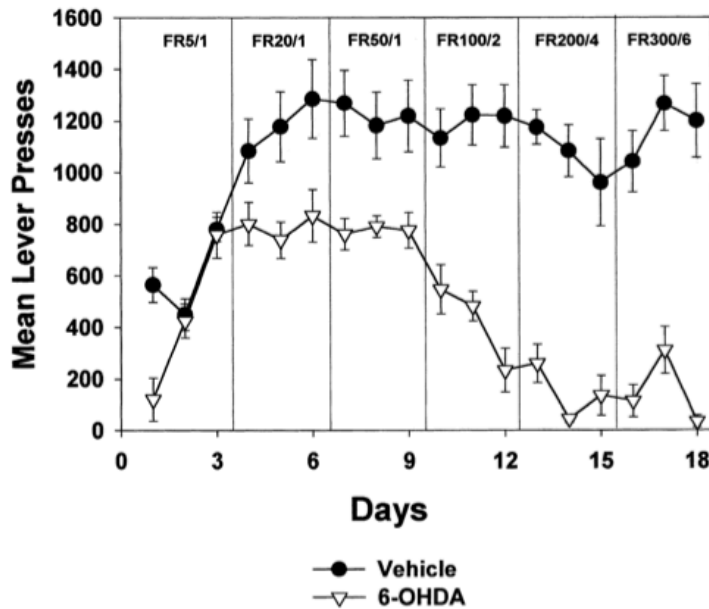
Other work relating to dopamine as coding for reward focuses on decreased dopamine receptor expression in the striatum. It has for instance been suggested that the Taq1 single nucleotide polymorphism (SNP) (That can be found near the D2-receptor gene in the genome.) is associated with lower expression of D2 receptors in the striatum and more prevalent in obese humans (Stice 2008), but this has been difficult to reproduce. The rationale is that less D2-receptors results in less reward and humans try to compensate for this by indulging in rewarding behavior like eating, or drug use (Volkow 2005). Recently, Johnson & Kenny associated decreased D2 expression in compulsive eating and increased reward threshold (Johnson 2010). These results seem to blend in nicely with reward homeostatis deficits or Koob's Hedonic Allostatic theory on drug addiction. This is the theory in which drug addicts try to compensate for the opponent processes associated with drug use. Drugs increased their reward threshold causing them to need more rewarding substances (drugs) to reach a 'normal' reward level.

George Koob is much appreciated for his work on the role of negative reinforcement, including withdrawal symptoms, in drug addiction. Dopamine as a mediator of reward is a highly contested idea however. Very compelling evidence comes from studies in mice that do not express any dopamine. These mice have show many deficits but they are still able to react to the rewarding aspects of (for instance) a sucrose solution. That is: they show conditioned flavor preference, but they are not necessarily 'motivated' to obtain the reward (Matson Cannon 2003, 2004). These results have been confirmed in many studies, including the ones from Salamone, discussed in the next paragraph.

Two types of wanting

While Berridge and Wise raise a lot of questions with there theories, Salamone proposed a more subtle (and less criticized) theory. Dopamine does not directly code for 'wanting', but rather for the willingness to perform effort to obtain a reward (Salamone 2002). To give an example: the situation where someone takes a bite of an apple that is right in front of him and the situation in which someone climbs a tree to get an apple refer both to 'wanting of the apple', but are

very different. According to Salamone, a distinction should be made between these two types of wanting, in that dopamine only plays a significant role in the second form (in which the participant had to exert effort (climb a tree) to get the apple.).



Incentive Motivation

“liking” vs. “wanting”

“Liking”

vs.

“Wanting”

Accumbens DA depletions blunt a component of “wanting”

Appetite to consume
i.e., reinforcer intake
food consumption

Activation to obtain
i.e., reinforcer seeking,
effort in working for food

Figure 9: Left: (Salamone et al. 2001) The fixed ratio is denoted as follows: FR “amount of lever presses necessary” / “amount of food pellets receive per completed cycle”. Right: (Salamone & Correa 2002) If wanting can be dissociated in two subtypes: Appetite to consume and activation to obtain. According to Salamone & Correa, Accumbens depletions impairs only one of these two subtypes.

The hypothesis of Salamone et al. was tested in an experiment in which rats were trained to press a lever in order to obtain a reward. The amount of lever presses necessary to obtain a reward varied between the sessions, but not within one session (fixed ratio). During sessions in which a high number of lever presses was necessary the rats receive a bigger reward (more pellets). Normal rats respond well to this paradigm and are motivated to press 300 times for a significant reward (FR300). In the case of the experiment shown in figure 8 the reward consisted of several food pellets and the subjects were food deprived rats.

Now dopamine depletion does not seem to impair normal functioning under this paradigm when the fixed ratios are low (FR 1 – 5). But when more effort is required to obtain a reward, dopamine dysfunction makes a big difference. As seen in figure 8, animals that are dopamine depleted in the accumbens are highly sensitive for higher fixed ratios. This can be seen in that even after a slight increase of the amount of lever presses necessary (starting at FR4) they start losing their motivation to work for food. The effect becomes more dramatic when the workload is increased, especially after FR10. In other words: they are highly sensitive for the amount of work required for a reward, even if the potential reward size is increased. This and other work resulted in the hypothesis of Salamone that dopamine is required for the willingness to exert effort to obtain a reward.

Dopamine in reward learning

Although dopamine may not be *necessary* for reward learning (Berridge 2007), animals still learn to prefer sucrose above water without dopamine (Matson Cannon 2003), it is prominently involved in reward learning.

One of the most frequently cited authors on dopamine in reward learning is Wolfram Schultz. According to Schultz, dopamine neurons encode an error-prediction signal. This signal is hugely important in computational theories of learning. It could serve as a feedback mechanism in learning systems. Suppose that a system has the task of performing an action based on a stimulus. Once it encounters the stimulus it will create a reward prediction and perform the corresponding action. Now in order for this system to *learn* there must be something to 'tell' the system whether or not the reward prediction was correct. Actually, if the prediction was correct no feedback signal will be given because the system functions just fine and no changes are necessary. Only if the reward turns out to be bigger or smaller does the system need a negative or positive return signal (the reward prediction error) to adjust future reward prediction and thus future responses to the same stimulus.

According to Schultz, dopamine neurons can fulfill this reward prediction error signal (Schultz 1997, 1998, 2000, Waelti 2001). Electrophysiology experiments in dopamine neurons showed increases in firing after a bigger-than-predicted reward and decreased in firing in a smaller-than-predicted reward. They also show that dopamine neurons (after learning) start responding to a signal predicting a reward.

This model is very elegant and it is indeed very likely that dopamine neurons play a role in reward prediction. But the arguments that dopamine is not absolutely *necessary* for reward learning / reward prediction are still true. (For instance the Cannon (2003) studies in which animals learned to discriminate between a bottle containing a sucrose solution and one containing water.) It is also very important to make a distinction between the function of dopamine *neurons* and dopamine itself. The firing of dopamine neurons does not necessarily have to result in dopamine release and incidental (phasic / burst) firing does not have to be of significant importance of the dopamine concentration in the striatum as a whole (extra synaptic). As a matter of fact, dopamine neurons have been shown to release glutamate in the nucleus accumbens (Tecuapetla 2010) and to create AMPA-mediate EPSCs in medium spiny neurons. An important distinction also has to be made between burst activity of individual dopamine neurons (such as described in the reward prediction theory) and tonic activity of a large population of dopamine neurons. Burst activity only increase the dopamine concentration within the synapse for a short amount of time. Dopamine is then rapidly removed via dopamine reuptake receptors (Floresco 2003). This activity presumably plays an important role relating to prediction error and the presentation of a stimulus indicative of a reward. Tonic activity by a population of dopamine neurons from the VTA is able to increase extrasynaptic dopamine concentration in the accumbens and this concentration may be related to the motivational aspects of dopamine previously described (Floresco 2003).

Dopamine in automated behavior and compulsion

Both the proposed role for dopamine in 'wanting' and in 'willingness to exert effort' point to dopamine as an 'activator'. Dopamine is involved in the 'vigor' of the behavioral output (Robbins 2007). This is actually a function of dopamine that goes relatively uncontested (Berridge 2007). Combined with the notion that dopamine is involved in learning, this forms the basis for the 'dopamine in automated behavior' theory. The theory states that addiction starts as a voluntary concept guided by activity in the accumbens shell and core but migrates to automated behavior mediated by the dorsal striatum. This process involves plasticity changes in the striatum mediated by dopamine. This relates to its function in reward learning.

As discussed in the previous chapters, drug addiction involved the switch from action-outcome behavior (ventral striatum) to stimulus – response behavior (dorsal striatum). Ito et al. have shown that this transition corresponds to extracellular dopamine concentrations in the ventral and dorsal striatum (Ito 2000, 2002). They showed that although dopamine levels in both core and shell respond to an infusion of cocaine, only levels in the accumbens core respond to non-contingent presentation of drug-associated conditioned stimuli. Dopamine levels in the dorsal striatum respond to conditioned stimuli when they are expressed in response to drug seeking. This fits nicely with data previously discussed showing that a dopamine antagonist in the dorsal striatum is able to inhibit cue-controlled drug seeking (Vanderschuren 2005) and data indicating that loss of the nigro (dorsal) striatal dopamine pathway inhibits habitual behavior (Faure 2005).

When a stimulus is sufficiently associated with a reinforcer and becomes reinforcing itself (conditioned reinforcers) animals will exert effort just to be exposed to the stimuli itself (not necessarily the reinforcer with which it used to be associated). This behavior is *not* dependent of dopamine, but can be amplified by dopamine as seen by the effect amphetamine injections have on this behavior (Everitt 2001). This, of course, ties into the (just discussed) theory by John Salamone about the influence of dopamine on the willingness of an animal to exert effort.

This doesn't mean that sensitization (as suggested by Berridge and al. to form the basis of compulsive behavior) doesn't play a role. In fact, it has been shown that sensitization using amphetamines results in *faster* habit learning (Nelson 2006). Amphetamines interact with dopamine projections in the dorsal striatum where they may interfere with the cortico – striatal loops and mediate signal – response type behavior (Nordquist 2007).

Adenosine and the A2A Receptor

If we define dopamine activity in the ventral striatum as a system primarily responsible for 'wanting' then adenosine may be responsible for 'not-wanting'. Especially the function of the A2A receptor has been well described (Wardas 2008). A2A receptors co-localize with D2 receptors on the cell membrane and have an opposite function on the production of cAMP (Fuxe 2005). It has been shown that stimulation of these receptors opposes dopamine functioning in that animals are no longer willing to work for palatable food, but instead prefer to eat

standard chow if that is freely made available to them (Nunes 2010). Treating animals with A2A antagonists (such as caffeine) has a opposite effect in that it is able to attenuate the effects of a dopamine antagonist (such as haloperidol) (Salamone 2009, Mott 2009). The adenosine system and the A2A-D2 heterodimer have been implicated in palatable food intake (Pritchett 2010) and even in cocaine use (Marcellino 2010).

Conclusion

The systems described in this chapter exist because they have been helpful in our evolution. Natural rewards are substances or actions (sex) that are actually good for us, so it is no surprise that needed to learn how to obtain them, thus the close link between 'wanting', 'liking' and learning. An action is perceived as 'good' and should therefore be learned until it can be easily (automatically) performed as a habit. Only when this system 'hijacked' by drugs do we 'over-learn' and start to express problematic behavior (Kelley 2002). This behavior may at first just be habitual, but after chronic drug use can become insensitive to aversive consequences and thus compulsive.

Multiple theories about the function of dopamine and opiates have been proposed and the most important conclusion is probably that there is no single function carried out by these substances. Opioids play a role in 'wanting', 'liking' and in 'disliking' dependent on the region in which they are active. The function of dopamine is debated, but most scientists attribute to dopamine a function related to 'wanting', 'salience' or 'motivation'. It is likely that dopamine performs this function while interacting with the adenosine system, which can be seen in the physical interaction between D2 and A2A receptors.

It is unlikely that dopamine codes for hedonic reward and that addiction is only mediated by increased reward thresholds and stress caused by withdrawal. That doesn't mean that this stress does not at all play a role in addiction however.

Zooming out

Addiction and obsessive compulsive disorders are diseases in which ‘wanting’, ‘liking’ and compulsion have been implicated. It is difficult for people to accept that these concepts are actually governed by cells and molecules and that these cells can be ‘sick’ just like any other cell in our body. It’s understandable that our brain is affected by drugs and that these drugs may cause our ‘inner drives’ to run loose. This is what we see in our animal experiments. But unlike animals, humans should be able to inhibit these inner drives because we are able to predict the negative consequences of certain behavior. A drug addict knows what’s best; it all comes down to a matter of willpower.

What these people need to understand is that the brain regions that *enable* us to inhibit our internal drives are actually ‘sick’ in these patients. It doesn’t matter that they know that performing a certain action is not a good thing, because their behavior is no longer based on the outcome. Drugs of abuse create severe cognitive problems, real physical damage in the brain regions that make us able to predict the outcome of our actions and to base our behavior on this. Think about the behavioral characteristics of Phineas Gage who had these regions ablated in a very unpleasant, more abrupt way than happens in most drug addicts.

Nora Volkow, current director of the National Institute on Drug Abuse puts it like this: “Drug addiction is a disease of the brain, and the associated abnormal behavior is the result of dysfunction of brain tissue, just as cardiac insufficiency is a disease of the heart and abnormal blood circulation is the result of dysfunction of myocardial tissue” (Volkow 2004). What she says becomes very relevant if you look at figure 10, a diseased heart and a diseased brain are not so different. Yet we still have individuals, even policy makers who base their opinion on a distorted view of addiction². As a matter of fact: even some addicts don’t admit that they are really addicted (I’m not addicted, I *choose* to smoke.).

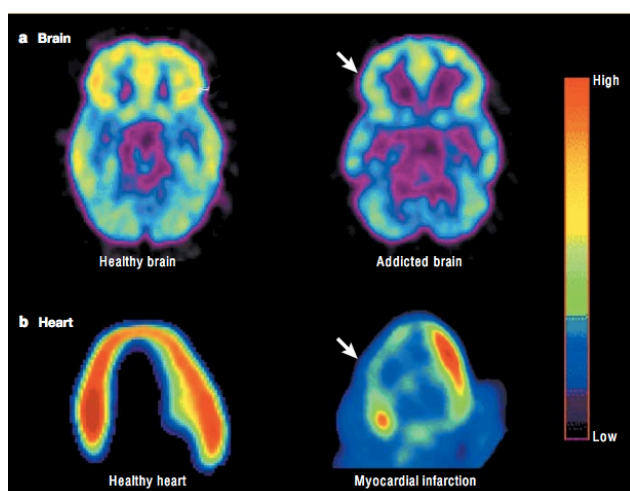


Figure 10: (Volkow & Li, 2004). The difference in glucose metabolism between healthy and diseased organs as seen using PET. Note the exact region of the brain damage, the OFC, and its function discussed in chapter two and three.

² As an example: Fleur Agema (PVV) a Dutch representative.

http://www.pvv.nl/index.php?option=com_content&task=view&id=375

Insight and Willpower

Do drug addicts realize that they are addicted and if so, why are they unable to control their addiction with willpower?

Insight into the severity of their disease is actually a major problem with drug addiction. As noted by Nora Volkow: more than 80% of all addicts fail to seek treatment. The two main brain regions involved in self-awareness and insight are the anterior cingulate cortex and the insula (Goldstein 2009). These regions have already been discussed in chapter two because of their relation with 'liking' and emotional states. Especially the insula is associated with phenomenal awareness, it receives sensory and emotional information from various regions of the brain including the amygdala, hippocampus, cortex and ventral striatum, making it a major integration center for interoception (Goldstein 2009).

It is not coincidental that the insula is involved in drug addiction. The insula is for instance associated with marijuana craving (Filbey 2009). An even more striking example comes from research from the group of Antoine Bechara (Naqvi 2007). Bechara showed that cigarette addiction could be dramatically disrupted by insula damage. Bechara studied 69 heavy smoking brain damage patients of which 32 quit smoking after the occurrence of the brain damage. 16 of these 'quitters' who probably quit because they wanted a healthier lifestyle after their brain damage, went to all the normal difficulties of quitting. The remaining 16 'quitters' had what Bechara defines as: 'a disruption of smoking addiction'. That is: 1. They stopped smoking within a day after the onset of their brain damage. 2. They never smoked again after they quit. 3. The rate of difficulty to quit as less than 3 on a 1 to 7 scale. They did not experience any urges to smoke. "As if my body forgot the urge to smoke" is a famous quote from one of the participants in this research. In these last 16 quitters with disruption of smoking addiction, patients with insula damage were greatly overrepresented (12 of 16 while only 19 of 69 total participants had damage to either the left or the right insula.). Statistical analysis showed indeed a strong correlation between having a disruption of smoking addiction and insula damage. Apparently, the very brain region that makes us capable of introspection is malfunctioning in addiction.

The role of impulsivity and the necessity to control (inhibit) the impulse to take drugs has been discussed before in this thesis. Impulsive persons have an increased risk to become addicted. But the use of drugs also damages the brain regions that inhibit impulsivity, the ventromedial prefrontal cortex (VMPC) (Bechara 2005). Drug addicts have difficulty with tests of impulsivity and decision making such as the Iowa gambling task. Bechara has shown that their decision-making capabilities are impaired. According to Bechara, willpower stems from the interaction of our impulsive system (bottom up) with our reflective system (top down) and these systems are both implicated in drug addiction. Addiction cannot be overcome with sheer willpower, because addiction is a disease of our willpower.

Conclusion

This thesis is by no means even more than an introduction to the neuroscientific background of wanting, liking and compulsion. Several important conclusions relating to the main and sub questions of this thesis can be made, however.

What is the neurobiological difference between 'wanting', 'liking' and compulsion? And the subquestion: Can 'wanting' and 'liking' be dissociated: is it possible to want something while not liking it or vice versa?

Liking, as in: the appreciation of sensory stimuli like taste, smell and sound cannot be pinpointed to one single brain region. In chapter two, several brain regions have been identified to be associated with liking. Some of these regions overlapped with the regions in which the actual sensory information of stimuli is coded, others with brain regions that have been shown to play a role in reinforcement. This corresponds to the fact that a stimulus that is liked may also be reinforcing. The difference between 'liked' and 'reinforcing' is an important distinction, as a matter of fact: a lot of the scientific discussion regarding 'liking' probably comes down to the semantic question behind it: 'How do you define 'liking'. What we (as humans) like is very subjective and difficult to describe. We can however speak about substances that are reinforcing in a pharmacological sense.

We 'want' substances that are rewarding, thus we are willing to work for it. A rat for instance may find chocolate or cocaine rewarding (and like it) and is because of that willing to work for it. At that point a distinction between 'wanting' and 'liking' is difficult to make. They are both present for this substance. The animal's behavior is governed by the outcome of its actions, as it is in humans who consciously seek something because they 'like' it (like a nice piece of chocolate). In both organisms the current behavior involves the ventral striatum and its interactions with memory (hippocampus, amygdala) and the representation of the outcome (cortex). Thus, if a choice had to be made which brain regions are involved in 'wanting' and 'liking' (as in rewarding) behavior, those would be it.

Yet it is possible to 'want' something while not 'liking' it. We may 'want' something for instance because we are afraid of the effect of not-having it. This is the case with withdrawal symptoms: the stress associated with the acute termination of drug intake. A behavior mediated by stress factors in the amygdala, and still outcome based. The question is: when we still work for something that we no longer like and we are not afraid of withdrawal (as in drug addict who have already gone to withdrawal), do we still 'want' it? This behavior is no longer outcome based and is actually compulsive behavior. In this thesis it has been hypothesized that this may be mediated by the motoric (automatic), dorsal part of our striatum.

To answer more of the main question of this thesis about the neurobiological basis of 'wanting', dopamine release in the striatum is definitely involved. Again there is the issue of the semantic definition of 'wanting', but if we define it as the willingness to work for something or, 'to exert effort to get it' dopamine release has absolutely been shown to be associated. Of course, there is a strong case to be made regarding the involvement of dopamine *neurons* in learning, and it is

likely that these neurons fulfill multiple functions, but several elegant pharmacological experiments have shown that dopamine plays a key function in the vigor with which an animal will respond to a stimulus to get a reward. Call it 'wanting' or 'attention' (relating to the stimulus) or 'willingness to exert effort'. It all relates to the presence and the vigor of the action that an animal expresses, in response to a stimulus, to get a reward.

Is there a common mechanism behind obsessive-compulsive disorder and addiction?

It would be interesting to know if there is a common neurobiological background to both addiction and OCD. The question is: is there even a common neurobiological background to all different types of addictions? As discussed at the beginning of chapter 3, different substances act via different pathways as summarized in this very nice overview from Eric Nestler (Nestler 2005):

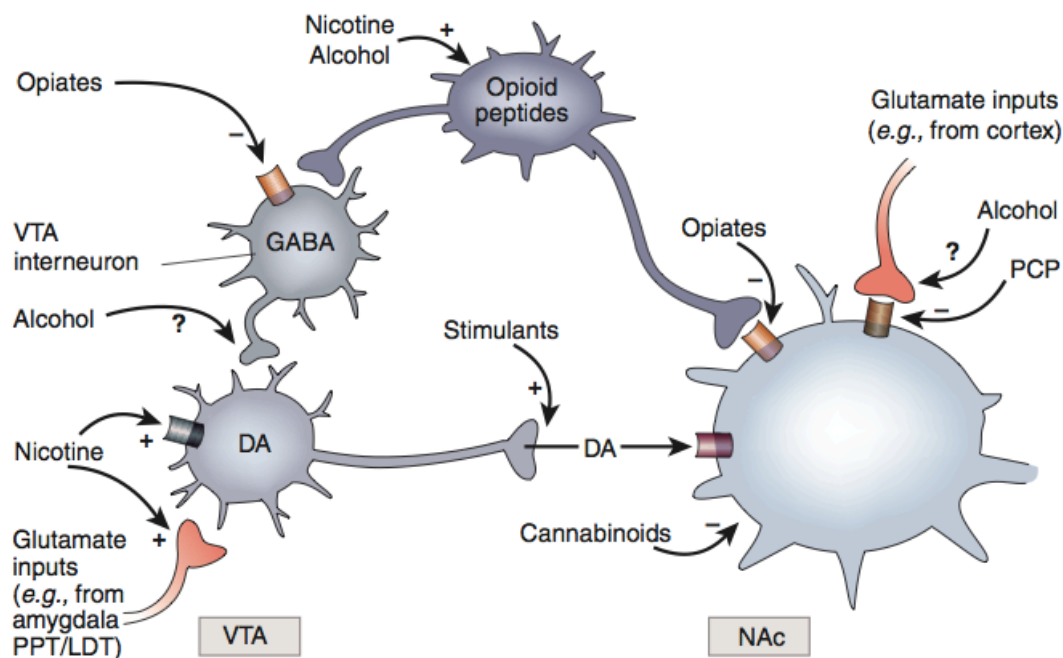


Figure 11: (Nestler 2005). Different drugs work via different mechanisms, and their initial effects may be very different (for example: stimulants vs., opioids). There is, however, a lot of overlap as well: all drugs in the end have an effect in the nucleus accumbens.

They do, however, all have an effect in the ventral striatum. This is presumably where an addiction starts (when the drug is still 'liked') after which different processes take over. Drug taking becomes habitual and finally compulsive, withdrawal from the drug becomes a stressful event. Although it is difficult to tell if the same mechanisms that mediate compulsive drug taking play a role in other compulsive disorders such as OCD, they do involve the same brain regions. Habit form in the basal ganglia (in collaboration with the cortex) is an important issue in both OCD (as described by Ann Graybiel) and in addiction (as described by Barry Everitt). Stress is also likely to play a role in both disorders. Withdrawal from drugs causes stress and not-executing an action can be perceived as extremely stressful in OCD patients.

How relevant is the known basis for these behaviors found in animals for humans, can we not consciously 'override' these systems?

The last sub-question is probably the most interesting question of this thesis, it deals with the validity of the animal models discussed in this thesis to describe the human situation. This is related to the issue that humans have difficulty to accept that our behavior can be explained by small molecules and electrical currents and that we are not so very different from non-human animals as we would like to be.

First of all, animal models have been used on humans including simple lever presses for morphine (Lamb 1991) but even second order schedules (signal lights and sounds included) (Panlilio 2005) and conditioned place preference (Childs 2009) have been tested using humans as test subjects. It appears these animal models are perfectly capable of predicting human behavior in the same situation.

There is the issue of human 'willpower'. We should be able to 'override' our inner drive because, other than rats and mice, we understand the *consequences* of our behavior. This issue has been dealt with in chapter five, the very brain systems that we need for this self awareness and to maintain behavior that is based on the outcome are malfunctioning in addicted individuals.

'Wanting', 'Liking' and compulsion are not just philosophical issues that neuroscientists talk about in their free time. They are real concepts, beautiful products of evolution, mediated by the nerves, fibers and cells of our brain.

Acknowledgements

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