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„The Role of Dopamine in Wanting of Primary Rewards"

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Theoretical background

The hedonic principle states that there are two basic motivational driving forces for human behavior: One is the avoidance of negative experiences, which is characterized by physical or psychological movement away from an unwanted object or consequence. The other is the approach towards positive experiences, which indicates movement in direction to a wanted stimulus or consequence which elicits pleasure in the individual (Elliot, 2006). This stimulus can also be called a reward. Rewards can be either primary, which refers to positive incentives that are necessary for survival, food or sex for example. Or rewards can be secondary, which are neutral stimuli that are associated with primary rewards and derive their rewarding nature through this relation. Money is one example of a secondary reward. The paper of a one hundred dollar bill holds little positive value itself but it is perceived as an incentive because it can be used to purchase other rewarding goods (Beck, Locke, Savine, Jimura, & Braver, 2010).

The distinction of avoidance of punishment and approach towards rewards is one of the oldest psychological concepts and first attempts of a definition go back to ancient Greek philosophers who were convinced that the best for an individual is to have as much joy and as little trouble as possible. The concept has served as the bases of political and economic theories and is deeply embedded in capitalist societies (Cornwell, Franks, & Higgins, 2014). Due to the omnipresence of this idea in other disciplines, it has been thoroughly investigated in various areas of psychological research as well, for example organizational psychology (e.g., Ferris et al., 2013), clinical psychology (e.g., Trew, 2011) and social psychology (e.g., Elliot, Gable, & Mapes, 2006). Neuropsychology has mainly tried to identify underlying mechanisms of perceiving a stimulus as rewarding. Food is one of the primary rewards that has been studied often since it’s easy to implement in the method and its consumption was commonly believed to be driven by the hedonic principle (Appelhans, 2009). It was suggested that humans tend to eat food that they perceive as rewarding and avoid food that they don’t. This principle is called hedonic feeding (Appelhans, 2009). The name gives the impression that the pleasure palatable food elicits is the most important component when assessing whether an edible item is regarded a reward. This was generally believed to be the case for some time in neuropsychology. The hedonic value of a stimulus was understood as the key component of processing positive experiences (Nash, 1997; Wise, 1982). Based on this belief the first important neuropsychological theory about reward mechanisms in the brain was established: The anhedonia hypothesis by Wise (1982).

The anhedonia hypothesis

First neuropsychological investigations in primary reward processing were done on rats with the goal of finding the neurotransmitter that regulates positive experiences. In these studies the dopamine receptor blocker Pimozide was given to the rodents, which leads to lower levels of brain dopamine. This resulted in decreased reward seeking behavior such as lever pressing (Wise, Spindler, deWit, & Gerberg, 1978). The lowered motivation for these behaviors was interpreted as the consequence of a decreased rewarding impact of the stimulus, in this case food. Accordingly, it was suggested that the brain's response to all pleasurable stimuli has to be a rush of the neurotransmitter (Wise, 1985). Due to these findings, it was commonly believed that dopamine was the key component to rewarding experiences until the late 1990s (Nash, 1997).

The theory was also known as the (an-) hedonia hypothesis (Wise, 1982). Liking an experience was the key element of this concept. A stimulus received its positive value through eliciting hedonic feelings in the animal recipient. Although it was observed that there was a motivational component to primary rewards as well, the striving for a positive stimulus was seen as the result of liking it (Wise, 1982). Therefore it was only indirectly regulated by dopamine. Consequently changes in wanting were expected to be proportional to changes in liking (Berridge & Robinson, 2016). Liking and wanting were regarded as so interchangeably usable that pleasure was often measured by the effort that was taken to obtain the reward, especially in animal studies (Bindra, 1974; Wise et al., 1978). This conception changed when Berridge, Venier, and Robinson (1989) found, that a 6-hydroxydopamine (6OHAD) lesion in the mesostratial dopamine system in a rat's brain, which results in a reduction of dopamine, doesn't change the animal's reaction to a pleasurable stimulus. The experience of pleasure was measured via recording hedonic facial expressions and stayed completely normal when receiving sweet food even though dopamine levels were nearly non-existent. One thing did change however: The rat's motivation to strive towards and consume the food was gone. Even though food was available, the rodent would not move and even starve to death, if not externally supported (Berridge et al., 1989).

Similar results were produced in a following study by Treit and Berridge (1990), in which the release of dopamine in rats was stimulated by giving them the dopamine agonist Apomorphine. Dopamine agonists are substances that activate dopamine receptors. This didn't lead to increased liking of palatable food rewards. Hence it was hypothesized that the dopaminergic system only regulates wanting of a primary reward but not liking (Treit & Berridge, 1990). The anhedonia hypothesis was further questioned when studies showed that do-

paminergic activation precedes reward consumption. This should not be the case if a pleasurable experience leads to a dopamine release and in consequence to liking of the stimulus. But it does give more proof to the theory that the neurotransmitter is activated when wanting a reward (Blackburn, Phillips, Jakubovic, & Fibiger, 1989). In addition to these findings, studies showed that when for monkeys a neutral stimulus, for example a light, was paired with food and repeatedly conditioned as an indication that a reward will be given, dopamine levels didn't rise anymore in response to the food, but only to the brightness of the light (Apicella, Ljungberg, Scarnati, & Schultz, 1991). All these findings led to a change of ideas in the scientific community and to the proposition of a new theory: The incentive salience hypothesis (Berridge & Robinson, 1998).

The incentive salience hypothesis

In contrast to the anhedonia theory, the incentive salience hypothesis suggests that wanting and liking are two distinct components of reward processing. Usually they are positively correlated, but they can also appear separately from each other (Berridge & Robinson, 1998). In this case individuals work hard for an outcome they won't enjoy that much when obtained or vice versa (Pool, Sennwald, Delplanque, Brosch, & Sander, 2016).

Three psychological processes that regulate incentive reward experiences were identified: *Hedonic activation* by the reward, which could be translated into liking the positive stimulus, for example palatable food. *Associative learning* which establishes a connection between the reward and a neutral stimulus as a cue, for example learning that a light indicates the distribution of palatable food. And third, the *attribution of incentive salience* to the conditioned stimulus or goal object which attributes motivational value to the cue. It transforms the pure perception that there is a light or food in the distance to an incentive and makes it possible to move physiologically or psychologically towards it in order to receive the reward. The last process makes the object wanted. This is to the same degree necessary as the first two steps to transform the stimulus into a reward. According to the authors only wanting is regulated by the dopamine system (Berridge & Robinson, 1998).

It is important to note that not only are wanting and liking separate components in incentive salience theory, but that wanting, and in consequence dopamine release, appears independently from the process of conditioning and learning. It has been hypothesized earlier by representatives of the reward learning theory that dopaminergic activation occurs because of a learned process of liking and a certain cue (e.g., Montague, Dayan, & Sejnowski, 1996). In incentive salience theory wanting a reward doesn't establish the connection between conditioned stimuli and hedonic events. Anticipatory dopaminergic activation doesn't occur be-

cause it is the result of a learning process, but because the attribution of incentive salience gives the conditioned cue itself incentive motivational qualities (Berridge & Robinson, 1998). Either noticing the reward in the distance or the conditioned stimulus that is associated with the reward leads to a release of dopamine and in consequence to wanting of the reward. In case of the conditioned cue reboosting is an important process. This mechanism occurs if the conditioned stimulus leads to the liked consequence in every re-encounter. In this case the cue holds its incentive motivational value. If the cue appears without the wanted consequence, deboosting happens which means that the incentive salience of the cue decreases (Berridge & Robinson, 1998).

Wanting systems in the brain

The dissociation of wanting and liking was further established by separating them not only by involved neurotransmitters but by brain activation as well. In a rat's brain there are dopaminergic circuits similar to how they exist in humans (Robinson, Fischer, Ahuja, Lesser, & Maniates, 2015). Based on electrolytic and 6OHAD brain lesions and electrostimulation studies with the rodents, the motivational component of primary rewards was localized as widely distributed within the mesolimbic circuit, mainly the ventral tegmental area (VTA), the nucleus accumbens (NAc), the dorsal striatum (DS), the ventral pallidum (VP) and in the amygdala (Berridge, 1996; Smith, Tindell, Aldridge, & Berridge, 2009). It is important to note that the NAc and VP are involved with liking of a reward as well, but they are doing so in form of hedonic hotspots (Richard, Castro, DiFeliceantonio, Robinson, & Berridge, 2013). Dopaminergic activation is a widespread process with many brain regions involved (Berridge, 1996). Earlier studies on rodents identified additionally the lateral hypothalamus as a structure that, when stimulated by electric impulses, influences behavior due to increasing the incentive salience of pleasurable food stimuli (Berridge & Valenstein, 1991).

These studies confirmed that dopamine and the brain regions that are directly influenced by it regulate wanting behavior in rats. All of the identified brain areas form part of the wide spread dopaminergic system, mainly the mesocorticolimbic circuit, and altercations in all of them lead to changes in reward anticipation and motivation (Robinson et al., 2015).

Separating wanting and liking in humans

Research results on a behavioral level

The previously listed results were first discovered and investigated in animals, mainly rodents (e.g., Berridge et al., 1989) and some in monkeys (e.g., Apicella et al., 1991). This raised the question whether these findings of a separate wanting system for food rewards were applicable to humans as well.

Concerns were raised in regards to how to adequately measure the phenomenon of distinct wanting and liking mechanisms in humans because asking subjects directly may not always give a valid representation of actual wanting (Finlayson, King, & Blundell, 2005). In this case wanting could get confused with the hedonic aspect of the reward. Furthermore when liking and wanting are investigated in close proximity, subjects may adjust their answers to avoid big differences between the two. Also participants may think that they are consciously aware of their motivation to get a certain positive stimulus, while incentive salience is not to be seen as the process of knowing that one wants something but wanting itself (Finlayson et al., 2005).

A study conducted by Finlayson et al. (2005) dealt with these problems and showed that in a healthy population the processes could be dissociated regarding generic food categories depending on the subject's saturation state. Liking was measured by asking the participants "How pleasant would it be to experience a mouthful of this food right now?", while wanting was assessed by presenting two food stimuli from different categories and asking the subject to select the food they would most likely eat. It was shown that when satiated, participants liked but did not want high fat savory food over low fat savory food and wanted but did not like low-fat sweet food over high-fat sweet food for example. In addition it was found that differences in wanting and liking of the food categories were bigger when participants were hungry.

In another food-related study (Born et al., 2011) liking was assessed by exposing healthy participants to pictures of food and asking "How much do you like this item, not considering if you want to eat it right now". Wanting was assessed by asking "How much do you want to eat this item right now?". Answers were given on a visual analog scale (VAS). The participants had to come to the experiment in a hungry state and were informed that the foods they rated highly in wanting will be given to them after the experiment. It was shown that even when asked directly liking and wanting were not significantly correlated. The liking for certain food items didn't change when participants were given food, while wanting ratings decreased.

These findings suggest that wanting and liking are not only separate processes in animals, but in humans as well. In these studies the motivational component was more variable over conditions than the hedonic component (Born et al., 2011, Finlayson et al., 2005). To date no published studies can be found that tested the hypothesis of a distinct wanting mechanism for food rewards on a behavioral level in healthy humans using pharmacological intervention. The use of medication to investigate certain processes in the brain is common in an-

imal studies and is adaptable to human test subjects as well. Dopamine agonists or antagonists should have an influence on primary reward seeking behavior according to the incentive salience hypothesis. It was shown however that administering a dose of L-Dopa to healthy volunteers, which leads to higher levels of brain dopamine, didn't have any influence on their mood (Liggins, Pihl, Benkelfat, & Leyton, 2012). It was hypothesized that if there was a connection between liking and dopamine, L-Dopa should have influenced their mood in a more positive direction. As this was not the case, the authors conclude that dopamine leads to goal-seeking behavior not by altering the liking component of a reward, but the motivational wanting aspect.

One study by Weber et al. (2016) investigated the effect of the dopamine D2/3- receptor antagonist Amisulpride on cue reactivity and reward impulsivity to drug-associated stimuli in healthy test subjects. Especially cue induced responding, but also the tolerance to delayed gratification, is influenced by the incentive salience of the stimulus. The experiment group received 400 mg of Amisulpride, while the control group was given a placebo. Both had to complete a Pavlovian-instrumental transfer task and a delay discounting task. The participants who received the dopamine antagonist showed significantly lower cue reactivity and reward impulsivity than subjects who received a placebo. These results show that dopamine plays an important role in reward responding as proposed by the incentive salience theory (Weber et al., 2016). To investigate wanting as a distinct mechanism further than on a behavioral level, researchers have turned to look at the associated brain structures.

Visualizing wanting in the human brain: FMRI results

Functional magnetic resonance imaging (fMRI) is used to investigate neural activity in the brain. The MRI tube generates a strong magnetic field, which affects the magnetic nuclei of atoms. Normally they are randomly oriented but become aligned with the direction of the field, when exposed to the MRI scanner's force. Because of this arrangement of magnetic signals, which in case of fMRI come from hydrogen nuclei in water, it is possible to measure their strength and differentiate between brain structures (Devlin, n.d.). By utilizing the blood oxygenation level dependent (BOLD) effect (Ogawa, Lee, Nayak, & Glynn, 1990) neural activation can be made visible. Oxygen-rich blood contains oxygenated hemoglobin, which goes against the magnetic field. Deoxygenated hemoglobin can be found in oxygen-low blood and supports the magnetic field. Neural activation leads to increased blood flow in associated regions of the brain, which in consequence leads to a reduction of deoxygenated hemoglobin. This reduction makes it harder for the atom to go back to its original state which results in longer relaxation times, which leads to a stronger fMRI signal and lighter areas in the brain

images. This process is also known as the BOLD contrast and it makes visualization of brain activation via fMRI possible (Arthurs & Boniface, 2002; Nalik, n.d.).

The previously mentioned study by Born et al. (2011) was extended by measuring the distinct wanting and liking mechanisms for primary rewards in an fMRI setting by using pictures of food as stimuli. It was shown that wanting of primary rewards was associated with higher activation of the striatum, while liking activated different brain structures. Activity in the NAc was related to wanting and liking alike.

Another study (Jiang, Soussignan, Schaal, & Royet, 2015) produced further results: Healthy women were included and asked to rate their liking of food (and non-food) odors and their desire to eat the food evoked by the odor. The ratings were given in a hungry and satiated state. The NAc and VP activation depended on the metabolic state of the participant. When the subject was in a hungry state NAc activation was higher in the liking than in the wanting task, while VP activation was higher when the subjected evaluated their wanting than when they evaluated their liking for the food odors. In a satiated state there was higher activity in the NAc during food wanting than liking. These results should be seen critically though, because of the close anatomical link between olfactory processes and hedonic experiences due to the direct connection between the primary olfactory cortex and the NAc (Newman & Winans, 1980; Price, 2009), which could result in higher ratings of liking (Jiang et al., 2015). The authors further argued that higher activity in the NAc during wanting in a satiated state could hint to a process of devaluation of food during satiety (Jiang et al., 2015), similar mechanisms were already linked to the NAc in rat studies (Singh, McDannald, Haney, Cerri, & Schoenbaum, 2010). Another brain structure that showed distinct activation for wanting in the study from Jiang et al. (2015) was the orbifrontal cortex (OFC). Wanting scores correlated positively with activation in the medial parts of the OFC, which have been linked in the past to responses to the attractiveness of food in a hunger state (Piech et al., 2009). A second structure which could be linked to wanting when hungry by this study is the hypothalamus. This connection had already been shown to exist in rats (Berridge & Valenstein, 1991), and was further investigated by linking hormones, that originate and play an important part in the hypothalamus, for example ghrelin, to reward-related areas of the brain (Malik, McGlone, Bedrossian, & Dagher, 2008).

Another study formed an additional condition to satiated or hungry state by measuring participants' cortisol level and dividing them accordingly to high or low hypothalamus-pituitary-adrenal (HPA) axis activation (Born et al., 2012). Behavioral wanting for food items, measured by an explicit rating, decreased after getting a meal in both HPA-conditions. Want-

ing task related signals (TRS) in the left anterior insula, the NAc and thalamus predicted wanting ratings in the pre-meal low-HPA condition. The areas of interest for measuring wanting TRS were modeled after an anterior study by the authors and are related to reward, taste and integrative processes (Born et al., 2011). In the post-meal low-HPA condition and pre-meal high-HPA condition no relation between wanting (and liking) and TRS in certain brain structures could be shown, but post-meal high-HPA wanting was associated with TRS in the caudate. Liking TRS in taste related regions predicted the liking rating in the pre-meal low-HPA condition, while post-meal high-HPA liking was associated with TRS in the left NAc (Born et al., 2012). These results show that wanting and liking are distinct from one another and can be dissociated by signals in related brain regions. Furthermore stress, measured by HPA activation, and state of satiation seem to be significant factors which should be taken into account when investigating wanting and liking processes.

There are no published studies available regarding primary rewards and dopaminergic wanting in healthy participants that combine fMRI and pharmacological intervention. But in one study by Hermann et al. (2006) the dopamine antagonist Amisulpride and fMRI were used to investigate the effect of a dopamine antagonist on wanting activated by alcohol-associated cues in abstinent alcoholics and healthy men. Before receiving one single dose of 400 mg of Amisulpride, abstinent alcoholics showed a higher BOLD signal in the right thalamus compared with the control group when presented with alcohol-associated stimuli. Earlier studies suggested the involvement of the dopaminergic pathways that include the thalamus in craving (aka wanting) for drugs (Volkow et al., 1996). After the administration of the medication, there was no longer a detectable difference. This could be first proof that the thalamus is a brain region associated with reward wanting, even though this hypothesis has to be further investigated for other rewards like food. Further research in this topic could lead to pharmacological therapy with dopamine antagonists to help alleviate cravings for people with addictions.

Summary

Taking everything into account, it was established that distinct wanting and liking processes for primary rewards can be found in animals (e.g., Berridge, 1996; Smith et al., 2009) and in humans as well. Behavioral wanting and liking of food were shown to be separate mechanisms that often don't correlate with each other (Born et al., 2011). Studies using pharmacological intervention to manipulate dopamine levels in participants showed the important role that the neurotransmitter plays in reward reactivity (Weber et al., 2016).

This distinction was further established in fMRI investigations of the underlying brain activation. Wanting of rewards in humans, which on a behavioral level was often times investigated by subjective ratings on a VAS, was associated with the dopaminergic pathways in the brain: The mesolimbic pathway, which includes the VTA, the ventral striatum with the NAc, the anterior insula (Born et al., 2011) and the VP (Jiang et al., 2015), the mesocortical pathway which includes the OFC (Jiang et al., 2015), the nigrostriatal pathway which includes the dorsal striatum with the caudate nucleus and the putamen, as well as the thalamus (Born et al., 2012; Hermann et al., 2006) and the incertohypothalamic pathway which influences the hypothalamus (Jiang et al., 2015). These results speak for a widespread activation during reward wanting. It was shown that liking activates structures differently, in case of the NAc for example (Jiang et al., 2015), or is associated with different brain regions entirely (Born et al., 2011). These findings lead to the conclusion that liking and wanting of primary rewards are separate processes in animals and humans alike and that they are founded on distinct neuropsychological bases.

However these results should be seen critically still. First, wanting is not a completely conscious process, so relying on subjective ratings on a VAS as the only form to evaluate wanting could be inadequate (Finlayson et al., 2005). Furthermore liking and wanting were often investigated in close proximity, which could lead participants to adjusting their answers. An additional more objective measurement of wanting would eliminate these concerns. Second, the primary reward itself was not present in these experiments. Food was represented by a picture or an odor, as eating while doing an fMRI is not possible. Nevertheless it is crucial to incorporate real primary rewards in the study design to achieve valid and generalizable results. Calorie dense drinks could replace food options in an fMRI environment because it is possible to swallow them while holding the head still. Third, there are currently no papers available investigating food rewards and the wanting system that use pharmacological intervention, a well-established method in animal research which is possible to conduct with human test subjects as well. Especially combining a pharmacological approach with fMRI could lead to clearer differences between the experiment and control group. Differentiating wanting and liking for rewards can be difficult because they both activate the NaC and VP (Jiang et al., 2015). Moreover when investigating healthy participants the differences between experiment and control group can be subtle and hard to identify as humans are a holistic system and pinpointing brain activation to one function is therefore a difficult task. Pharmacological intervention in studies with humans would also lead to higher comparability to the results acquired in animal studies, because most results there have been achieved by manipulating brain

processes artificially (Berridge, 1996; Berridge & Valenstein, 1991; Smith et al., 2009). Fourth, all studies investigating the distinct wanting mechanism of primary rewards in an fMRI setting are rather new and there are currently not many research papers available which deal with this subject. This makes it clear, that further investigation in the matter is needed, especially if it includes real primary rewards and an additional, more objective measurement for wanting than ratings on a VAS.

Potential implications for clinical psychology

Investigating reward experiences for humans further and dissociating wanting and liking in the process is not only important because it is an essential part of everyday life, but because there is a high probability that the understanding of certain disorders could benefit from this distinction. One that is still poorly understood, yet displays that a dopamine dysregulation can lead to serious consequences is Dopamine Dysregulation Syndrome (DDS), typically present in patients with Parkinson's disease. Parkinson's disease is characterized by the loss of dopaminergic neurons in the substantia nigra. In consequence dopamine levels in the brain decrease, especially in the striatum (Elbaz, Carcaillon, Kab, & Moisan, 2016). The most common therapy for patients with this disorder include the prescription of a dopamine agonist like L-Dopa (Rascol et al., 2007). DDS can occur if the dose of the medication is not well adjusted and it is taken over a long period of time. One of the main symptoms is an intense craving for the prescription drug and it is often accompanied with impulse control disorders (ICD). These ICD behaviors include pathological gambling, hypersexuality and compulsive eating (Witjas, Eusebio, Fluchére, & Azulay, 2012). Generally speaking, patients treated with dopaminergic medication can, when not adjusted correctly, develop a pathological reward-seeking behavior. This gives further proof to the thesis that dopamine is responsible for wanting rather than rewarding experiences in general and in consequence regulates the motivation to move towards positive stimuli.

A second cluster of disorders that could potentially benefit from further investigation into wanting and liking mechanisms are addiction disorders. The incentive-sensitization theory of addiction (Berridge & Robinson, 2016) is based on the incentive salience hypothesis and proposes that (drug) addiction forms due to an excessive amount of wanting that gets triggered by certain cues, while there is no increase in liking. According to this theory, the brain dopamine systems get sensitized, in other words hyper reactive, due to drug abuse which leads to abnormally high reactions to cues and contexts associated with the drug of choice. These cues hold high incentive salience and sensitization can last for years, which could explain why people with addictions have strong urges to abuse their drug of choice and relapses

can happen even after years of sobriety. It has been hypothesized that the same mechanism of increased reactivity could play a role in drug-unrelated addictions as well (Berridge & Robinson, 2016). Due to the novelty of the theory it has still not been thoroughly researched, but investigating reward processing further could give answers to remaining questions.

A third group of disorders which is in certain areas linked to addiction and could be equally more understood with a wanting/linking distinction are eating disorders. The topic of this paper is especially relevant for these psychological conditions because the compulsive behaviors include food as a primary reward. Excluding food addiction as an eating disorder because evidence is still not clear whether this condition really exists, obsessions about food are a main symptom of binge eating disorder, anorexia nervosa and bulimia nervosa (Berridge, 2009). Though there is still not much evidence to suggest an incentive-related cause of these pathological behaviors, there are various mechanisms imaginable how distorted reward processing could be involved with obsessive food intake or rejection. First, increased wanting without liking could lead patients to take in excessive amounts of food without having a hedonic experience. This obsessive wanting could get triggered by certain cues that hold high incentive value for the person (Berridge, 2009). Decreased wanting and dopamine levels could in consequence lead to decreased motivation to seek out food as a reward. Second, distortions in the reward-processing-system could be the result of disordered eating that is practiced over a long period of time (Berridge, 2009). In both cases treatment could be adjusted accordingly if research shows that eating disorders are associated with impairments in the dopaminergic wanting systems in the brain.

All in all it is plausible to suggest that distortions in reward processing lead to serious consequences, therefore it is urgently necessary for psychologists to understand these mechanisms completely. Separate wanting and liking systems in the brain is a concept that, as of right now, can be regarded as not completely established in mainstream psychology and research in this area has focused for a long time on animal studies. For this reason investigations involving human test subjects and real reward experiences is needed to generate further proof for the theory.

Aim of the study

The distinction between wanting and liking of primary rewards which is based on the incentive salience theory is a concept thoroughly researched in studies with animals. It was shown on a behavioral level that decreasing brain dopamine through a neurochemical lesion leads to a lowered motivation to seek out primary rewards without changing the hedonic pleasure elicited by the positive stimulus (Berridge et al., 1989). Furthermore wanting and

liking could be dissociated by identifying the brain areas activated by these processes. By drug administration, neurochemical lesions in the brain and electrostimulation it was shown that brain regions that are associated with wanting in rats are: The VTA, the NAc, the DS, the VP, the lateral hypothalamus and the amygdala (Berridge, 1996; Berridge et al., 1991; Smith et al., 2009). These regions form part of the dopaminergic mesocorticolimbic pathway in rodent brains (Robinson et al., 2015). These findings led to the proposition of a dopamine regulated wanting process which controls the craving for a primary reward.

First attempts have been made to find these mechanisms in humans as well. Liking and wanting could be dissociated on a behavioral level regarding different food categories and hunger states (Finlayson et al., 2015). FMRI studies suggest that the VTA, the NAc, the VP, the OFC, the caudate nucleus and the hypothalamus are dopaminergic regions in the human brain that are activated specifically by wanting for primary food rewards (Born et al., 2011; Born et al., 2012; Jiang et al., 2015). However a specific wanting mechanism for primary rewards in humans is far from established. Most studies regarding this topic have been published fairly recent and as of right now there are not many available. Wanting has not been investigated yet using tangible primary rewards, nor by manipulating dopamine levels in the brain, for example by pharmacological intervention, as it has already been done in animals. This scientific void and the high relevance reward processing has, not only in daily functioning but in clinical psychological disorders as well, demand further research on the matter. Therefore the goal of this study was the investigation of the role of dopamine in the wanting of primary rewards using a methodological approach that combines pharmacological intervention and fMRI.

Wanting

As some authors (e.g., Finlayson et al., 2005) suggested, asking the participant directly to rate their wanting for a reward on a VAS could not be a sufficient way to evaluate wanting. For that reason in this study the evaluation of a subject's wanting of a primary reward was not only done via a subjective rating, but also by measuring the effort the participant is willing to put in to obtain the food reward. Effort has been established to be a valid measurement for the motivation to get a reward (Waugh & Gotlib, 2008), which could be described as wanting the reward in other words. There is a lack of studies with food rewards and healthy participants that took advantage of this connection to have an additional wanting rating, so the methodological approach of this experiment is a new one.

Primary reward

Most studies regarding the topic focused on food as a primary reward (Born et al., 2012; Jiang et al., 2015), so this experiment used edible incentives as well. Most importantly and unlike previous studies, a tangible reward was administered into the fMRI scanner to investigate wanting processes in close temporal proximity to reward administration. To gain understanding about specific reward processing, different types of rewards were given to the participants: A high incentive food reward, which was very desirable and two low incentive food rewards, which were not as attractive.

Pharmacological intervention

Until now dopamine agonists and antagonists have been used mainly in animal studies to investigate primary reward processing (Treit & Berridge, 1990; Wise et al., 1978). In studies that used a different kind of reward has been shown that these medications are suitable for investigations of wanting in human test subjects as well (e.g. Hermann et al., 2006; Liggins et al., 2012). In this study dopamine levels in healthy participants were manipulated by using a dopamine antagonist by the name of Amisulpride. This medication is a dopamine D2/D3 receptor antagonist, but works distinctively depending on the doses. In high doses it leads to decreased dopaminergic activation in the brain, while eliciting activation in low doses (Di Giovanni, Di Mascio, Di Matteo, & Esposito, 1998). This medication is usually used as a treatment for acute and chronic schizophrenia, but it has already been used successfully in psychopharmacological studies on healthy participants as well (Hermann et al., 2006). Based on these studies the one time dose given to the subjects was set to be 400 mg, to be high enough to get the dopamine decreasing effect and low enough to reduce the risk of side effects in the participants as higher doses were found lead to mild cognitive impairments (Rosenzweig et al., 2002). The experiment group therefore received one 400 mg dose of Amisulpride, while the control group received a placebo pill that looked the same.

FMRI

The reward task was completed in an fMRI scanner to visualize the potential differences in brain activation of subjects who received a dopamine antagonist and subjects who received a placebo in response to food rewards. It is important for various reasons to combine pharmacological intervention with fMRI when investigating primary reward processing in humans:

First, animal studies have been using dopaminergic medication to investigate reward wanting for a long time. And even though fMRI is not done with animals, involved brain regions were thoroughly investigated using other methods (Berridge, 1996; Berridge & Va-

lenstein, 1991; Smith et al., 2009; Treit & Berridge, 1990; Wise et al., 1978). It is important to use similar methodologic approaches when investigating the same brain mechanisms in humans to be able to compare the results.

Second, investigating brain activation associated with primary reward wanting in healthy individuals presents the problem that humans are a holistic system. Various brain mechanisms are needed to come to execute a function. A design most studies regarding this topic used is a pre/ post comparison of states in a single subject (e.g. Born et al., 2012; Jiang et al., 2015). Here it is difficult to attribute changes to one cause. Dissociating wanting from liking in the brain in general is challenging (Havermans, 2011). The processes are partly associated with similar regions which adds to the difficulty of pinpointing neural activities to one cognitive function. With pharmacological intervention and a between subject design it is easier to attribute potential differences between the groups to the manipulation, especially when working with healthy participants only.

Third, due to these hardships there are not many studies available that deal with the motivational aspect of primary reward processing in humans, especially ones using fMRI. For these reasons the topic and methodological approach of this study are highly relevant and results will lead to further insight on how dopamine regulates primary reward experiences in humans. In this experiment a difference between experiment and control group regarding wanting ratings for food rewards were expected. Additionally it was theorized that brain activation in regions associated with wanting would differ in the groups.

Research questions & hypotheses

Research question 1: Are there differences in wanting ratings and effort depending on the type of primary reward?

Hypothesis 1a: Wanting ratings on a VAS will be significantly higher for high incentive food rewards than for low incentive food rewards.

Hypothesis 1b: Effort to obtain the reward will be significantly higher for high incentive food rewards than for low incentive food rewards.

Research question 2: Are there differences in wanting of a primary reward in the experiment (dopamine antagonist) group and the control (placebo) group?

Hypothesis 2a: The experiment group will show lower subjective ratings on a VAS for wanting a high incentive food reward than the control group during a reward task.

Hypothesis 2b: The experiment group will show lower subjective ratings on a VAS for wanting a low incentive food reward than the control group during a reward task.

Hypothesis 2c: The experiment group will show lower effort to get the high reward than the control group during a reward task.

Hypothesis 2d: The experiment group will show lower effort to get the low reward than the control group during a reward task.

Research question 3: Can these differences in wanting between the experiment and control group be shown as differences in brain activation as well?

Hypothesis 3: The experiment group will show less activation in brain regions previously associated with wanting than the control group during a food-reward task.

Methods

This study was conducted as a psychopharmacological experiment in an fMRI-environment with a mixed between-within subject design.

Participants

Forty subjects were tested (15 male, 25 female). Their ages ranged from 18 to 33 years old (M = 23.55, SD = 3.96). Five subjects (12.5%) stated their current highest level of education as being compulsory schooling, 14 (35%) had graduated from secondary academic school, 5 (12.5%) from higher vocational school and 16 (40%) had a university degree. All of them spoke German at least on level C1on the European frame of reference, as people were only included if they didn't meet any of the exclusion criteria presented in table 1.

Table 1

Exclusion criteria

General criteria	Specific criteria
1. Demographic variables	
	- Younger than 18 or older than 35
	- Not heterosexual
	- No fluent German skills
2. Personal variables	
	- Psychiatric or neurologic illness
	- Major health impairment (diabetes, hypo or hyperthyroidism, liver or kidney disease, previous operation or disease of the heart or the nervous system)
	- Left-handed
	- Addiction to alcohol or drugs
	- BMI under 17 kg/m^2 or over 35 kg/m^2
	- Former or current psychology student
	- No normal or corrected sight

General criteria	Specific criteria
2. Personal variables	- Acute or chronic respiratory disease - Intolerance of dairy or cocoa products - Smoking more than five cigarettes a day - Participation in medication studies in last two months - Hearing problems - Intake of medication that could affect the HPA-axis or the mental state - Consumption of alcohol, cannabis or other drugs twelve hours before testing
3. Eligibility for fMRI	- Pregnancy - Metal implants - Permanent make-up - Big tattoos - Non-removable piercings - Metal screws - Artificial heart valve - Prior head injuries - Claustrophobia
4. Eligibility for Amisulpride	- Allergy to or current intake of Amisulpride - Strongly limited kidney function - Intake of Levodopa - Intake of medication that could affect the dopaminergic system - Intake of medication that could lead to heart arrhythmias - Prolactin-dependent tumors or tumors of the adrenal medulla - Family history of sudden cardiac death or arrhythmias

Recruitment

Promotional flyers and posters were distributed in public places, for example cafes that are frequently visited by students and universities. Additional advertisements were published in various Facebook groups, mainly ones with a focus on students, university, work possibilities, side jobs and internships. The promotional material directed potential participants to an E-Mail address. As a next step they were sent questionnaires which screened for some exclusion criteria: The Health and Taste Attitudes Questionnaire (Roininen,

Lähtenmaaki, & Tuorila, 1999), which collects information about cravings for sweet food, the habit to use food as a reward and the pleasure that food elicits, The Social Touch Questionnaire (Wilhelm, Kochar, Roth, & Gross, 2001); the 20-item Toronto Alexithymia Scale (Bagby, Parker, & Taylor, 1994); the short version of the Autism Spectrum Quotient questionnaire (Freitag et al., 2007) and the Behavioral Inhibition/Behavioral Approach System questionnaire (Strobel, Beauducel, Debener, & Brocke, 2001). If these were completed without being excluded, the subject was instructed to write another E-Mail with their phone number. Then they were contacted by a member of the research team and the participants were given a date for the first test appointment.

On the first test day the participant was screened for the remaining exclusion criteria, which took 70 minutes per subject. First the potential participants had to read and sign the conditions of participation. Then the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998) was conducted, which is a short screening for psychiatric disorders. A doctor conducted an electrocardiogram, took a blood sample and later evaluated whether a person could participate in the second test day. Subjects were compensated with ten euros for the first test appointment.

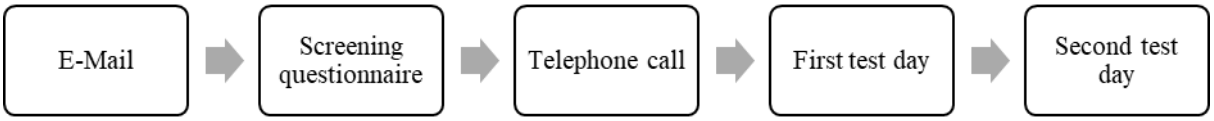

Figure 1. Recruitment procedure

Rewards

The task offered three potential food options to investigate reward processing for different levels of reward: Chocolate milk, sugared milk (52 g of sugar per liter) and a mixture of both (75% sweetened milk and 25% chocolate milk). All three contained the same fat and sugar content (1.5 g of fat and 10 g of sugar per 100 g).

In a previous study, it was shown that subjects enjoyed the drink options to a different degree (Korb et al., 2019). Usually the chocolate milk was the most preferred option, followed by the mix and the sweetened milk was the least preferred option. Based on these results chocolate milk was regarded as the high reward option, the mixture as a lower reward and the sweetened milk as the lowest reward option in this experiment. Participants were ad-

ditionally asked in the screening process whether they liked chocolate milk, so it can be assumed that they would generally enjoy the high reward.

Tap water was used for rinsing after each trial. The drinks were administered via computer controlled pumps which gave out 2 ml of the milk drinks in every trail. The pumps, which were located outside of the scanner room, were connected to plastic tubes. These tubes led to the MRI scanner and ended in changeable mouth pieces which were placed in the subject's mouth. Over the whole task, including pretesting, participants consumed 196 ml of liquids (98 ml of water and 98 ml of the three milk options).

Measures of wanting

How much the participants wanted the specific food option that was presented was measured in two ways: The subjective self-wanting rating was collected by asking participants "How much do you want the presented drink option?". They then gave a rating by pressing buttons on a box of the amount of wanting on a VAS from *Not at all* on the left to *Very much* on the right. The participant was additionally asked to regulate the probability to obtain the presented food option with applied pressure to a hand dynamometer. This was done in every trial to assess the effort the subject is willing to take to get the reward option. The maximum voluntary contraction (MVC) was measured before and after the complete task for comparison. The percentage of MVC applied in one trial was then the probability of getting the presented food option.

Procedure

This experiment was part of a bigger study investigating wanting and liking of primary and secondary rewards in an fMRI environment using dopamine and opioid antagonists. The following explanation of the procedure includes the parts that are not relevant for the research question this paper is describing.

Pre reward task

The second testing took 6 hours and 25 minutes (See table 2). The participants were asked to come to the experiment empty-stomached, to increase the susceptibility for the drinks. Additionally participants were not allowed to have access to their mobile phone during testing to decrease foreign influences. For the secondary reward experiences it was important that participants were heterosexual and female test subjects were tested by female experimenters and male test subjects were tested by male experimenters. After arrival every subject completed the positive and negative affect schedule (PANAS; Watson, Clark, & Tellegen, 1988) regarding their current feelings. Then they were asked to give a urine sample to check for drugs or alcohol. If they hadn't consumed these substances, they were given either 400 mg

Amisulpride (Solian®), a dopamine antagonist, 50 mg of Naltrexone (Dependex®), an opioid antagonist, or 650 mg of Mannitol (sugar), a placebo, by the doctor. It was randomly decided whether a subject was put in the experiment or the control group and all pills looked identical, so neither the participant nor the experimenter knew which medication was given. For the presented research question only the placebo and Amisulpride group are included in the evaluation. After pill administration participants received a small breakfast which consisted of one granola bar (425 calories) and water. After that, two computer tasks were practiced, which evaluated their ability to estimate probabilities and their attention span and vigilance. This was followed by a waiting period of 45 minutes in which the participants were allowed to read magazines given to them by the experimenter. Then the doctor checked on the participants' state by using the Abnormal Involuntary Movement Scale (AIMS; Buhmann, Rizos, Emmans, & Jost, 2016) and the Barnes Akathisia Rating Scale (BARS; Barnes, 1989). With these questionnaires it was evaluated whether the participant could go on with the reward task.

Reward task

If the participants were cleared by the doctor, they were introduced to the fMRI-scanner, a Siemens 3Tesla PrismaFit. A 64-channel head coil was used. The structural T1-weighted mp2rage sequence was acquired with 1x1x1 mm slice thickness. The T2-weighted echo-planar imaging sequence was acquired with the following factors: TR = 1 s, TE = 35 ms, 3mm slice thickness, 2.3x2 mm, 3x3 mm Voxel size, 40 slices, multiband factor 4. The field of view was 220x200 mm and the interslice gap 0.3 mm.

It was ensured that the participants felt comfortable and were not stressed by explaining the various parts of the following reward task in a calm environment. First, the subject had to lay down on the padded patient table to test the hand dynamometer and the button box, which were used to measure wanting ratings later. In three trials the participant's maximal power was evaluated to be able to compare future measurements of effort. Then they were given earplugs and additional padding. Then the head coil, which was needed to be able to see the screen in the bag of the scanner, was put on and the tubes were put in the participant's mouth. The subjects tested the three drink options still outside of the MRI tube, to be able to do altercations. Then they were put inside to test the secondary rewards, which were touches administered by the experimenter on a 9 cm field on the subject's forearm. As a second step participants had to complete a training session of the whole procedure which consisted of two trials of each block with the scanner still turned off. When these trainings were completed successfully, the scanner was turned on.

The following main task was conducted 3 hours after taking the pill to achieve the biggest effect of the medication. The reward task consisted of four blocks, two with primary and two with secondary rewards which were done alternately. It was decided at random which block was the first. Each block consisted of 16 trials. In each trial a picture of the stimulus which could be achieved was presented first. So in the primary reward block an image of one of the three food options was shown to the subject (See Figure 2). Then participants had to rate how much they wanted the presented drink by using the button box. The subjective wanting rating was given on a VAS scale going from *Not at all* to *Very much*. For the additional wanting rating via effort, the probability of receiving the option, was regulated by pressing the hand dynamometer. Depending on the effort given, the subject received either the presented drink or an alternative through the tubes. The participant then rated how much he or she liked the drink on a scale from *Not at all* to *Very much*. In the end of the trial, water for rinsing was administered. One food trial took 51 seconds and the whole block 13.6 minutes. Overall the whole scanning session lasted about 1 hour and 10 minutes and 830 volumes were acquired for each food block.

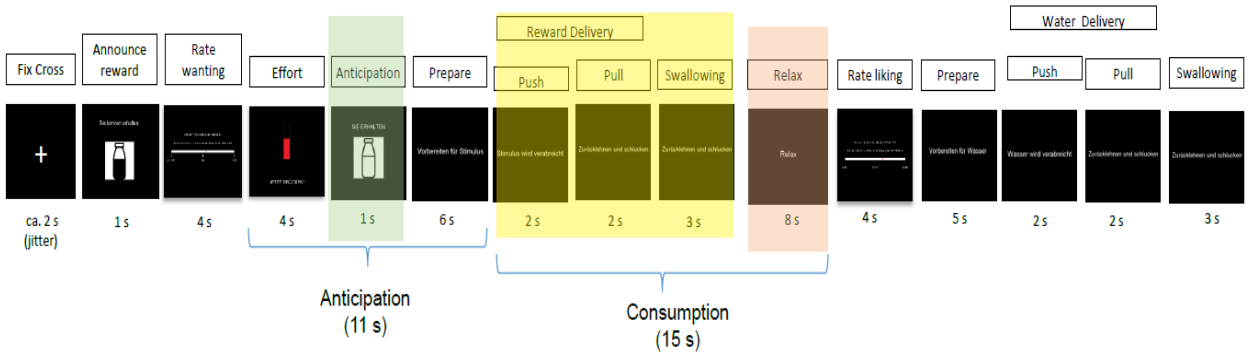

Figure 2. Timeline for one food trial of the reward task

Post reward task

After completing the reward task, participants had to complete the PANAS questionnaire (Watson, 1988) again. Then they were given another snack consisting of another granola bar and water. The next task was a facial mimicry task, in which they were instructed to look at video sequences of human faces changing emotions or fruit/vegetables changing state of ripeness. They were instructed to press a button whenever they felt like the state had changed. During the task, activity of the facial muscles corrugator supercilii, levator labii superioris

alaeque nasi and zygomaticus major were recorded by six electrodes on the left part of the face (electromyography; EMG).

Afterwards participants had to redo the computer tasks they had practiced earlier in the day. The amount won in these tasks was later given to the participant additionally to the participation money. 5 1/2 hours after taking the pill the doctor did a last check-up by using the BARS (Barnes, 1989) and by taking a blood sample. Lastly subjects had to fill out a debriefing questionnaire. Compensation for the second test day was 90 euros, so people who had partaken in the study received 100 euros plus the money they had won in the computer tasks.

Table 2

Timetable for the second test day

Activity	Duration	Total duration
Subject preparation*	5 minutes	5 minutes
PANAS I**	5 minutes	10 minutes
Urine sample and pill*	10 minutes	20 minutes
Breakfast snack*	5 minutes	25 minutes
P-Weighting task (practice)	20 minutes	45 minutes
Learning of control task (practice)	20 minutes	1 hour 5 minutes
Waiting period*	40 minutes	1 hour 45 minutes
Checkup Doctor (AIMS, BARS)*	15 minutes	2 hours
Preparation for MRI and testing of equipment*	1 hour	3 hours
Reward task**	1 hour	4 hours
Structural scan*	10 minutes	4 hours 10 minutes
Break for dressing and snack*	15 minutes	4 hours 25 minutes
PANAS II**	5 minutes	4 hours 30 minutes
Preparation for EMG	15 minutes	4 hours 45 minutes
EMG	25 minutes	5 hours 10 minutes
Learning of control task	25 minutes	5 hours 30 minutes
Checkup (BARS) and blood sample*	20 minutes	5 hours 50 minutes
P-Weighting task	20 minutes	6 hours 10 minutes
Working memory task	10 minutes	6 hours 20 minutes
Debriefing*	5 minutes	6 hours 25 minutes

Note. *Relevant for research question. **Data analyzed for this study

Results

Behavioral data

The behavioral data was analyzed by using the statistics program IBM SPSS Statistics (Statistical Package for the Social Sciences) Version 25.0 for Windows. Graphs were created in Windows Excel and Windows PowerPoint (2013).

The data of the two PANAS questionnaires (Watson et al., 1988) was evaluated and a t-test for independent samples showed that the experiment and control group did not differ in their current mood; divided in negative and positive feelings, before getting the pill (positive: $p = .868$, negative: $p = .344$) and after the reward task (positive: $p = .637$, negative: $p = .566$).

The study contained two factors which were suspected to influence the dependent variables (wanting ratings and effort): One between-subject factor (drug or placebo) and one within-subject factor (high or low reward). Therefore a mixed design analysis of variance (ANOVA) was the appropriate statistical model to use for analysis (Field, 2013). To be able to calculate a mixed design ANOVA, a list of assumptions have to be proven: The dependent variable has to be at least interval-scaled, which was the case for the wanting ratings and the effort measurement. Both factors have to be independent and coded nominally, which was the case for the type of reward and the group assignment. Moreover there shouldn't be any severe outliers in the data (Field, 2013). This assumption was reviewed by creating boxplots for the Amisulpride and placebo group which show the median, the 25th percentile or 1st quartile (1Q) and the 75th percentile or 3rd quartile (3Q) (see table 3). Any data that lies outside of 1.5 times the inter quartile range (IQR) from Q1 or Q3 is regarded as an outlier, which was the case for the wanting rating for low rewards of subject 21 ($p = -6.667$) and the wanting rating ($p = -7.025$) and the effort ($p = 22.816$) for high rewards of subject 2. It was decided to not exclude the subjects from the study because they aren't severe outliers. Severe outliers are defined as being further away from Q1 or Q3 than 3 times the IQR. These mild outliers cannot be expected to distort the results (Field, 2013).

Another requirement for a mixed-design ANOVA is the normal distribution of the residuals of the dependent variable. This was examined by running the Shapiro-Wilk test (S.-W.), in which $p > .05$ with a chosen $\alpha = .05$ indicates that normal distribution can be presumed (Field, 2013). As presented in table 3, three groups (Wanting rating of high rewards in Amisulpride and placebo group and effort for high rewards in placebo group) show a low significance ($p \leq .05$), which means that normal distribution cannot be presumed in these groups. It was decided to ignore these deviations, because the mixed-design ANOVA is relatively stable to violations of this requirement.

Table 3.

Box plot and S-W. Test results

Drug	Reward type	Variable	*1Q*	*Mdn*	*3Q*	*p* (S.-W.)
Amisulpride	High	Rating	4.044	7.493	9.731	.026*
	Low	Rating	2.338	4.525	6.525	.098
Placebo	High	Rating	2.367	5.550	8.131	.038*
	Low	Rating	1.440	3.330	6.644	.124
Amisulpride	High	Effort	61.079	78.331	88.030	.078
	Low	Effort	55.969	71.819	81.845	.630
Placebo	High	Effort	63.046	81.547	91.441	.005*
	Low	Effort	54.009	75.876	87.360	.066

Note. *$p \leq .05$

The last and most important assumption for a mixed-design ANOVA is the similarity of variances between groups inside the within-subjects factor, this is otherwise referred to as homoscedasticity. Levene's test is typically used to examine the homogeneity of the variances of residuals. If the test is not significant, groups can be presumed to have similar dispersion of residuals (Field, 2013). For all levels of the within-subjects factors the test showed no significance (wanting ratings of high reward: $p = .097$, wanting ratings of low reward: $p = .517$, effort for high reward: $p = .354$, effort for low reward: $p = .560$), which means homogeneity of variances of residuals can be presumed for all conditions. Secondly Box's M test is used to prove equivalence of covariances across groups. If this test shows no significance, homogeneity of covariances can be presumed (Field, 2013). Neither wanting ratings ($p = .131$) nor effort ($p = .218$) were significant, so this assumption can be presumed as proven.

As all requirements have been met, two mixed ANOVAs with type of reward being the within-subject factor, the between subject factor being group (drug or placebo) and either wanting ratings or effort as dependent variable were calculated. Means in three out of four conditions were higher for the Amisulpride group as depicted in table 4 and figure 3 and 4, but only one significant effect was found ($\alpha = .05$). The main effect in wanting ratings regarding the reward type was significant ($p = .016$), so generally wanting assessed by ratings on a VAS was higher for the high rewards than for the low rewards. Effort regarding reward type was not significant ($p = .099$), but the trend indicates that more effort was put in to obtain high rewards in comparison to low rewards. Neither the interaction effect between wanting

ratings and group (p = .283) nor between effort and group (p = .694) were significant. This shows that participants' wanting ratings and effort for high and low rewards didn't depend on them belonging to the experiment or control group.

Table 4

Means and standard deviations

		High rewards		Low rewards	
		M	*SD*	*M*	*SD*
Wanting ratings	Amisulpride	6.942	2.795	4.090	3.750
	Placebo	4.358	4.918	3.223	4.144
Effort	Amisulpride	75.170	15.591	68.757	18.157
	Placebo	74.058	23.670	70.077	20.844

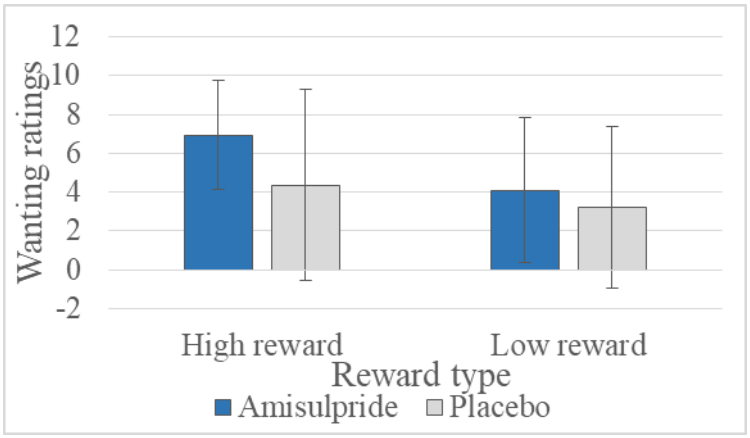

Figure 3. Means and standard deviations of wanting ratings for high and low rewards in the Amisulpride and placebo group

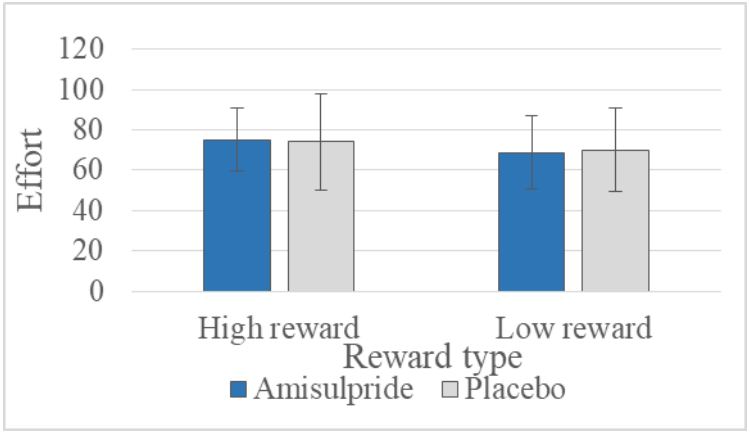

Figure 4. Means and standard deviations of effort for high and low rewards in the Amisulpride and placebo group

Additionally to these statistical analyses Pearson correlations between wanting ratings and effort for high and low rewards for both groups were calculated (see table 5).

Table 5

Correlations between wanting ratings and effort and Fisher's Z

		Pearson's *r*	Fisher's *Z*
Amisulpride	High reward	.527*	0.528
	Low reward	.616*	0.719
Placebo	High reward	.875*	1.354
	Low reward	.809*	1.124

Note. *Correlation is significant (α = .05)

The correlations were compared by using Fisher's z-transformation for one sided comparisons with a significance level of α = .05 (Eid, Gollwitzer, & Smith, 2011). For high rewards, there was a significant difference between the groups (z = -2.209, p = .021), while no such difference could be found for low rewards (z = -1.183, p = .119). This shows that the link between wanting ratings for highly desirable food rewards and the effort given to obtain them was significantly weaker in the Amisulpride group. The link between the two measurements of wanting for food rewards of low desirability was not significantly affected.

FMRI data

The fMRI data was analyzed and graphs were created by using the Statistical Parametric Mapping (SPM) software package Version 12 for Windows, which was run supported by the Matrix Laboratory (MATLAB) software Version R2019b. Three subjects had to be excluded from the analysis. For one participant no fMRI data was available and the data of two participants was not evaluable with the design matrix ($n_{\text{Amisulpride}}$ = 18, n_{Placebo} = 19).

First, the raw data of each subject was preprocessed to remove noise and correct errors in the sample. This preprocessing involved the realignment and unwarping, normalization and smoothing of the functional images, as well as the coregistration with the structural images and the segmentation of the structural images into different tissue types. In the subsequent first level analysis the design matrix and contrasts were specified according to the task (see figure 2). The interscan interval was defined as 0.704, chocolate milk was registered as the high reward and sweetened milk and the mixture or both were registered as low rewards. The following twelve contrasts were then determined: First announcement of high and low rewards, second announcement of obtained high and low reward, preparation for high and low

reward delivery, high and low reward delivery, relaxation after high and low reward, preparation for rinsing and rinsing. Since this study is only evaluating wanting of rewards, the four announcement contrasts were further analyzed in a second level analysis in which a statistical test can be implemented. The test design was specified as full factorial ANOVA. Group, anticipation and reward level with two levels each were determined as factors. Also the interaction between group and reward level was analyzed. The results of the statistical analysis with a defined significance threshold of $p_{uncorrected} \leq .005$ can be found in table 5 and figure 5–10.

Table 5

Results of second level analysis

	$p_{uncorrected}$	*T*	Coordinates mm mm mm	Corresponding brain area
Positive effect of	.002	2.90	-34 -60 -24	Cerebellum VI
Anticipation vs Baseline	.003	2.83	-6 -68 4	Lingual gyrus
(Figure 5)	.004	2.68	30 20 -10	Insula
Positive effect of high	.001	3.24	24 -46 10	Precuneus
rewards vs low rewards	.002	2.94	16 -50 78	Superior parietal gyrus
(Figure 6)				
Positive effect of low	.001	3.03	26 44 24	Middle frontal gyrus
rewards vs high rewards	.003	2.79	-2 6 30	Cingulate gyrus anterior
(Figure 7)	.003	2.75	58 -42 52	Inferior parietal gyrus
	.005	2.63	66 -34 22	Superior temporal gyrus
Positive effect of	.002	2.99	-56 -2 -2	Superior temporal gyrus
placebo vs Amisulpride	.005	2.64	-44 -78 24	Middle occipital lobe
(Figure 8)				
Positive effect of	.001	3.03	36 -56 -34	Cerebellum crus I
Amisulpride vs placebo	.002	2.94	40 -18 -12	Hippocampus
(Figure 9)	.002	2.93	-64 -4 30	Postcentral gyrus
	.004	2.70	44 -4 12	Rolandic operculum
	.004	2.69	32 -70 -18	Cerebellum VI
Positive interaction of	.003	2.80	-4 -42 -6	Cerebellum IV/V
group x reward level	.004	2.66	-24 -22 64	Precentral gyrus
(Figure 10)				

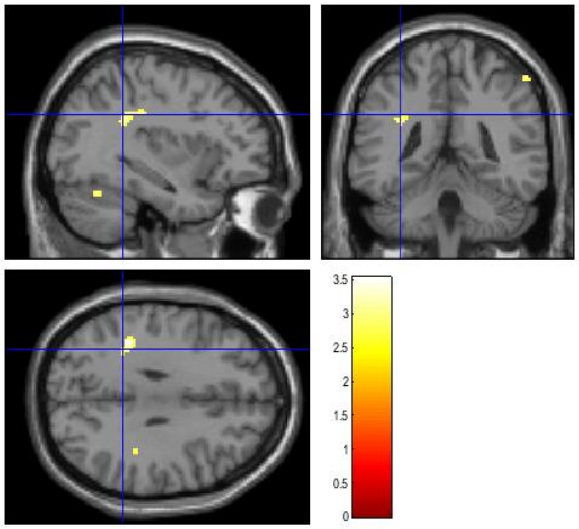

Figure 5. Anticipation vs Baseline

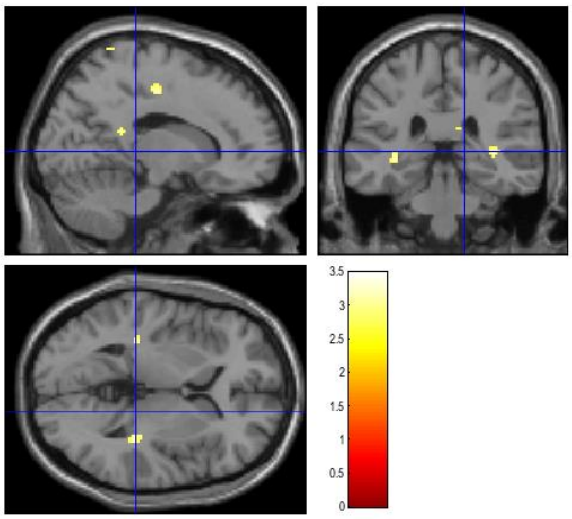

Figure 6. High rewards vs low rewards

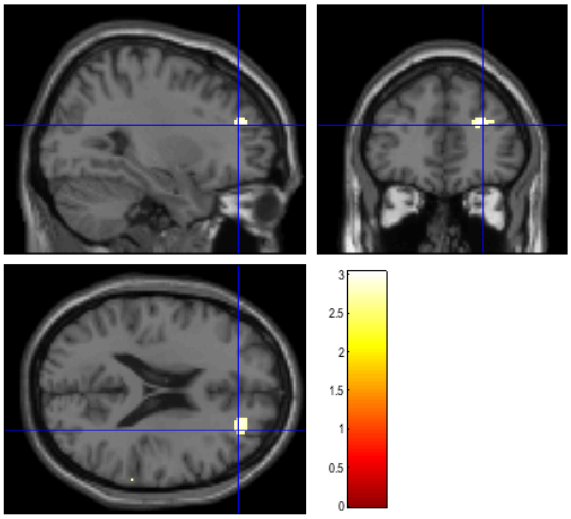

Figure 7. Low rewards vs high rewards

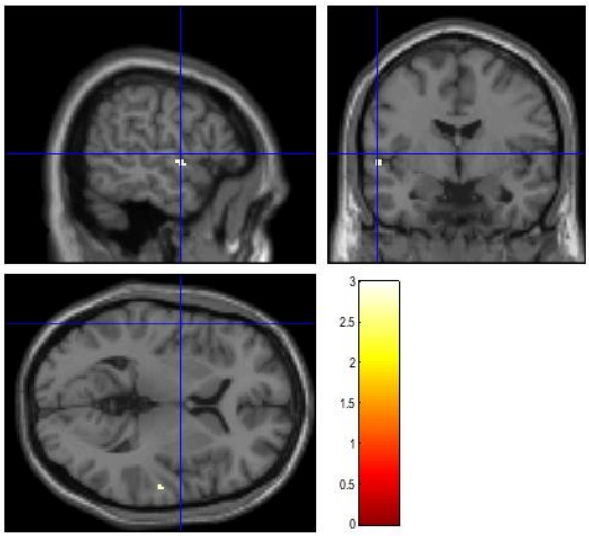

Figure 8. Placebo vs Amisulpride

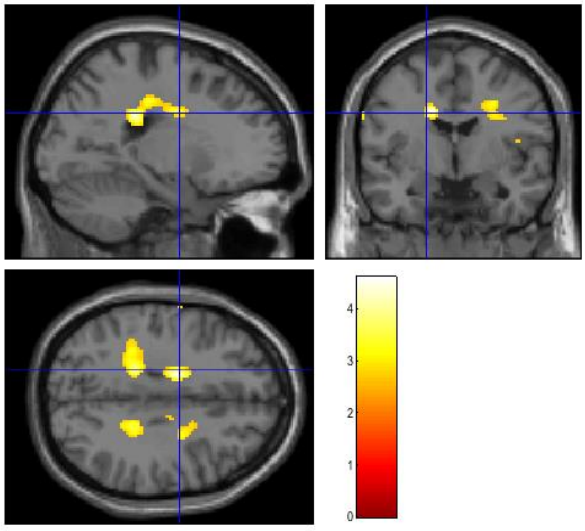

Figure 9. Amisulpride vs placebo

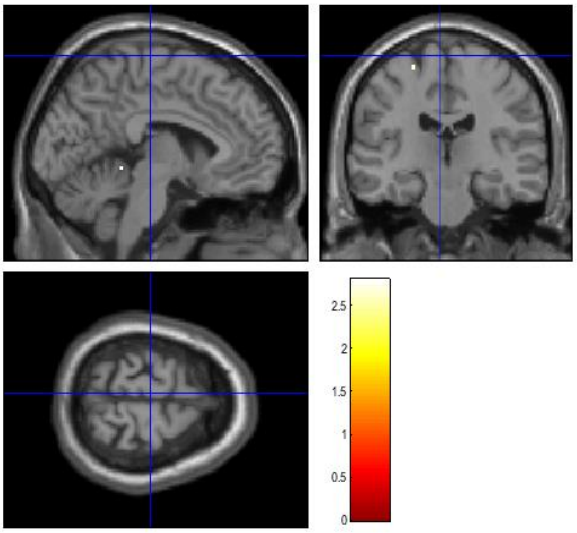

Figure 10. Group x Reward level

Discussion

The goal of this study was the investigation of wanting of primary rewards in healthy individuals depending on reward type, high and low, and the role of dopamine in this process using placebo and dopamine antagonist medication. The analysis included behavioral data in form of wanting ratings and given effort to obtain the reward, as well as fMRI data which gave further depth to the examination. In the fMRI scanner, participants were shown a picture of one of three drink options which had different levels of desirability: Chocolate milk (a highly desirable reward), sweetened milk (reward of lowest desirability) or a mixture of both (medium desirability). They then rated their wanting for the presented option and regulated the probability to get it by applying pressure to a hand dynamometer. It was shown which reward was obtained and it was then administered into the subject's mouth via plastic tubes. The experiment group received a dopamine antagonist of the name of Amisulpride 3 hours before completing the reward task, while the control group received a placebo pill. A general difference in wanting ratings and effort depending on the type of reward was suspected. Furthermore it was hypothesized that the groups would differ in their wanting ratings and the effort measurements and that the difference depended on the type of reward. Additionally the brain activation during the reward announcements was analyzed, to show possible group and reward level differences in activation in brain regions that were previously associated with wanting of primary rewards.

Behavioral results

Only the difference of subjective wanting ratings for a high reward versus subjective wanting ratings for a low reward was significant. A trend was found for effort depending on

the reward type, but no significant difference. Most importantly there was no significant group difference between the Amisulpride and the placebo group for high and low rewards in wanting ratings and effort. Subsequently only the initial hypothesis predicting a difference in wanting ratings for high and low rewards could be confirmed.

It comes as a surprise that there was only a trend indicating higher effort to achieve higher rewards compared to lower rewards and no significant difference, since this measurement was implemented as an additional rating of wanting in a more objective and subconscious manner. Now, different conclusions could be drawn from these results. Effort to maintain a primary reward may not be a reliable way to measure wanting. Neuropsychological processes of reward wanting specifically are still poorly understood, so it's possible that other factors influence the decision of how much effort should be given to maintain a reward to a greater extent. Another concern that could arise is that the incentive value that a primary reward holds is more available to the person when asked directly and not so much when trying to assess it in other ways. Even though many studies assessed wanting only by asking the participants (e.g., Born et al., 2011), critics demanded that a more objective way of assessment should be implemented additionally (e.g., Finlayson et al., 2005) which this study did.

To confront these possible concerns, the correlations between wanting and effort were calculated additionally. This analysis showed that wanting rating and effort correlated highly in all conditions (Cohen, 1988) and can subsequently be regarded to measure at least similar constructs. As long as wanting of primary rewards as a distinct process is not completely recognized, it should be examined with more investigative techniques than ratings on a scale in future studies. Effort to obtain a reward seems to be an appropriate measurement of wanting, even though slight changes in the methodological approach are encouraged in further investigations. For instance the high and low rewards could be more different to one another or the MVC measurement could not be visualized for the subject, as it is possible that seeing their force could lead them to apply more pressure even for low rewards.

Another surprising finding was the lack of group difference in wanting ratings and effort for high and low rewards. Dopamine has been shown to play an important role to generate wanting in animals (Berridge, 1996; Smith et al., 2009) and humans alike (e.g., Born et al., 2011). So since a 400 mg dose of Amisulpride has been shown to decrease brain dopamine (Rosenzweig et al., 2002), it was hypothesized that the experiment group should display significantly less wanting of primary rewards. The results of this experiment don't support the hypothesis, but this doesn't mean that wanting of primary rewards is not regulated by dopa-

mine. The limitations of this study which are stated below could account for the lack of confirmation of previous studies' results.

Furthermore a group difference was found in the correlations between wanting ratings and effort. The Amisulpride group showed a significantly smaller connection between the two constructs when offered a high reward than the placebo group. These findings give first indications to the theory that Amisulpride and subsequently a lack of dopamine may alter the relationship between conscious wanting and the willingness to obtain a primary reward. This link should be investigated further in future research.

FMRI results

The scans done while presented the food rewards were contrasted to baseline scans to see which brain areas are active in anticipation processes. While confronted with a cue that leads to the reward, the state of expectation triggers the incentive salience of the reward in the participant (Berridge & Robinson, 1998). In this situation the cerebellum (IV), the left lingual gyrus and the insular cortex were more active than in in the baseline comparison. The cerebellum is responsible for executive function, motoric control and embodied cognition, as well as anticipatory control mechanisms (Koziol, Budding, & Chidekel, 2012). The latter is most likely to have led to the activation in this case. The left lingual gyrus is most commonly associated with processing local features of visual stimuli and reading (Mechelli, Humphreys, Mayall, Olson, & Price, 2000), but is also believed to be active when the subject is required to make a stimulus specific response (Price, Moore, & Friston, 1997). So this activation can be explained due to the fact that in the reward task a picture of the drink that could be or was obtained was shown and participants knew they had to subsequently rate the option. The third anticipation activation was located in the insular cortex, which is associated with sensorimotor processing, socio-emotional processing and higher cognitive functions, like attention and salience processing (Uddin, Nomi, Hebert-Seropian, Ghaziri, & Boucher, 2017). The higher activation could therefore be explained by the higher mental processes that were necessary to perceive and interpret the stimulus cue. The insula has also be identified in a study by Born et al. (2012) to be involved in wanting processes for food rewards, so this could indicate that wanting was active during the anticipation period.

The second analysis contrasted brain scans obtained during high reward anticipation and low reward anticipation. Two brain areas that were especially active when presented a high reward option were the precuneus and the superior parietal gyrus. These two brain regions form part of the Default Mode Network which is active while doing nothing (Harrison et al., 2008) which could be a possible explanation for the activity. Besides that the precuneus

plays a central part in visuo-spatial imagery, episodic memory retrieval and self-processing operation like agency operations (Cavanna & Trimble, 2006). It's possible that the confrontation with different levels of reward, especially with a high reward, triggers a self-assessment of one's ideas about the self. A connection of the high reward drink to earlier memories in many participants is also a plausible explanation. Meanwhile the superior parietal lobe is responsible for sensorimotor integration and maintaining an internal representation of the body's state (Wolpert, Goodbody, & Husain, 1998) which doesn't seem relevant for high reward anticipation specifically.

Low reward anticipation triggered activation in the middle frontal gyrus, the cingulate gyrus anterior, the inferior parietal gyrus and the superior temporal gyrus. The dorsolateral prefrontal cortex, which lies in the middle frontal gyrus and is known to play an important role in decision making and working memory (Levy & Goldman-Rakic, 2000), which are cognitive functions necessary to process different levels of rewards. The anterior cingulate gyrus is theorized to be responsible for self-regulation and active when receiving rewards as well as pain (Posner, Rothbart, Sheese, & Tang, 2007). The superior temporal gyrus is a structure that lies between amygdala and the prefrontal cortex and is mainly responsible for auditory processing and social cognition (Bigler et al., 2007). Its location could be the reason for reward related activity. The inferior parietal lobule is involved in agency, similar to the precuneus (Chaminade & Decety, 2002), so it seems like the sense of being able to generate action seems an important process when confronted with different levels of reward.

The goal of the third analysis was to compare the brain activation of the Amisulpride group with the placebo group in response to the stimuli cues to confirm or reject the third hypothesis. Group differences were observed in the superior temporal gyrus, the middle occipital lobe, the cerebellum (crus I and VI), the hippocampus, the postcentral gyrus and the rolandic operculum. As stated before the superior temporal gyrus is responsible for sensorimotor integration which doesn't seem relevant to the reward task, but could indicate mental preparation for the drink (Wolpert et al., 1998). The occipital lobe is mostly known for its several functional areas for vision (de Schotten, Urbanski, Valabregue, Bayle & Volle, 2014), while the hippocampus is believed to play a role in memory (Morris, 2007). It is currently not clear how these structures relate to dopaminergic functioning in the brain. The postcentral gyrus, the location of the primary somatosensory cortex, is responsible for processing somatic information (Geyer, Schleicher, & Zilles, 1999). A possible explanation could be that the medication altered the conception of the tubes inside the subject's mouth, since there was no other somatic sensation present during the reward announcements. The cerebellum being re-

sponsible for executive functions like anticipatory control mechanisms (Koziol et al., 2012) could be a hint to altered wanting in the experiment group in contrast to the control group. In earlier fMRI studies the cerebellum has not been linked to wanting of primary rewards yet and reward anticipation is a complex process with more influential factors than just wanting (Zhang, Li, Wang, Liu, & Zheng, 2017), but future research should investigate this connection further. Lastly the rolandic operculum is associated with many different functions like sensory, motor, autonomic and cognitive processing, as well as language (Mălîia et al., 2018). It is hard to pinpoint the increased activity in one group to one of the functions, especially because the rolandic operculum has not been connected to wanting in previous research, but it should be noted that the rolandic operculum is also located in close proximity to the dopaminergic circuits in the brain.

The last analysis involved the interaction between the factors group and reward level. A significant difference was found in the cerebellum, which has already been listed in the anticipation and group evaluation, and the precentral gyrus. The precentral cortex is responsible for movements (Boschert & Deecke, 1986). The anticipatory control mechanisms that take place in the cerebellum and could hint to a difference in wanting have already been discussed.

Conclusions

The most important results of the behavioral part of this study were that wanting ratings differed depending on the level of food reward, while effort to obtain them only showed a trend towards higher effort for higher rewards. The fact that wanting ratings and effort did correlate highly in every condition shows however that effort to obtain a reward is an adequate way of measuring wanting as well. Amisulpride didn't have a significant influence on wanting ratings and effort for food incentives. But it was shown that in the experiment group the correlation between ratings and effort for high rewards was significantly weaker than in the control group.

In the fMRI analysis no connection was made to the results of earlier studies that located wanting processes for rewards mainly in dopaminergic brain regions like the VTA, the NAc (Born et al., 2011), the VP, the OFC, the hypothalamus (Jiang et al., 2015), the caudate nucleus and the putamen, as well as the thalamus (Born et al., 2012; Hermann et al., 2006). In this experiment subjects with lower brain dopamine levels didn't show less activation in these brain regions when in a state of anticipation for a food reward. One interesting outcome was the activation of the cerebellum in the anticipation and group condition, as well as the interaction analysis between group and reward level. While the cerebellum is not part of the dopa-

minergic pathways, it has been known to play a role in anticipatory processes and has been suspected to play a role in wanting processes as well (Zhang et al., 2017).

Limitations and outlook

Even though this experiment could not confirm the hypotheses which were based on results of previous studies, the existence of a distinct wanting process for primary rewards which is regulated by dopamine should not be negated entirely. The methodological approach of combining pharmacological intervention and fMRI is important to put into practice in research which regards brain processes, like wanting, which are difficult to differentiate distinctively. But this kind of experiment brings unique and hard to overcome challenges, which are stated in the next paragraph as the limitations of this study.

Separate dopamine regulated wanting processes for primary rewards and associated brain regions have been thoroughly researched in animals (Berridge, 1996; Berridge & Valenstein, 1991; Smith et al., 2009; Treit & Berridge, 1990; Wise et al., 1978). But neuropsychological research into the matter with human test subjects has only just begun. Especially fMRI studies to identify involved brain areas are still few and far between. This preliminary study is a first step to propone a methodological approach to investigate the issue, but results should still be seen critically and in context with previous study results.

For time management reasons and because of the long testing time for one subject only 40 instead of 60 participants were included in the analysis. Three more had to be excluded from the fMRI part, which makes an uncomplete sample. The explanatory power of the results and interpretations are therefore limited and cannot be generalized to a greater population. This study was part of a bigger experiment which will include all subjects and results will be more reliable.

It was important to design an experiment in which the food reward is obtained and directly afterwards received by the participant. This has not been done in the reference studies, where the food incentives were either hypothetical or not given directly in the fMRI scanner (e.g., Born et al., 2011; Jiang et al., 2015). To imitate a real life situation in the artificial testing environment it was essential to investigate wanting in close proximity to the real obtainable food reward. This design resulted in increased participant movement inside the scanner due to the long scanning process (about 1 hour and 10 minutes) and due to the motion produced by drinking and swallowing the liquids. The SPM analysis of the data was not tailored to correct this increased movement and this may have led to activation not being attributed correctly. All this will be kept in mind for the fMRI evaluation of all subjects in the bigger study.

One part of the experiment that should be revised in future studies is the effort rating taken by MVC. It is essential to implement an additional wanting evaluation apart from ratings on a VAS scale which is less subjective and explicit (Finlayson et al., 2007). But the results of this experiment let the question arise why ratings but not effort were dependent on reward type and if effort is a suitable way of measuring wanting. According to the correlations, ratings and effort are strongly connected. Also effort to obtain a reward has been proven in previous studies (Waugh & Gotlib, 2008) to be an appropriate wanting measurement. But the way the effort rating was obtained could be revised. An MVC measurement of the maximal power was obtained before and after the task. During the task participants were instructed to regulate the probability to get a specific drink option by pressing the hand dynamometer. If a lot of pressure was applied, the probability rose. Subjects were able to see how strongly they pressed with a red bar graph which could lead them to press harder than necessary even for the low rewards. They might have wanted to see how strong they can press or they might have wanted to fill in the bar. Participants were also instructed to press as hard as they could for the first MVC measurement, which was then used for comparison. Some subjects pressed really hard which made it difficult to obtain high rewards later in the task. So the instructions could be adapted or maximal power measures could also be taken during the task, not only before and after. These concerns should be taken into account in future experiments that want to include effort as an additional wanting rating.

The last concern that should be considered in future research is the food reward itself. Even though participants were screened before the experiment for their liking of sweet food and their habit of using it as a reward by completing The Health and Taste Attitudes Questionnaire (Roininen et al., 1999), it can't be completely ruled out that some participants may have found the low reward more or equally palatable in comparison to the high reward. Wanting ratings did differ in favor of the chocolate milk but there was only a trend in effort to obtain the chocolate milk instead of the sweetened milk. The distinction of high and low reward has been based on results of a previous unpublished study by Korb et al. (2019), but for future research it should be examined on testing day which food or drink option each subject prefers.

To summarize, this study did not confirm the hypothesis that Amisulpride and the subsequent decreased dopamine levels in the brain lead to lower wanting for food rewards. This was shown on a behavioral level, by assessing wanting ratings and the effort that was presented to obtain the reward, and by examining the brain activity of the experiment and control group to find differences in regions that have been identified to play a role in primary reward wanting in previous studies. Due to the limitations of this study that mostly stem from the

complex study design, these results should still be seen critically. More so, the fact that no significant effect was found should inspire future research to look further into the topic of dopamine regulated wanting processes and to avoid the stated limitations. It is of great importance to investigate reward processing in humans with different levels of reward, with measurements of wanting besides explicit ratings, with tangible food rewards being available in the testing situation and with a methodological approach that is able to show even subtle differences in behavior and brain activation. That is why a combination of pharmacological intervention and fMRI is especially useful for investigations in this field. Future research with a similar method should include a complete sample to generate generalizable results and should correct for increased movement in the scanner. Furthermore reward levels should be classified for each subject and the measurement of effort could be revised. In addition to these improvements of the procedure, future studies should examine the role of the cerebellum in wanting processes further. This study showed in form of a group difference between the Amisulpride and the placebo group regarding high and low rewards that cerebellum activation was dependent on dopamine levels in the brain. It has been theorized that the cerebellum is involved in wanting through its anticipatory control function (Zhang et al., 2017), but the concept is still new and not thoroughly explored.

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Appendix

- Abstract (English)
- Abstract (German)
- Promotional flyer
- Instructions for reward task

Abstract

In this study primary reward processing in healthy participants was investigated. It was theorized that wanting of rewards is a separate dopamine regulated cognitive process in incentive experiences and is located in specific brain areas. For the investigation 40 participants were separated into two groups: The experiment group was given a dopamine antagonist while the control group received a placebo. Every subject had to complete 16 trials of a reward task in an fMRI scanner. First, they were presented one of three drink options (high reward, low reward or medium low reward), then they had to state their wanting for the option by VAS rating. Additionally, the effort they were willing to put in to obtain the option was measured. Lastly, they received the presented drink or an alternative depending on the effort. The behavioral analysis revealed a difference in wanting ratings depending on the reward level, while no difference was found for effort. The mixed design ANOVA showed no interaction effect of group with neither wanting ratings nor effort. The fMRI analysis didn't show the expected results neither. One outcome which should be further investigated in future studies was the difference in cerebellum activation in an anticipatory state and in the group evaluation. These findings don't disprove the results of previous studies regarding a dopamine regulated wanting process for primary rewards in humans, as these limitations could have had an influence on the results: The sample was not complete, t-he fMRI analysis did not correct for the movement in the scanner and reward preferences were not evaluated for each subject.

Keywords: wanting, primary rewards, food rewards, dopamine, Amisulpride, fMRI

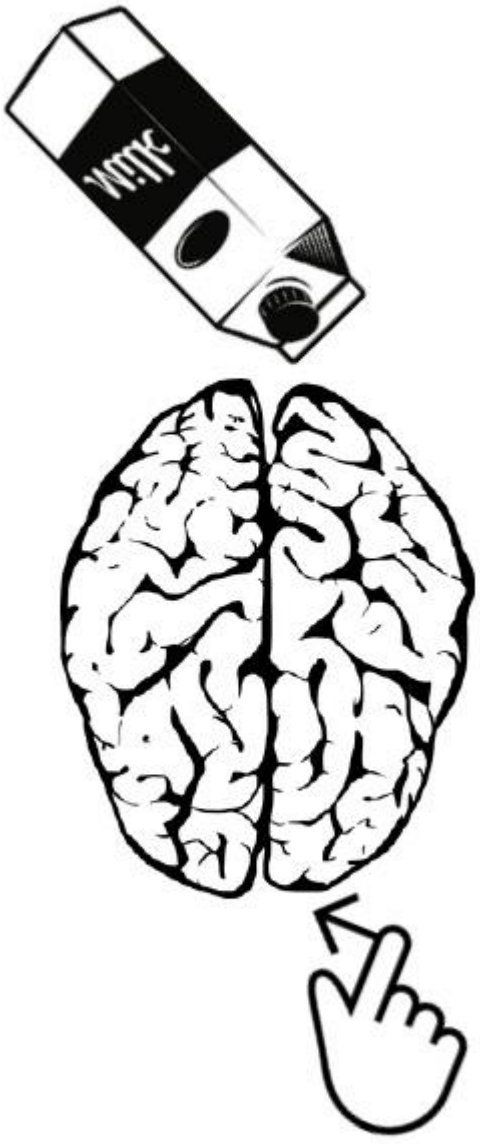
Abstract (German)

In dieser Studie wurde der Belohnungsverarbeitungsprozess von gesunden TeilnehmerInnen bezüglich positiven Nahrungsstimuli untersucht. Es wurde vermutet, dass Wollen einen separaten, Dopamin-regulierten kognitiven Prozess im Belohnungserleben darstellt und daher in speziellen Gehirnarealen angesiedelt ist. Für diese Studie wurden 40 TeilnehmerInnen in zwei Gruppen eingeteilt: Die Experimentgruppe bekam einen Dopaminantagonisten, während die Kontrollgruppe ein Placebo erhielt. Alle TeilnehmerInnen absolvierten 16 Runden einer Belohnungsaufgabe in einem fMRT Scanner. Ihnen wurde eine von drei Getränkeoptionen präsentiert (hohe Belohnung, niedrige Belohnung oder mittlere-niedrige Belohnung). Dann konnten sie auf einer VAS ihr Wollen für die Option angegeben und es wurde die Anstrengung gemessen, die sie gewillt waren auf sich zu nehmen, um das Getränk zu erhalten. Zuletzt erhielten sie die angezeigte Option oder eine Alternative, abhängig von der eingesetzten Bemühung um das Getränk. Die statistische Verhaltensanalyse zeigte einen Unterschied in der Bewertung des Wollens abhängig von der Höhe der Belohnung, während solch ein Unterschied nicht für die gemessene Anstrengung gefunden wurde. Die mixed design ANOVA zeigte keinen Interaktionseffekt von Gruppe mit Bewertung des Wollens und Anstrengung. Die Analyse der fMRT Daten zeigte ebenso nicht die erwarteten Ergebnisse. Ein Zusammenhang, welcher in künftiger Forschung weiter untersucht werden sollte, war die gesteigerte Aktivität des Cerebellums während der Belohnungserwartung und im Gruppenvergleich. Diese Ergebnisse widerlegen nicht die These vorheriger Forschung bezüglich eines Dopamin-regulierten Wollens für primäre Belohnungsreize in Menschen, da die Limitationen des Experiments einen Einfluss auf diese gehabt haben könnten: Die Stichprobe war nicht komplett, die fMRT Analyse war nicht dafür ausgelegt für die gesteigerte Bewegung zu korrigieren und die Belohnungspräferenzen wurden nicht für jede/n TeilnehmerIn erhoben.

Keywords: Wollen, primäre Belohnungsreize, Nahrungsbelohnungen, Dopamin, Amisulprid, fMRT

Promotional flyer (original language)

TEILNEHMER_INNEN FÜR STUDIE GESUCHT



Was passiert im **Gehirn**, wenn einem angenehme Dinge passieren?

Sie sind **zwischen 18 und 35** Jahre jung, **gesund**, und mögen **Kakaomilch** und **sanfte Berührungen**?

Dann melden Sie sich, um bei unserer Studie mitzumachen und dafür eine **finanzielle Entschädigung** zu erhalten. Sie können auch ein Bild Ihres Gehirns mit nach Hause nehmen.

INHALT

Die Studie wird von der Abteilung für Neuropsychopharmakologie und Biopsychologie durchgeführt und untersucht die Funktionsweise gewisser Rezeptoren bei der Beeinflussung von sozialer Kognition, Motivation und Entscheidungsfindung. TeilnehmerInnen erhalten einmalig einen von zwei zugelassenen **Arzneistoffen**, oder ein entsprechendes Scheinpräparat (Placebo). Danach füllen sie am Computer Fragebögen aus und lösen innerhalb eines Magnetresonanztomographen (MRT) verschiedene Aufgaben, bei denen auch Kakaomilchproben und Berührungsreize am Unterarm beurteilt werden.

DAUER

Insgesamt dauert die Studie **7 Stunden** und findet an **2 Tagen** statt. Zwischen den Terminen dürfen maximal 60 Tage liegen.

ORT

Univ. Klinik für Psychiatrie & Psychotherapie, Allgemeines Krankenhaus, Währinger Gürtel 18-20& Exzellenzzentrum Hochfeld-Magnetresonanz, Bauteil 32, Lazarettgasse 14; 1090 Wien, Medizinische Universität Wien

Bei Interesse schreiben Sie bitte eine E-Mail mit Angabe Ihrer Telefonnummer an **psy.wien@gmail.com**.

Instructions for reward task as shown to the participants (original language)