universität wien

# MASTERARBEIT / MASTER'S THESIS

Titel der Masterarbeit / Title of the Master's Thesis

## „ The role of dopamine on 'wanting' social rewards: A psychopharmacological fMRI study "


verfasst von / submitted by

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angestrebter akademischer Grad / in partial fulfilment of the requirements for the degree of

Master of Science (MSc)

Wien, 2022 / Vienna 2022

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|---|---|
| Studienkennzahl lt. Studienblatt / degree programme code as it appears on the student record sheet: | UA 066 840 |
| Studienrichtung lt. Studienblatt / degree programme as it appears on the student record sheet: | Masterstudium Psychologie UG2002 |
| Betreut von / Supervisor: | Assoc.-Prof. Giorgia Silani, PhD |

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# Theoretical Background

## Introduction

Rewards have a decisive influence on our entire lives. The scientific debate about rewards, their motivational power, and how they influence our behavior has a long history. It goes back to ancient Greece with the philosophical approaches of Plato, has gained further attention through prominent psychological concepts of early behavioralists (including Skinner and Thorndike), and is still an exciting part of neuroscientific discourse into the present day. In the process, earlier research has already gained remarkable insights in its understanding of the underlying neural mechanisms. One currently prominent theory has been able to identify at least two psychologically and neurologically distinguishable components of reward processing (Berridge & Robinson, 1998). According to this, a motivational component, of 'wanting', is involved, which appears to be dopamine-mediated, whereas the hedonic component, or 'liking', is primarily based on the opioidergic system. However, this distinction has so far been demonstrated mainly in animals, while evidence for its transfer to humans is still limited (Delgado, 2007).

Moreover, the class of social rewards in particular has recently gained increased interest in social cognitive science (Wake & Izuma, 2017). Social rewards are an influential determinant of all social species and a major driving force for what we seek or avoid in our lives. They are as complex as they are diverse, ranging from a simple smile, everyday interaction, and touch to social recognition and appreciation (Bhanji & Delgado, 2014). Previous research has shown that social rewards are as necessary for our survival as, for instance, food or sex (Trezza et al., 2010). Their relevance is further underpinned by negative consequences when they are absent, as illustrated by the dramatic consequences of perceived loneliness on well-being and health (Cacioppo et al., 2015). Studies on various clinical disorders, such as autism spectrum disorders or substance dependencies, point in particular to a disturbed function of 'wanting' when 'liking' is intact (Clements et al., 2018) or, conversely, to a hyperreactive 'wanting' in the absence of 'liking' (Berridge & Robinson, 2016). A deeper understanding of the normal processing of 'wanting' social rewards has therefore important clinical implications and might help to create effective, sustainable prevention and treatment services that could significantly improve the lives of those affected.

To address this knowledge gap in the literature, the main objective of the present thesis is to investigate the role of dopamine on the motivational component of social reward processing in healthy humans, by using a psychopharmacological intervention combined with neuroimaging techniques.

To achieve this goal, 60 healthy subjects were assigned to an experimental or a control group, each was administered either a dopamine antagonist (400 mg amisulpride) or a placebo. Subsequently, a recently developed reward task was performed during which neural activation was recorded. During this task, subjects received three different social (touch) reward stimuli consisting of gentle stroking of the forearm at different speeds, which thus varied in their reward level. In the anticipation phase, a cue was presented announcing a stimulus with a high reward value. Self-report ratings were conducted to assess how much the participants subjectively want to receive the stimulus. Additionally, they pressed a dynamometer, influencing the likelihood to obtain the offered reward or a lower rewarding alternative, with proportionally increased probability with greater exerted effort. Based on the literature, it was hypothesized that the blockade of dopamine results in reduced wanting of reward stimuli at both behavioral (subjective ratings and exerted effort) and neural levels (in corresponding brain regions associated with the reward system).

The present thesis is structured as follows: first, the theoretical background is outlined, the reward system in general, more specifically the functional role of dopamine in reward processing as well as the state of research on social rewards to date, with a particular focus on studies involving pharmacological manipulation or neuroimaging. Social touch is then presented as a particularly powerful type of social reward, as well as the CT fibers which are proposed to encode affective touch. The first part concludes with a selection of clinical and social implications of the topic. From these considerations, the research question and hypotheses are subsequently derived. Next, the methods used to investigate the hypotheses are explained. In the third part, the results of the analysis, divided into behavioral and neural, are presented. Finally, the findings are discussed in the last part of the paper, and possible limitations and perspectives on future directions are addressed.

## The reward system: Dopaminergic pathways

Among species, the reward system refers to a broad neural circuit that is involved whenever something rewarding is experienced and processed. The brain responds to a reward stimulus with an increased release of the catecholaminergic neurotransmitter dopamine (Schultz, 2002; Wise, 2009). Accordingly, the group of structures considered to be part of the reward system is localized mainly along the major dopaminergic pathways, including (among other regions) midbrain dopaminergic areas, the striatum, and the ventral and medial prefrontal cortex (Haber & Knutson, 2010).

Three major dopaminergic pathways, namely the *nigrostriatal* (also termed *mesostriatal), mesolimbic,* and *mesocortical* pathway, which project from the midbrain to the basal ganglia, have been distinguished on the basis of their anatomically (and to some extent functionally) distinct components (Arias-Carrión et al., 2010; Björklund & Dunnett, 2007; Wise, 2009).

The *mesolimbic pathway* is the one that has been most commonly associated with reward in literature (Baik, 2020; Schultz, 2002). It originates in an area in the brainstem called the ventral tegmental area (VTA). The VTA is one of the most important dopamine-producing areas in the brain (the other being the substantia nigra) (D'Ardenne et al., 2008). The dopamine-containing neurons project from the midbrain to several limbic structures, the largest projection is to a region in the ventral striatum (VS) called the nucleus accumbens (NAcc) (Ward, 2020) as well as the olfactory tubercle (Arias-Carrión et al, 2010), innervating the amygdala and the hippocampus (Wise, 2004). In humans, in particular, the striatum is a key component in the reward circuit, strongly associated with a broad spectrum of social functions, including the modulation of reward experiences in social interactions, the evaluation of social rewards, and enforcing of social norms (Bhanji & Delgado, 2014).

The second major dopaminergic pathway also originates in the VTA but projects to the cerebral cortex, particularly to the frontal lobes, such as the prefrontal or the cingulate cortex, therefore called the *mesocortical pathway* (Arias-Carrión et al., 2010). The projections of this pathway are very diverse and include a variety of functions, such as emotion, motivation, and executive functions (Phillips et al., 2008; D'Ardenne et al., 2008; Wise, 2004). Collectively, because of the overlap between these two pathways, they are referred to as the *mesocorticolimbic dopamine system* (Wise, 2004).

The third pathway, called the *nigrostriatal pathway*, originates in the pars compacta of the substantia nigra (SNc) (the second largest dopamine-producing area in the brain), located also in the midbrain next to the VTA (Arias-Carrión et al., 2010). It extends its fibers into the caudate nucleus and the putamen (Arias-Carrión et al., 2010), both located in the dorsal striatum, which is part of the basal ganglia (Robbins & Everitt, 1992; Bhanji & Delgado, 2014). The *nigrostriatal system* plays an essential role primarily in motor function and the control of voluntary movement (Smith & Villalba, 2008) and was therefore a long time mainly in focus of research regarding the Parkinson´s disease (Smith & Villalba, 2008; Wise, 2009). Recently, however, there has been increasing evidence that this projection, likewise the *mesocorticolimbic dopamine system*, is associated with reward processing (Schultz, 2002; Wise, 2009).

## The functional role of mesolimbic dopamine activity in reward processing

The functional role of mesolimbic dopamine in terms of its contribution to reward has been an ongoing debate with competing theories over the past decades (Berridge, 2006). The most prominent explanations can be summarized under the three psychological categories of learning, 'liking', and 'wanting' (Berridge & Kringelbach, 2015; Berridge et al., 2009; Robinson et al., 2005). Berridge and Robinson (2003) divided each of the three categories into implicit and explicit processes respectively. While these were often identical, they can also occur independently. To make this distinction clear, 'wanting' and 'liking' were written in quotation marks in accordance with this theoretical background. Whereby, 'wanting' refers to the mesolimbic motivational process of the incentive salience of 'wanting' in contrast to the conscious wanting (explicit desired, cognitive incentives) used in everyday language. 'Liking' is applied when the term refers specifically to the behavioral or neural hedonic responses regardless of whether those objective affective reactions are accompanied by a corresponding conscious, explicit feeling of liking or pleasure (Berridge & Kringelbach, 2015).

While one group of researchers proposed that dopamine mediates learned predictions of future rewards, causes prediction error teaching signals, and stamps in associative links (learning) (Schultz et al., 1993; Schultz et al., 1997; Schultz, 1998; Hollerman & Schultz, 1998), other researchers argued instead for dopamine mediating primarily the hedonic impact of rewards ('liking') (Wise et al., 1978, 1982). However, the hypothesis that has become more

widely accepted over time and consistent with growing evidence indicates that dopamine motivates reward-seeking specifically by attributing causally incentive salience to reward-related stimuli ('wanting') (Berridge et al., 2003, Berridge, 2009). Those three perspectives of the role of dopamine in those dissociable psychological components of reward were discussed in more detail as follows.

***Learning: Reward prediction error***

From a behavioral point of view, rewards are defined as events or objects that generate approach and consummatory behavior and accordingly produce learning of these behaviors (Schultz, 2004; Schultz, 2010). Learning is an essential component of rewards since most of the things that are wanted and liked were learned previously.

Reward-directed, associative learning is based on Pavlovian conditioning (whereby an initially neutral stimulus is associated with a reward) or on instrumental conditioning (response-contingent reinforcement) (Berridge & Robinson, 2003; Schultz, 2004).

Once reward-related cues are learned, these cues predict the associated rewards. According to the 'associative learning hypothesis', dopamine signaling is required for humans and animals to learn these cue-reward associations. Several groups of researchers have shown that changes in the firing pattern of dopamine neurons (Hyland et al., 2002; Nishino et al., 1987; Schultz, 1998), as well as temporary increases in striatal dopamine concentrations (Phillips et al., 2003; Roitman et al., 2004), correlate significantly with behavioral adaptations during reward-related learning in rodents and primates (Robinson et al., 2005).

However, early studies by Wolfram Schultz in the 1990s captured the attention of neuroscientists during this decade, providing the main idea, that the fast, phasic responses of dopamine neurons to reward delivery appeared to code a prediction error (Hollerman & Schultz, 1998; Schultz et al., 1993; Schultz et al., 1997) rather than the stimulus-reward pairing alone, indicating the difference between predicted and actual rewards (Schultz, 2002).

Schultz and colleagues (1997) used single-unit recordings to examine the activity of dopaminergic neurons in monkeys when they received rewarding food stimuli, such as a morsel of apple or a small quantity of fruit juice, preceded by neutral stimuli (light). The researcher found initially that the firing pattern of dopamine neurons changed after the animals learned to associate the previously neutral stimulus with the reward. After repeated pairings of the cues followed by the reward, dopamine neurons changed the time of their

activation from just after reward delivery to the time of conditioned cue onset and subsequently to the *anticipation* of the reward. However, in trials in which the reward was not delivered at the appropriate time after the cue was presented, dopamine neurons were depressed below their basal firing rate at precisely the time when the reward should have occurred.

Accordingly, the prediction-error equation states that a reward that is better than predicted induces dopamine activation (positive prediction error), a reward that is fully predicted evokes no response, and a reward that is omitted or worse than predicted elicits depression (negative error) (Schultz et al., 1993; Schultz et al., 1997; Schultz 1998; Schultz, 2010).

However, there have also been contrary lines of research questioning this interpretation of the dopamine role in reward processing. For instance, Robinson and colleagues (2005) examined genetically engineered dopamine-deficient mice for the acquisition of an appetitive T-maze task with and without endogenous dopamine signaling. The results revealed that dopamine is not necessary for mice to learn new associations between salient cues and rewards. Additional lesion studies (Berridge & Robinson, 1998) confirmed that dopamine does not seem to be necessary for reward association learning. Animals could still learn new reward values even after near-total lesions of dopamine systems (Berridge & Robinson, 2003). Instead, it is hypothesized that anticipatory mesolimbic dopamine activity mediates learned ‘wanting’ (Berridge et al., 2003).

### *‘Liking’: The anhedonia hypothesis*

For a long time, the prevailing view of psychologists and neuroscientists has been that people allocate their limited resources to obtain that reward event which they *like* the most (Delgado, 2007; Pool et al., 2016). For many people and common sense, the term reward is associated with something that produces a conscious experience of subjective pleasure (Berridge & Robinson, 2009). Therefore, for decades, the perhaps most influential interpretation of the functional role of mesolimbic and mesostriatal dopamine in reward processing has been the ‘anhedonia hypothesis’, developed by Wise and colleagues (Wise et al., 1978, 1982). The initial version (which Wise himself later revised), posited that under dopamine depletion (after the administration of dopamine antagonists) “all of life's pleasures - the pleasures of primary reinforcement and the pleasures of their associated stimuli - lose the ability to arouse the animal” (Wise, 1982, S. 52). Thus, according to this hypothesis, the role

of the dopamine system would be mediating the pleasure produced by both unconditioned (such as food, drugs or sex) and conditioned (elicited by secondary reinforcers) incentives (Berridge & Robinson, 1998). It passed so prominently into common knowledge that even the public media reported dopamine as the 'brain´s pleasure neurotransmitter' (e.g. Nash, 1997; Watson, 2021).

The broad acceptance of the hypothesis was further reflected in research on addiction. Several researchers indicated that the suppression of dopamine was responsible for anhedonia in drug withdrawal, leading to a 'hedonic homeostatic dysregulation' and that individuals with substance use disorders consequently were seeking drugs which activate the dopamine circuits (such as cocaine) in order to regain 'hedonic homeostasis' (Koob et al., 1997; Koob & LeMoal, 1997; Volkow et al., 1997). Moreover, this view also influenced the investigation of depression, in which anhedonia is considered a major symptom. From this perspective, depression would be due to the reduced experience of pleasure regulated by dopamine (Salamone & Correa, 2012).

At that time, the intrinsic relationship between hedonic pleasure and motivation was so deeply integrated into affective neuroscience that pleasure has been operationalized in related animal studies mainly by equating it with the motivation to obtain a reward. The idea was that changes in measured 'wanting' were proportional to corresponding changes in 'liking' (Berridge & Robinson, 2016). Accordingly, the concepts of 'liking' and 'wanting' were considered to be causally connected or even identical processes and subsequently used in research as synonyms and mostly interchangeable (Berridge & Robinson, 2003). Thus, the traditional behavioral method to measure 'liking' has been to quantify the preferred choice, consumption of a target object, or instrumental behavior such as approaching or pressing a bar. In this way, the liking of a stimulus was determined by the behavioral evidence of an animal wanting it, by measuring whether it chose and consumed the stimulus, and worked to obtain it (Berridge & Robinson, 1998). This operationalization was mainly because the pleasure liking of animals could not be verbally expressed (Toates, 1998). Using this approach, Wise and colleagues (1978, 1982) argued, after early studies with haloperidol or pimozide-treated rats that the observed reductions in food intake and preference after some treating days with the dopamine antagonists were due to reduced reward value and thereby diminished induced pleasure.

In contrast, Berridge and colleagues (1998) approached the investigation of the hedonic impact of dopamine in reward from an entirely different perspective using affective behavioral responses. In this approach, compared to the measurement of instrumental behavior, affective facial expressions were measured during the actual consumption of reward stimuli. These usually reflect the emotional impact of a motivating event rather than the wanting of it in advance. The researchers tested the 'liking' by using the 'taste reactivity task', which is based on the assumption that humans (particularly newborns), monkeys and even rats show different facial reaction patterns to bitter or sweet tastes (Berridge, 1996). Surprisingly, the results indicated that the blockade of dopamine systems did not reduce the hedonic palatability of tastes or cause a shift towards an aversion of the palatable food (Berridge et al., 1998). Furthermore, a follow-up study revealed that administration of dopamine agonists in turn, did not increase the hedonic reactions to palatable tastes either (Berridge et al., 1998). However, these rats ate four to five times as much as they usually did, even when the food was disgusting rather than liked for them. They obtained the same results from lesion studies in which the ascending dopamine neurons of rats were largely destroyed by intracranial administration of dopamine-selective neurotoxins such as 6-hydroxydopamine (6-OHDA). These rats would have starved to death without artificial feeding despite intact motor abilities and easily available food, whereas the 6-OHDA lesions, however, neither enhanced nor suppressed hedonic response patterns. Therefore, Berridge and Robinson (1998) concluded that the manipulations of mesolimbic and neostriatal dopamine systems alter the motivational ('wanting') but not the hedonic component ('liking') of reward. Consequently, in contrast to the previously dominant perspective, they consider 'wanting' and 'liking' to be two separate processes. Moreover, they suggested that both rely on distinctive brain mechanisms.

In order to investigate other neurotransmitter systems regarding their potential role in processing the 'liking' of rewards, the taste reactivity task was also suitable and used for this purpose. Indeed, subsequent research revealed that pleasure is generated by a much smaller and functionally fragile system (Berridge & Robinson, 2016) which is more associated with opioidergic rather than dopaminergic activity (Chelnokova et al., 2014; Berridge & Kringelbach, 2015). In particular, a collection of interactive sites that appear to generate pleasure have been found in limbic structures (e.g., the nucleus accumbens shell or the ventral pallidum), which were referred to as 'hedonic hotspots' (Berridge, 2009; Smith & Berridge, 2007; Smith et al., 2009).

### *'Wanting': The incentive salience theory*

Based on the unexpected findings outlined above, Berridge and Robinson derived the 'incentive salience hypothesis' in the 1990s, which effectively challenged the widely accepted anhedonia hypothesis (1998).

According to the incentive salience theory, 'wanting' is not just a drive of desire, but rather a brain response to a certain percept. When the dopaminergic circuits were activated, reward stimuli become tremendously potent, such as the smell of food when we are hungry. This particular type of desire is based on Pavlovian conditioning. By attaching incentive salience to a cue through association with a reward, it becomes attractive and thus captures attention. The first feature of dopaminergic mediated incentive salience is subsequently, that the cue and the associated reward can trigger a momentary peak of temptation which suddenly become enhanced motivational targets. The second feature is that the cue itself become a motivational magnet, which pulls the attention and makes it difficult not to react to the triggered cue which generates the desire to consume the associated reward. Subsequently, the incentive salience value depends both on the current neurobiological states as well as the pre-existing reward-related associations (Berridge, 2006).

As mentioned initially, Berridge and Robinson (2003) distinguish implicit from explicit wanting. Incentive salience corresponds subsequently to the implicit 'wanting' since it does not necessarily require conscious awareness (Berridge & Robinson, 2009). It can be defined more precisely as a conditioned motivational response of the brain, usually triggered by the interaction between the perception of a reward-related cue present in the environment and an individual in a specific state (Berridge, 2006; Pool et al., 2016). In turn, explicit wanting (also referred to as cognitive incentives) is not driven by Pavlovian associations, but rather by goal-directed action strategies. These are influenced by subjective expectations, as well as episodic memories of previous or current hedonic experiences elicited by the consumption of the reward (Berridge & Robinson, 2003). This theoretical distinction is particularly important for the successful operationalization of the present study (Korb et al., 2020; Massaccesi et al., 2021). Another relevant implication of the incentive salience theory is the timing (Pool et al., 2016). The dopamine-mediated 'wanting' is particularly activated during the anticipation of the reward, whereas during consumption the activation switches to the opioid-mediated 'liking' component (Berridge et al., 2009; Kohls et al., 2012).

Regarding the operationalization, incentive salience can be measured by the motivation to mobilize effort to receive the reward (Pool et al., 2016). It can be assumed that 'wanting' is highest before performing the instrumental action (hereafter referred to as the *pre-effort anticipation phase*) and to some extent also after exerting effort and immediately before consumption (referred to as the *post-effort anticipation phase*). However, if the incentive is presented during the post-effort anticipation phase, the processing is likely more related to reinforcement learning rather than incentive motivation and already might overlap with 'liking' in this time window (Pool et al., 2016).

The separation in the processing of the motivational ('wanting') and hedonic ('liking') components stand in contrast to the previous assumption of the interchangeability of motivation and pleasure. Supporters of the incentive salience theory argued, contrarily, that the pursuit of a reward is not always directly proportional to the pleasure derived from receiving it (Pool, 2016). In fact, there are many situations in which individuals invest considerable effort to achieve a goal even though they do not feel any pleasure after achieving it (Berridge, 2009). Some examples of this lack of correlation between the two components of 'wanting' and 'liking' were different types of addiction (such as substance use disorders or in case of social rewards, e.g. social media dependency) or eating disorders (Berridge & Robinson, 2016; Kuss & Griffiths, 2011). A few of those theoretical implications will be discussed further below.

Nevertheless, it is important to note that much of the evidence supporting this theory is based on animal studies so far. In fact, research on the separation of the components in humans is still in its infancy. However, while some studies support this theory in humans (Leyton et al. 2002, 2005; Volkow et al., 2002), there are also competing lines of research (Finlayson & Dalton, 2012; Havermans, 2011).

The researcher Havermans published a review in 2011 providing a critical view on the distinction of 'wanting' and 'liking' components of food reward processing in humans. He argued that even though lesion studies could successfully show a change in one of the components without necessarily influencing the other one. Nevertheless, the adaptation of the model to human reward processing seems to be difficult. He proposed the two components to be too much interconnected to manipulate exclusively one without causing a change in the other one. Furthermore, Havermans (2011) criticized the lack of evidence as well as large

inconsistencies due to no clear operationalization of true ‘wanting’ and ‘liking’ in the majority of studies.

To conclude, learning, ‘liking’, and ‘wanting’ can be considered as three distinct but equally important aspects in the processing of rewards that may be usually positively correlated but also occur independently (Berridge & Robinson, 2003; Berridge, 2009). In regard to the functional role of mesolimbic dopamine activity in particular, the ‘wanting’ component appears to be mediated by this neurotransmitter and neural circuit.

## Psychopharmacological intervention by amisulpride

The utilization of pharmacological intervention has been a common method in animal studies to investigate the functioning of neurotransmitter systems. As described above, various experiments have been conducted with dopamine agonists (such as L-DOPA) or antagonists (such as haloperidol or pimozide) to study reward processing in rodents or non-human primates (Berridge et al., 1998; Wise et al., 1982). The use of these drugs in humans poses some difficulties due to methodological challenges, which is reflected in the comparatively limited research results in this area to date (Grimm et al., 2021). Nevertheless, this approach offers valuable insights into reward processing in humans. In particular, when combined with the advancing neuroimaging techniques, this methodology may be very fruitful. In the following, a brief overview of how pharmacological manipulation works generally will be provided. Thereafter, the dopamine antagonist amisulpride used in this study will be presented, along with some examples of previous studies that have used the same drug.

Depending on the pharmacological manipulation applied, other functions are affected as most of the substances bind to specific dopaminergic receptor subtypes. The functions that dopamine modulates range from motor control to cognition, emotion, and reward (Chen et al., 2010; Muñoz & McKinney, 2018). Before turning to its interventions, it is important to understand the organization of the receptors. In general, a total of five dopaminergic receptor subtypes have been distinguished, usually divided into two main classes: the D1-like (with D1 and D5) and the D2-like (D2, D3, and D4) receptors (Jaber et al., 1996). While D1-like receptors are anatomically distributed mainly postsynaptically, D2-like receptors are located both pre- and postsynaptically (Jaber et al., 1996).

The primary receptor involved in the regulation of motivation and 'wanting' is the D2 receptor (Robbins & Everitt, 1992). Particularly the D2 neurons in the NAcc have been shown to respond to reward anticipation and seem to be important for the encoding of expected rewards (Kirsch et al., 2006). Previous evidence on the role of the D2 receptor in the processing of reward stimuli derives mainly from clinical studies on the use of dopaminergic drugs in the treatment of neurodegenerative diseases such as Parkinson's or Tourette's syndrome (Palminteri et al., 2009; Voon et al., 2010) or schizophrenia (Xiberas et al., 2001). Whereas, to date, only a small number of studies using D2 agonists or antagonists have begun to elucidate the role of dopamine in the normal processing and learning of reward stimuli in healthy subjects (Eisenegger et al., 2014; Kahnt et al., 2015; McCabe et al., 2011; Weber et al., 2016).

For the present study, the dopamine antagonist Amisulpride was chosen, which is one of the most selective D2/D3 blockers currently available for humans (Ersche et al., 2011; Grimm et al., 2021). Amisulpride is an atypical antipsychotic usually prescribed in the treatment of schizophrenia. In low doses (50 - 300 mg/d), it increases dopamine release by preferentially blocking presynaptic D2/D3 receptors (Schoemaker et al., 1997), which reduces the negative symptoms of patients (Curran & Perry, 2001). Whereas in higher doses (400 - 1200 mg/d) it leads to a decrease in dopaminergic transmission by antagonizing postsynaptic D2/D3 receptors (Schoemaker et al., 1997), particularly in the limbic system, which in turn has a positive effect on positive symptomatology (Curran & Perry, 2001). Accordingly, a dose of 400 mg was administered for this study, leading to a dopamine receptor occupancy of around 85% (Lako et al., Soutschek et al., 2021). The same dose has been used in several previous studies with minimal side-effects (e.g., Korb et al., 2020; Soutschek et al., 2021; Weber et al., 2016).

For example, one study by Weber and colleagues (2016) examined interrogated reward processing in terms of cue reactivity as well as reward impulsivity after administration of 400 mg of amisulpride. Using a Pavlovian-instrumental transfer task (to measure cue-induced responding) and a delay discounting task (for reward impulsivity), the researchers showed that the blockade of D2/D3 receptors indeed significantly suppressed reactivity to incentives and impulsivity compared to a placebo group. Furthermore, a neuroimaging study conducted by Khant and colleagues (2015) revealed that blockade of D2 receptors (also after administration of 400 mg amisulpride) leaded to enhanced content-specific representations of reward signals in the medial orbitofrontal cortex, by a dopamine-mediated increase in pattern

(reward vs. no reward) separation. Moreover, in line with the initial theoretical remarks, a study by Eisenegger and colleagues (2014) (who used 300 mg of the DA antagonist sulpride) confirmed that, contrary to long-held beliefs, the role of postsynaptic dopamine D2 receptors is indeed not in mediating reward prediction errors, but rather the motivational aspects of reinforcement learning. Finally, another study by the same group of researchers (Eisenegger et al., 2013) demonstrated that striatal dopamine transmission facilitates reward learning about the prosocial preferences and cooperative behavior of others.

These results are related to the incentive salience theory, indicating that amisulpride indeed appears to be a suitable substance to pharmacologically influence the 'wanting' of reward stimuli.

## fMRI and social reward processing

Reward research has focused for a long time predominantly on the investigation of primary food rewards in animals, even though many different things can be rewarding (Pool et al., 2016). As imaging techniques have advanced, a large amount of evidence from animal literature can be applied increasingly to the human brain (Delgado, 2007). In addition, recently, the class of social rewards is gaining attention with growing research interest in the 'social brain' and social cognition (Frith, 2007).

Interestingly, in social species, both animal and human research has shown that social rewards seem to be valued as even more rewarding than food rewards (Mason et al., 1963; Trezza et al., 2010). For example, thirsty male rhesus macaques are willing to sacrifice a fluid reward for the possibility to view images of socially significant others (such as females or high-status males), but not for low-status monkeys (Deaner et al., 2005). Similarly, humans substitute money with the possibility of seeing pictures of attractive others of the opposite sex (Hayden et al., 2007).

Currently, in the field of social neuroscience, two competing lines of evidence are in ongoing debate regarding the question of whether different types of rewards were processed neuronal identically or in distinct networks (Matyjek et al., 2020; Ruff & Fehr, 2014; Wake & Izuma, 2017). The first theory postulates a 'common neural currency schema' which states that social as well as non-social rewards are encoded by the same neural networks. It assumes

that identical neural processes thus assign motivational relevance to reward information (Ruff & Fehr, 2014). In contrast, proponents of the second theory of the 'social valuation specific schema' argue that social and non-social rewards are processed by different populations of neurons and thus a dedicated neural circuitry has evolved encoding specifically social-specific cognition (Matyek et al., 2020).

Methodologically, the majority of studies were examining those theories by comparing the neural processing of social to monetary or food reward stimuli (Izuma et al., 2008; Rademacher et al., 2010, 2013; Spreckelmeyer et al., 2009; Wake & Izuma, 2017).

Indeed, there are several neuroimaging studies supporting the idea of a 'common neural currency', consistently reporting that social rewards were equally processed like non-social rewards in the reward system (including the striatum, the anterior cingulate cortex, ventromedial prefrontal cortex, and midbrain) (Bhanji & Delgado, 2014; Gu et al., 2019).

In particular, the similar activation of the striatum (as one of the main areas of the brain's reward circuits) constitutes a strong argument for the common currency hypothesis (Delgado, 2007; Haber & Knutson, 2010). For example, Izuma and colleagues (2008) found significant activation of the striatum (specifically the left caudate nucleus and left putamen) for both social and non-social stimuli, in the same participants performing tasks involving money or good reputation from others. Furthermore, Rademacher and colleagues (2010) demonstrated a similar activation in the ventral striatum during the anticipation of social approval compared to monetary incentives. Interestingly, this independence from the type of incentive was found only for the anticipation phase, whereas, in contrast, different activation patterns for social and monetary rewards were elicited during consumption. Previous studies investigating also the anticipation phase of reward processing confirmed these results (Ernst et al., 2004; Kirsch et al., 2003) and highlighted the key role of the NAcc as the mediator of reward prediction (Kirsch et al., 2006; Knutson & Cooper, 2005). Spreckelmeyer and colleagues (2009), who similarly used an incentive delay task with the same reward types, also showed the same activation in the ventral and dorsal striatum (including the NAcc) for both incentives. In addition, they demonstrated proportionally higher striatal activation as a function of reward level (increasing activation with higher reward value). Besides the striatum, the orbitofrontal cortex is another region involved in value encoding and reward prediction in social reward processing (Rademacher et al., 2013; Spreckelmeyer et al., 2009).

Another important region in reward processing is the ventromedial prefrontal cortex (vmPFC), an area particularly relevant for decision-making based on the different values of stimuli. Several studies confirmed overlapping structures for reward magnitude and stimuli value during a decision phase in the ventromedial prefrontal cortex (vmPFC) for social compared to monetary rewards (Lin et al., 2012; Smith et al., 2017).

Nevertheless, there is likewise emerging evidence emphasizing differences in the neural processing of distinct reward types in line with the theory of 'social specific cognition' (Ruff & Fehr, 2014). Many adherents of this second perspective agree that common brain circuits exist for processing different types of rewards (Martins et al., 2021; Sescousse et al., 2010; Smith et al., 2010). However, they also propose that social reward processing in particular may involve additional brain regions, which are considered to be crucial for social-cognitive processes (Martins et al., 2021; Sescousse et al., 2010). Those structures include the temporoparietal junction, the precuneus, the dorsomedial prefrontal cortex, and the superior temporal sulcus (Barman et al., 2015; Goerlich et al., 2017; Spreckelmeyer et al., 2013). Subsequently, those researchers suggest that there are both distinct circuits as well as similarities in processing (Sescousse et al., 2010; Ruff & Fehr, 2014).

Various groups of researchers argue that the contrasting results are due, in part, to the lack of spatial resolution of fMRI (Lin et al., 2012; Wake & Izuma, 2017). Accordingly, largely separate populations of neurons specialized for the respective rewards might actually exist but be located in close proximity in the same brain region, which might be detected with more adequate spatial resolution in future research.

Another argument for the competing results was proposed by Matyjek and colleagues (2020). They pointed out that many of the previous comparisons of different reward types are inadequate because, especially in the class of social reward stimuli, different dimensions of the stimuli should be considered. These include among others, naturalness, familiarity, source or temporal proximity.

In conclusion, however, a clear picture of the specific neural circuits involved in the processing of social rewards is still lacking. This is partly due to the fact that the stimuli and designs used are very inconsistent, leading to a variety of different results in the areas identified (Martins et al., 2021).

## Social reward operationalized as touch reward

Generally, social rewards are broadly positive experiences (i.e., outcomes or interactions we pursue) in which other people are involved (Bhanji & Delgado, 2014). In previous human studies, due to the lack of a clear definition of social reward, there has been inconsistency in what has been termed a social reward. In the literature, moreover, social rewards have often been confounded with sexual reward stimuli (Sescousse et al., 2013; Chelnokova et al., 2014). Therefore, a variety of different types of stimuli have been operationalized and used as social rewards (Bhanji et al., 2014; Izuma et al., 2015). These include receiving compliments (Demurie et al., 2012), being positively evaluated by others (Izuma et al., 2008), gaining positive social feedback in form of being liked (Flores et al., 2018) or seeing approvingly smiling faces (Demurie et al., 2012; Rademacher et al., 2010; Spreckelmeyer et al., 2009), or sexually attractive faces (Bray & O'Doherty, 2007; Chelnokova et al., 2014), showing prosocial behavior, making voluntarily donations (Harbaugh et al., 2007), reciprocal altruism and cooperation (Rilling et al., 2002).

Affective interpersonal touch represents a particularly interesting and powerful type of social reward. Astonishingly, the rewarding value of touch has been reported to be so strong that it rivals that of illicit drugs (Cascio et al., 2019). Moreover, it appears to be so potent that social touch may even be a protective factor against substance use disorders (Zernig et al., 2013). Furthermore, it is of great importance to both humans (Gazzola et al., 2012; Nummenmaa et al., 2016; Sailer et al., 2016) and other social species (Dunbar, 2010).

Interpersonal touch is a necessity for survival in human life, just like the air we breathe and the food we eat. Touch shapes our entire lives from birth, over adulthood to old age (Gallace & Spence, 2010) and makes us social beings. It influences how we perceive stress (Ditzen, & Heinrichs, 2014), negative emotions, or pain (Liljencrantz et al., 2013; Mancini et al., 2014; Herrington & Chiodo, 2014), but can also be a source of comfort, safety or relief (Ellingsen et al., 2016) and is highly associated with feelings of pleasure (Morrison et al., 2010). In particular, strong emotions such as love, or compassion can be even better conveyed through physical touch than be communicated via speech (McGlone et al., 2014) and serves as the transmission of more genuine meanings or intention in social communication (Dunbar, 2004, 2010).

Social touch is exceedingly important across the entire lifespan. Interestingly, the first sense to develop ontogenetically is the touch sense (Gallace et al., 2010). Moreover, the

earliest way humans create their first contact with the external world is through the tactile sense (Barnett, 1972). Especially through touch between baby and parent, humans learn to differentiate what their own body is and where the outside world begins (Böhme et al., 2019). Therefore, touch is the initial modality to distinguish the 'self' from 'other' and may play a fundamental role in the development of the 'social brain' (Cascio et al., 2019; McGlone et al., 2014), by experiencing the boundaries between self and non-self (Tsakiris, 2016). Throughout the lifespan, social touch retains its unique significance through interpersonal, everyday interactions (Field, 2014). While the tactile sense and discriminative touch decline with age, the perceived pleasant sensation of affective touch remains unchanged (Cascio et al., 2019). In fact, it becomes even more appreciated in old age (Sehlstedt et al., 2016).

Furthermore, social affective touch creates a sense of proximity in social groups, establishes human connection (Ravaja et al., 2017), helps to form bonds and to stay peaceful (Gallace et al., 2010), by regulating cohesion between people through rewarding processes and providing a sense of security and belonging. Interestingly, studies have demonstrated the positive effects on emotions by casual touch even between complete strangers (Cascio et al., 2019; Hertenstein et al., 2009). Particularly slow-affective touch has been reported to decrease feelings of social exclusion (von Mohr et al., 2017). The evolutionary perspective on the importance on this affective touch system is that the chances of group survival increases, through affiliative behavior that promotes bonding between conspecifics (Ackerley, 2014).

The importance of social touch in human life is further illustrated by various examples of consequences and clinical implications when touch was absent or inadequate during infancy. For instance, an early multicultural study, published by Prescott in 1979, revealed a strong relationship between a lack of natural rewarding touch during childhood and subsequent higher aggressive behaviors in adulthood. Moreover, as mentioned earlier, social touch from caregivers in the early years of life is relevant to the development of the social brain. If this is deprived or even absent, there may be an increased risk of sensory behavior problems (Lin et al., 2005), such as hypersensitivity. In addition, the avoidance of social touch during childhood can be a strong predictor for the development of autism spectrum disorders (ASD), since it is assumed that it is not perceived as pleasurable. The overwhelming perception of sensory input in general and the deviating responsiveness to social touch specifically leads to social withdrawal (McGlone et al., 2014) which might have further effects on the developing brain (Cascio et al., 2019). Furthermore, a phenomenon that is known as "touch hunger" has been documented, as many people in today´s population suffer

from a lack of tactile stimulation in general (Gallace & Spence, 2011). This in turn has severe negative effects on the well-being and mental and physical health of individuals, as has been widely confirmed by research conducted by the Touch Research Institute in Miami, Florida (Field, 2014).

With regard to the normal processing of social touch, it is important to emphasize that the positive, rewarding effect of touch is highly context dependent. While touch that is sociocultural appropriate and associated with positive intentions is experienced as pleasurable, the same touch stimulus may be equally evaluated as unpleasant or repulsive, depending on contextual cues, leading to avoidance (Ellingsen et al., 2016). Consequently, only when touch occurs in a socially desirable context and is associated with pleasant feelings, does it lead to increased activity in brain circuits involved in reward processing (Triscoli et al., 2014). Another property of touch is its relative robustness to satiation (the decrease in reward value with repeated exposure). Accordingly, the hedonic and rewarding aspect of touch persists over a longer period of time (at least 50 minutes) and appears to occur only when the stimulation lasts for a longer period of time (Sailer et al., 2016). Based on these considerations outlined, affective touch was selected as the social reward stimulus for the present study.

## CT afferent fibers

As described previously, two types of touch (discriminative and affective) can be distinguished, each relying on distinct physiological and neural processing. The following section addresses the question of which mechanisms underlie the social aspect of touch and how they differentiate pleasant from unpleasant touch.

While previous tactility research has focused particularly on the sensory-discriminative aspects of touch (Liljencrantz & Olausson, 2014; Ree et al., 2019) mediated by large-diameter, myelinated, fast-conducting Aβ fibers (Abraira & Ginty, 2013), there is growing interest and evidence in literature for a second, slower touch system specialized on the affective experience of touch (Löken et al., 2009; McGlone et al., 2014).

This second distinct neurophysiological system, which specifically mediates and encodes gentle, affective touch, involves tactile C (CT) afferent fibers. It was first discovered

in humans by Johansson and colleagues (1988). CT afferents are a type of unmyelinated, slow-conducting, low-threshold mechanoreceptive nerve fibers found exclusively in non-glabrous (hairy) skin (Liu et al., 2007; Olausson et al., 2010; McGlone et al., 2014). In contrast to the Aβ fibers, which are responsible for the perception of tactile properties such as force, texture, velocity and pressure (Vallbo & Johannson, 1984), the CT fibers not only give us sensory information about the outside world but also about the emotional aspect whether we like or dislike physical contact (Gallace and Spence, 2010).

As already indicated above, the 'affective touch hypothesis' proposes that the essential role of the CT system is to provide or support behavioral, emotional and hormonal responses to skin-to-skin contact between conspecifics (Olausson et al., 2010). Consistent with this hypothesis, Löken and colleagues (2009) demonstrated that CT afferents fire more when the skin is stroked at a pleasant, caress-like speed between 1 and 10 cm/s, and thus likely signal affiliative social body contact, while faster or slower stroking resulted both in less activation (Löken et al., 2009; McGlone et al., 2014). Moreover, the discharge frequency of the CT fibers correlates significantly with the subjective hedonic experience and corresponding psychophysical ratings of tactile pleasantness (Löken et al., 2009; Morrison et al., 2011). Both faster and slower stroking each generate less firing of the CT fibers, consistent with the notion that touch stimuli require appropriate properties (low force, low speed, dynamic) for being an "adequate stimulus" for the CTs (McGlone et al., 2014). Additionally, CT fibers are tuned to be responsive specifically to tactile stimuli delivered at normal, typical skin temperature, corresponding to the thermal characteristics of gentle touch (Ackerley et al., 2014). The firing decreases with cooler or warmer temperature, also reinforces the affective touch hypothesis (Ackerley et al., 2014). Several neuroimaging studies have demonstrated that the primary cortical target area for CT afferents in humans is the posterior insula (Olausson et al., 2002, 2008; Björnsdotter et al., 2009; Morrison et al., 2011), a region associated with affective processing, and homeostatic balance (Paulus, 2007).

To sum, these two systems described, the first sensory-discriminative and the second motivational-affective pathways, are dissociable but not separate, parallelly activated and interacting. The combination of the fast Aβ and the slow CT afferents is necessary for the complete feeling of pleasant touch on hairy skin (Morrison et al., 2010).

## Clinical relevance and implications

A better understanding of the role of mesolimbic dopamine on the 'wanting' of social rewards is of major clinical relevance for various motivational, mood, or addictive disorders (Berridge, Robinson, & Aldridge, 2009). Some of these were illustrated in the following section, including autism spectrum disorders, substance use disorders (with the associated compulsive pursuit of rewards), depression, or the mental health implications of social isolation. Subsequently, prevention programs and treatment approaches can be improved and more appropriately adapted to the living conditions of affected individuals. In addition, the Covid-19 pandemic is exemplarily illustrated as a crisis in which many of the mentioned disorders were aggravated by the social restriction policies. Thus, this exceptional situation illustrates the impact of the underlying mechanisms of social reward processing in society in an unprecedented way.

### *Autism Spectrum Disorders*

Understanding the underlying neuropsychological mechanisms of 'wanting' social rewards is particularly important for the investigation and appropriate treatment of autism spectrum disorders (ASD).

ASD consist of a complex of neurodevelopmental disorders. These are characterized by deficits in reciprocal social interactions and socio-communication skills, impairments in social cognition and a limited range of interests and repetitive, stereotypical behavior (Patil et al., 2016; Pavăl & Micluția, 2021; Ruta et al., 2017).

While for three decades the focus of ASD research was primarily on the impairment of social cognition (especially Theory of Mind), it has recently shifted to the particularly salient behavioral feature of reduced social motivation. This manifests as a lack of interest in attending to social stimuli and a lack of desire to engage with others or enjoy social interactions (Chevallier et al., 2012).

The 'social motivation theory' states that decreased social motivation appears in individuals with ASD because of a deficit in representing the rewarding value of social stimuli compared to individuals with neurotypical function (Chevallier et al., 2012; Clements et al., 2018; Kohl et al., 2013). Subsequently, from early age, children with ASD have fewer opportunities for social learning, due to the diminished attention or responsiveness to social information or signals (such as faces or gaze directions) (Dawson et al., 2005; Ruta et al.,

2017; Schultz, 2005). For instance, Ruta and colleagues (2017) reported that children with ASD showed a lower relative preference for social rewards, as measured by a lower proportion of touches on a button associated with images of social rewards. This lack of social learning opportunities may in turn negatively impact the typical development of the 'social brain' (Pelphrey et al., 2011).

One explanation is the prominent dopamine hypothesis of ASD, which proposes that the lack of social motivation can be attributed to the disfunction of the mesocorticolimbic reward system (Kohls et al., 2013; Pavăl et al., 2021). Indeed, several fMRI studies confirmed this hypothesis (Kohls et al., 2012; Chevallier et al., 2014). Some of them adapted the paradigm from the reward literature of dividing reward into separate processes of 'wanting' and 'liking'. Clements and colleagues (2018) summarized the results of six fMRI studies using such a design in an exploratory meta-analysis. The findings that were consistent across all studies were that individuals with ASD have greater difficulty with 'wanting' rather than 'liking' social rewards. The results indicated that 'wanting' is indeed disrupted in ASD, as evidenced by striatal hypoactivation during the anticipation phase, while hyperactivation is present during the 'liking' of social stimuli (Clements et al., 2018; Damiano et al., 2015; Delmonte et al., 2012; Dichter et al., 2012; Kohls et al., 2013, 2018; Scott-Van Zeeland et al., 2010). According to these studies, developmental abnormalities of reward circuitry that provide the neurobiological basis for atypical social motivation functioning in ASD include, in particular, the nucleus accumbens (Nacc), anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), and amygdala, among other regions of the frontostriatal and limbic areas (Dawson et al., 2005; Kohls et al., 2013; Neuhaus et al., 2010; Schultz, 2005).

In conclusion, since ASD represents an extreme case of diminished social motivation, the deeper understanding of the disrupted 'wanting' component in this disorder can accordingly provide an important contribution to comprehending the inherent drive of humans to seek social acceptance or to prevent rejection.

### *Substance Use Disorders*

Another example that illustrates the consequences of deviant 'wanting' processes of rewards is substance use disorder (SUD). SUD is defined as a chronically relapsing disorder characterized by: "(1) compulsion to seek and take the drug, (2) loss of control in limiting intake, and (3) emergence of a negative emotional state (eg, dysphoria, anxiety, irritability)

reflecting a motivational withdrawal syndrome when access to the drug is prevented." (Koob & Volkow, 2010, p. 217).

According to the World Drug Report, annually released by the United Nations Office on Drugs and Crime (UNODC), worldwide 36 million people suffered from SUD in 2021. Nevertheless, relapse rates of around 50% to 60% for SUD within the first year suggest only moderate efficacy of treatment programs (Luijten et al., 2017; Sinha, 2013). The urgency of the topic underlines the need and relevance to understand the underlying mechanisms of SUDs for effective evidence-based treatment approaches. Moreover, a better understanding of the chronic and relapsing nature of SUD can further eliminate the stigma and discrimination most of the individuals suffering from this disease were facing (Volkow et al., 2017).

At the time, when the theory of incentive salience was developed by Berridge and Robinson (1998), addiction was one of its original targets. As described earlier, cognitive desires and incentive salience 'wanting' were often congruent processes. However, SUD provide a powerful example of the consequences if these two forms of wanting (vs. 'wanting') were dissociated. For example, if a person with SUD in withdrawal or recovery has an explicit desire to stay abstain from the drug, they may still 'want' the drug. This 'wanting' in that case takes place either completely unconsciously, without any cognitive desire, or in complete opposition to it (Berridge & Robinson, 2016).

Berridge and Robinson (2016) argued that many drugs of abuse (including cocaine, heroin, amphetamine, alcohol, nicotine) tend to sensitize the mesocorticolimbic dopamine system, especially when the drugs were taken repeatedly and at high doses. Subsequently, the dopamine system develops a hyper-reactivity to drug-related cues and contexts. Thus, this hyper-reactive state generates pulses of increased dopamine release and motivation that can last a few seconds or minutes (Robinson & Berridge, 2008). This process can additionally develop in susceptible individuals who have developed also tolerance. The development of sensitization and tolerance are two parallel, independent processes. While tolerance disappears shortly after withdrawal or discontinuation of the substance, the changes in dopamine-related motivation systems of sensitization were much more long-lasting and permanent. Contrarily to tolerance, sensitization sometimes even increases after some time during abstinence (Berridge & Robinson, 2016).

The 'incentive-sensitization theory of addiction', based on these assumptions, demonstrated by Berridge and Robinson (2016) posits that individuals with sensitization of

their dopaminergic system and the resulting hyperreactivity outlined, experience extraordinarily strong urges as soon as they were exposed to drug-related cues. The intensity of the triggered urge depends firstly on the cue's reward association and secondly on the individuals' current state of dopamine-related brain systems. The interaction of those two factors can lead to the 'state-dependent amplification' of incentive salience, which means that 'wanting' peaks were amplified by brain states that increase dopamine reactivity (e.g., stress, emotional excitement or intoxication) (Anselme, 2016; Robinson & Berridge, 2013). This was assumed to be one reason why it might be so difficult for people suffering from SUD to stop after just one hit, even without the experience of pleasure during consumption. According to the incentive-sensitization theory, the researchers hypothesized that the essence of SUD is therefore the excessive amplification of 'wanting', triggered by incentive cues, without necessarily reinforcing 'liking'. Berridge and Robinson (2016) concluded that "Addiction is not so much about satisfaction, pleasure, need or withdrawal, by this view, as it is about 'wanting'." (p.3).

Several neuroimaging studies by Nora Volkow and colleagues (2010, 2015) indicated that repeated administration of drugs results in various neuroplastic changes. Besides the hyper-reactivity to drug-related cues, other consequences were additionally reduced sensitivity to natural rewards (non-drug cues), weakened self-regulation (resulting from a dysfunctional prefrontal cortex), and increased sensitivity to stress stimuli (Volkow & Morales, 2015). This combination of long-lasting neural changes enhances the vulnerability to relapse, even after several years of abstinence. Consistent with these findings were the results of a meta-analysis of neuroimaging studies conducted by Luitjen and colleagues (2017). They confirmed that individuals with SUD showed relatively higher activation of the ventral striatum to drug cues and, in contrast, lower activation to non-drug cues compared to a control group. Furthermore, Koob and LeMoal (2005) proposed that in SUD, drug use progresses in a cycle from impulsivity to compulsivity. Thereby, they distinguish three stages: first, binge/intoxication, second, withdrawal/negative affect, and third, preoccupation/anticipation. Koob and Volkow (2010) revealed in another neuroimaging study that each of these stages were mediated by certain neural circuits. The focal points for the first stage (intoxication) are the VTA and VS, a key element for the second stage (withdrawal) plays the amygdala and a broad network is involved in the anticipation stage, including the orbitofrontal and prefrontal cortex, the hippocampus, and insula (particularly involved in craving) and the cingulate cortex, inferior frontal cortices, and dorsolateral prefrontal (involved in the disrupted inhibitory control). As soon as neuroplastic changes occur within these circuits, the transition

to addiction takes place. Especially the anticipation phase and the disruption of the related structures were responsible for the relapsing nature of the disorder (Koob et al., 2010).

Consequently, future interventions should be tailored to the personalized context of the individual, require a chronic care model and focus on strengthening executive control to improve long-term success and recovery (Volkow et al., 2015, 2017). Moreover, Berridge & Robinson (2016) emphasized that future neurobiological treatment techniques should aim to reverse the neuroadaptations on which sensitized mesolimbic hyper-reactivity to drug-related cues relies, without affecting normal motivations or causing adverse side effects.

### *Social isolation*

A powerful example of the importance of social rewards, particularly through their severe negative consequences, is social isolation (Cacioppo et al., 2011, 2015). Social species, like humans, by definition, create structures that extend beyond the individual (Cacioppo et al., 2011, 2014). Nevertheless, in individualistic, industrialized societies and a digitalized world, with less physical contact and reduced quality and quantity of social relationships, perceived loneliness has become an increasing mass phenomenon (Holt-Lunstad et al., 2010). For more than a quarter-century perceived and objective social isolation, has been recognized as a major risk factor for morbidity and mortality in humans (Cacioppo et al., 2015). A meta-analysis, published in 2010, revealed that the increased mortality from loneliness was comparable to well-established risk factors (including smoking or alcohol consumption), was twice as high as for obesity, and even four times as high as for air pollution (Holt-Lunstad et al., 2010).

The ‘social control hypothesis’ is the most common explanation for the association between loneliness and (both physiological and psychological) morbidity and increased mortality, which emphasized the influence of family and friends on a person's health behaviors (Cacioppo et al., 2014). However, neuroscientists argue that this cannot sufficiently explain the aforementioned relationship. Instead, the opposing approach of the social neuroscience model focuses on the brain as a key organ in building, monitoring, and keeping salutary relationships with others (Cacioppo et al., 2014). Representatives of this approach argued that the neuronal mechanisms of the brain in response to social isolation were dedicated to increasing the organism's chances of survival in the state of being separated from others.

Evidence from behavioral and neuroimaging studies (Cacioppo & Hawkley, 2009, Cacioppo et al., 2009; 2014; 2015) suggests that social isolation and perceived loneliness functionally affect several brain mechanisms. First, it appears to lead to hypersensitivity to negative social information (Cacioppo et al., 2009a). The amygdala, anterior insula, and anterior cingulate were involved in this monitoring of social threats (Bickart et al., 2012; Cacioppo et al., 2009; Eisenberger & Cole, 2012; Klumpp et al., 2012). Second, increased attention to self-preservation has been demonstrated (increased activity in, e.g., superior temporal sulcus, temporal parietal junction, orbitofrontal cortex, medial prefrontal cortex) (Cacioppo et al. 2009, 2013; Eisenberger & Cole, 2012; Klumpp et al., 2012).

Furthermore, lonely individuals appear to experience reduced reward from positive social stimuli (such as interpersonal relationships). Consistent with these findings are the results of an fMRI study suggesting that perceived social isolation is associated with weaker activation of the ventral striatum in response to pleasant social images compared to pleasant nonsocial images, while nonlonely individuals showed the reverse pattern (Cacioppo et al., 2009b).

These findings suggest that lonely people think differently about other people and perceive the social environment as potentially more threatening and punishing, which also leads to poorer sleep (Cacioppo et al., 2014) as they feel more vulnerable and unsafe (Cacioppo et al., 2009a). Furthermore, several other physiological and psychological processes were associated with loneliness, such as increased stress responses, higher blood pressure (Hawkley et al., 2006; 2010), increased depressive symptoms (Cacioppo et al., 2010), and lower subjective well-being (Vanderweele et al., 2012), which have a negative impact on morbidity and mortality.

### *Covid-19 Pandemic*

The ongoing Covid-19 pandemic has exacerbated some of the concerns illustrated above and raised research interest in the impact of social reward on mental health (Hagerty & Williams, 2020; Juarascio et al., 2021; Loades et al., 2020; Sequeira et al., 2021). In an era of social distancing, the importance of social touch in humans, the rewarding processes it elicits, and especially what happens when it is absent, has become increasingly apparent. As previously outlined, touch is existential for human beings and has serious physical and psychological consequences if it is missing for too long (Field, 2014). The pandemic sets an unprecedented situation in this regard. Never before in evolution and history have primates

been instructed not to touch each other. Even though smartphones and the internet can provide a certain form of closeness and connection with family and friends during this time, they cannot replace physical closeness and social distancing is therefore a threat to the basic need for human connection (Hagerty et al., 2020).

Several researchers examining the consequences of pandemic-induced social distancing, the disruption of social networks and the associated isolation and loneliness pointed to the enormous negative impact on mental health as well as the associated risk factors for a range of disorders such as depression, substance use or eating disorders (Hagerty & Williams, 2020; Juarascio et al., 2021; Loades et al., 2020; Shah et al., 2020; Sequeira et al., 2021). Studies have shown that particularly in adolescence, limited rewarding social experiences were an important risk factor for increased symptoms of depression (Sequeira et al., 2021) and emerging suicidal thoughts and behaviors during Covid-19 (Fortgang et al., 2021; Hutchinson et al., 2021).

One approach to explaining the development or reinforcement of these disorders during the pandemic is the ‘reward imbalance theory’ proposed by Juarascio and colleagues (2021). According to this, reduced exposure to natural reward sources such as social relationships and interactions with limited opportunities to experience rewards in everyday life, firstly, can lead to a hypo-reward response to stimuli that were conventionally rewarding (Hagerty et al., 2020). Neuronally, this is manifested by low activation of mesocorticolimbic and -striatal dopaminergic pathways. This in turn decreases motivation to engage in typically pleasurable activities. Because the activities that do take place generate low levels of reward, they are thus inadequately reinforced, which in turn leads to worsened motivation to participate further in social interactions and appears to promote a blunting of reward over time. Thus, Hagerty and Williams (2020) argued, that Covid-19 cruelly creates the perfect conditions for the emergence of the described ‘cycle of social anhedonia’, which in turn is associated with the onset or worsening of depression (Juarascio et al., 2021).

Juarascio and colleagues (2021) further assume that those affected by the first vicious cycle may enter a second one, characterized in reverse by a hyper-reward response (i.e., high activation of dopaminergic pathways). Due to the lack of everyday rewards, affected individuals are likely to feel a strong urge to seek alternative, intense, and immediately stimulating sources of reward. This could lead to an increased engagement in highly rewarding behaviors (such as the consumption of tasty food) or substance use. The resulting

overreliance or overuse of one particular reward source may in turn further reduce the ability to experience rewards from everyday activities, again leading to consumption of highly rewarding stimuli, which subsequently may result in risky behaviors. Accordingly, this second vicious circle is particularly involved in disorders characterized by compulsive engagement with highly rewarding stimuli despite negative consequences (e.g. substance use disorders, eating disorders) (Garfield et al., 2014; Shah et al., 2020). Combined, those two cycles described form the reward imbalance. It is important to emphasize that this imbalance existed outside the pandemic as well, but the social restrictions almost certainly exacerbate it considerably (Juarascio et al., 2021).

# Research Question and Hypotheses

Based on the theoretical and methodological considerations presented in the first chapter of this thesis it can be concluded that the neuropsychological evidence on social reward processing in healthy humans is still scarce. As outlined above, social rewards are gaining increasing importance and attention in scientific discourse. Nonetheless, the majority of studies examining the currently prevailing 'incentive salience theory' of reward processing are focusing on primary food rewards in animals (Berridge, 1996, 2009; Finlayson & Dalton, 2012). There is an ongoing debate if the evidence that emerged from those studies can be applied to the human brain (Delgado, 2007; Pool et al., 2016). Moreover, the scientific controversy in whether the neural circuits for social reward processing are different or the same compared to non-social reward processing results in the need for further research.

The present study intends to fill this knowledge gap in the literature. To investigate the impact of dopamine on the 'wanting' component of social reward processing in healthy humans, several limitations of previous studies need to be addressed and overcome.

First, a well-established approach in the field of animal research is the use of lesions, which, however, cannot be applied to humans for ethical reasons (Sescousse et al., 2013). One disadvantage of this technique is its focus on only specific brain structures instead of a holistic picture of the brain. The use of functional magnetic resonance imaging instead can be optimally applied in humans and additionally enables visualization of the activity in the whole brain during a certain task (Sescousse et al., 2013). In order to address this limitation, the present design was developed as an innovative approach combining a psychopharmacological intervention of the dopaminergic system with neuroimaging techniques (Korb et al., 2020). This approach allows the behavioral observations as well as neuronal activity patterns to be attributed to the influence of the neurotransmitter system in the experimental compared to the control group.

Second, previous studies with humans focused mainly on participants with several disorders related to reward processing (such as substance use or eating disorders) (Berridge, 2009; Berridge & Robinson, 2016; Volkow & Morales, 2015). In contrast, this study contributes to the understanding of normal neuronal reward processing in healthy subjects.

Third, inconsistencies in the definition of social rewards as well as the confounding with erotic rewards in literature have led to ambiguity in the results. In addition, secondary

(learned) rather than primary social rewards were frequently used. Thus, the present study chose the potent primary social reward of affective interpersonal touch as stimuli. Moreover, in contrast to many previous studies, skin-to-skin touch represents a real stimulus instead of commonly used pictures (e.g., of smiling faces) of social rewards (Rademacher et al., 2010; Spreckelmeyer et al., 2009).

Forth, the unique combination of implicit and explicit measurement methods in the same person allows conclusions to be drawn about the actual differentiation of incentive salience 'wanting' and cognitive wanting as proposed by Berridge and colleagues (2003).

The hypotheses investigated in this thesis are as follows:

H1: Selective blockade of postsynaptic striatal D2 and D3 dopamine receptors by amisulpride in healthy participants will lead to reduced 'wanting' in response to cues indicating social rewards, operationalized by:

*H1a*: reduced subjective ratings of wanting a cued social reward

*H1b*: reduced exerted effort to obtain a cued social reward

*H1c:* reduced brain activation in corresponding areas associated with the anticipation of social rewards (VTA, VS and vmPFC).

# Methods

The hypotheses were investigated as part of a study conducted by the Clinical and Social Neuroscience (CSN) unit of the University of Vienna under the direction of Giorgia Silani and her colleagues. It took place at the Department of Psychiatry and Psychotherapy of the Vienna General Hospital (Allgemeines Krankenhaus/AKH, Währinger Gürtel 18-20, 1090 Vienna).

The aim of the entire study was to determine the role of the dopaminergic and opioid systems in modulating 'wanting' (motivational component) and 'liking' (hedonic component) of primary food and social rewards in healthy humans, and hence to examine the *common currency hypothesis*. However, the present thesis will focus on the social reward only and on the anticipation phase of the reward task.

## Study design

The so-called "Taste and Touch" study was designed as a basic research study (monocentric, randomized, double-blind, placebo-controlled, three-armed). The hypotheses were investigated in an fMRI environment as a psychopharmacological experiment. A mixed design was used, with type of medication (either dopamine or opioid antagonist or placebo) as a between-subjects factor, and type of reward (social or non-social) and reward level (high or low) as a within-subjects factor. Social rewards were operationalized as touch stimuli (gentle caresses of the forearm) and non-social rewards as food stimuli (chocolate milk).

## Participants

The participant sample consisted of 60 volunteers (35 females, 25 males) aged 18 to 33 years ($M$ = 23.67; $SD$ = 3.79). The average Body Mass Index (BMI) was 22.92 ($SD$ = 2.39; range = 18.82 – 29.41). Participants were randomly assigned to one of two drug groups: Amisulpride (N = 32, 18 females) and Placebo (N = 28, 17 females).

In order to be included in the study, participants had to fulfill certain criteria. All subjects reported being right-handed, smoking less than five cigarettes a day, being heterosexual, having no history of current or previous substance abuse, being free of psychiatric or neurological disorders, and not suffering from lesions or skin diseases on the right forearm. Further exclusion criteria included contraindications for MRI (e.g., metallic implants, claustrophobia) as well as common contraindications to amisulpride intake (e.g.,

current pregnancy, regular medication intake, strongly limited kidney functions).
Two participants were excluded from the analysis because of missing fMRI data, both belonged to the Amisulpride group. Accordingly, the final sample comprised 58 participants (Placebo: N = 28; Amisulpride: N = 30) for the fMRI analysis. Whereas the behavioral analysis included the data of all 60 participants without exclusions.

The study was approved by the ethics committee of the Medical University of Vienna and was conducted in agreement with the Declaration of Helsinki (World Medical Association, 2013). All participants signed an informed consent form before taking part in the study and received financial compensation for their participations.

## Drug Administration

The study employed a randomized, placebo-controlled, double-blind between subject design. To investigate the role of the dopaminergic system in the 'wanting' of social touch, participants were orally administered with either a dopaminergic antagonist or a placebo. The study also included a group of participants administered with an opioid antagonist, which will not be described here as it is out of the scope of the present thesis. As the dopaminergic antagonist, 400 mg of amisulpride (*Solian)* was orally administered. The medication is approved in Austria and has been used for decades mainly as an antipsychotic in the treatment of schizophrenia. As previously outlined is amisulpride particularly suitable for research purposes due to its minimal side-effects at this dose (Korb et al., 2020; Soutschek et al., 2021). Amisulpride concentration reaches maximal concentration in the serum in a first peak after 1 hour and in a second higher peak after approximately 4 hours. The elimination half-life is 12 hours (Curran & Perry, 2001; Rosenzweig et al., 2002). For this reason, the main experimental task was performed 3 hours following drug administration. Placebo consisted of capsules containing an inactive substance (650 mg of mannitol, i.e., sugar), which were visually identical to the ones containing amisulpride.

## Recruitment and Questionnaires

As a first step in the recruitment process of participants, the study was advertised via the distribution of flyers and posters in public places, frequently visited by students, as well as via the publication of advertisements in various Facebook groups with a focus on student activities (such as university, internships or job opportunities). Through the promoted materials, interested volunteers were able to contact the research team via email. Following,

respondents were requested to complete several questionnaires online, before coming to the laboratory.

The questionnaires used were the following: The Social Touch Questionnaire (STQ) (Wilhelm et al., 2001); the Health and Taste Attitudes Questionnaires (HTAS) (Roininen et al., 1999), which is not relevant for this thesis; the 20-item Toronto Alexithymia Scale (TAS-20) (Bagby et al., 1994) and the short version of the German Autism Spectrum Quotient (AQ-k) (Freitag et al., 2007). The purpose of completing these questionnaires in advance was mainly to screen for some exclusion criteria. Moreover, the questionnaires were used to assess possible group differences in personality traits and characteristics relevant to the processes investigated, i.e., social touch appreciation, alexithymia, autism spectrum disorders, and their general health conditions. After completing the online survey, eligible participants were contacted by phone to schedule their first laboratory appointment.

On this first test day, participants were checked for the remaining exclusion criteria. Those who were eligible received another phone call to arrange a second appointment and were again informed comprehensively about the entire procedure of the main testing. Additionally, participants got a reminder to come to the study empty-stomached, without having consumed alcohol and other drugs. Furthermore, they were given the opportunity at this point of recruitment to clarify any questions or remaining uncertainties about the study procedure personally with a team member.

## Procedure

As already mentioned, the conduction of the study was divided into two separate dates, termed *T0* and *T1* respectively. Before any examination or task was performed in the laboratory, participants signed a written informed consent form. This document contained comprehensive information about the study procedure as well as possible, unwanted side effects and risks of the medication. Prior to participating, subjects were also informed they could withdraw from participation at any moment, without providing any reason and without consequences.

Both appointments were monetarily compensated. Participants received 10 € after completion of *T0* and 90 € after completion of *T1*. On both dates, additional compensation could be gained based on the performance of two computer tasks. These additional earnings

ranged from 1 to 10 € (with an average of 5 €) per test day. Consequently, participants in total earned at least 102 € and up to 120 € for full participation in the study.

The first appointment (*T0)* lasted approximately 70 minutes. The main aim of this appointment was to determine the eligibility of the interested participants. This assessment was undertaken by a study doctor who carried out a series of medical examinations. Firstly, an electrocardiogram was recorded, a blood sample was drawn and furthermore, breathing, and cardiac monitoring were obtained with a stethoscope in order to identify the general state of health. Subsequently, in addition to the medical checks, a psychological screening was conducted. The Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) was used for this purpose. The MINI is a short diagnostic interview for the diagnosis of current and previous psychiatric disorders (including substance use disorders) of participants. In the case that all requirements were met, and no exclusion criteria was revealed either, the second appointment was scheduled.

The second appointment (*T1)* required a total of 6.5 hours, approximately, during which the main experimental task was performed. The maximum time interval between *T0* and *T1* was 8 weeks. *T1* can be divided thematically into three parts, namely the pre-reward (approx. 2 h), reward (2,5 h), and post-reward part (2 h).

**Pre-reward part.** Upon arrival at the laboratory, participants first completed the Positive and Negative Affect Schedule (PANAS) (Watson et al., 1988), a questionnaire used to assess current mood. The PANAS was repeated later in the post-reward part to assess possible changes in mood over time due to the drug. Afterwards, a urine sample was taken by the study doctor to ensure the absence of substance use and of potential pregnancy in case of the female participants. The urine test is sensitive among others to cocaine, opiates, amphetamine, and methamphetamine. If the urine test was negative, the study doctor administered the capsule containing either amisulpride or a placebo to the participant. To establish comparability of drug effects, the subjects were instructed to take the drug on an empty stomach. After pill administration, they were given a standardized breakfast consisting of a granola bar (425 calories) and water. Afterwards, the participants performed two computer tasks examining the perception of probabilities and attention. These tasks will not be further described as they are beyond the scope of this thesis. During the approximately 40-minute waiting period that followed, subjects were allowed to read magazines (provided by the experimenter) but not to use their mobile phones. This condition served to deprive the

participants of social contact and to ensure comparability of the waiting time between subjects. Finally, at the end of the pre-reward part, the subjects' general well-being and state were checked by the study doctor. Two scales were used for this purpose: The Abnormal Involuntary Movement Scale (AIMS) (Buhmann et al., 2016) and the Barnes Akathisia Rating Scale (BARS) (Barnes, 1989).

**Reward part.** If the medical examination did not reveal any abnormalities or side effects of the medication, it was feasible to proceed with the main part of the study which took place in the fMRI-scanner. The start of the reward task was scheduled for exactly 3 hours after taking the pill, in order to ensure the maximum effect of the drug.

After arriving at the MR center, subjects were requested to sign another informed consent form specifically for this part of the study and were subsequently prepared and instructed on how to perform the main task in the scanner. Care was taken to provide them with all the information in a calm manner and environment, ensuring that participants felt both physically and mentally relaxed and comfortable in the testing situation.

The equipment relevant to the task was explained and tested. Among them were a button box and a hand dynamometer (HD-BTA, Vernier Software & Technology, USA). The button box was taped to the left hip of the subject and operated with the three middle fingers of the right hand. The hand dynamometer was held with the left hand placed at a right angle of the arm above the abdomen. Both devices were used to measure the 'wanting' of an announced reward either by subjective ratings or exerted physical effort. In addition, the recording of whole brain neuronal activity (BOLD signal) by fMRI served as an implicit measure of 'wanting'.

Immediately before the main task, the dynamometer was individually calibrated, by asking the participants to squeeze the dynamometer with the left hand as strong as possible for three consecutive trials for three seconds. The maximum voluntary contraction (MVC) was measured in Newtons (N). The peak force across the three trials depicted the MVC of the participants. The same procedure was repeated just after the end of the reward task to check for possible muscle fatigue effects.

After the dynamometer was calibrated, the experimental design was explained to the participants. The subject completed two training sessions one each for the food and the touch condition. Time was provided for any remaining questions to be clarified. As soon as the

subject felt sufficiently prepared, the main task was started. The reward task is described in more detail separately below.

**Post-reward part.** The two hours of the third and final part of the study served as a follow-up. After returning to the laboratory, participants again completed the PANAS questionnaire (Watson et al., 1988). In addition, the participants' general condition was reassessed using the BARS (Barnes, 1989) and possible side effects of the drug were queried. Exactly 5 ½ hours after taking the pill, another blood sample was drawn by the study doctor to evaluate whether the drug had been metabolized. Finally, the *T1* session terminated with a debriefing.

## Stimuli

The social reward stimuli were operationalized as affective touch rewards consisting of gentle caresses of the participants' forearm by the experimenter at different speeds. The caresses were performed over a previously marked nine-centimeters area of the participants' right forearm, starting from the wrist towards the elbow. According to the literature on 'liking' of caresses at different speeds, caresses between 3 and 10 cm/s activate CT fibers (CT optimal) and are perceived as more pleasurable (Löken et al., 2009). Therefore, the following three different stroking frequencies were applied for seven seconds by a same-sex experimenter: six cm/s (CT-fibers optimal), 21 cm/s and 27 cm/s (CT-fibers non optimal). The efficacy of these stroking speeds in determining three different levels of 'liking' and 'wanting' was confirmed by four independent studies (Korb et al., 2020a, 2020b, Massaccesi et al., 2021, Massaccesi et al., 2022). Accordingly, the different speeds of caressing contain a reward value to varying degrees. The slow frequency of six cm/s is perceived as the option with the highest reward value (most pleasurable) compared to the two faster options (21 and 27 cm/s) which are considered to be low and very low rewarding. Correspondingly, in the following, the three stimuli will be referred to as 'high' (6 cm/s), 'low' (21 cm/s), and 'very low' (27 cm/s) rewards.

Even though performing touch, by using for instance a brush has some advantages, such as more controlled tactile stimulation (as it is independent of skin temperature and humidity) (Rosenberger et al., 2018), the choice was made to deliver the touch by direct skin-to-skin contact (performed by the experimenter with the index and middle finger) to enhance the social aspect of touch. Since interpersonal touch has a strong affective component (Strauss et al., 2019), it accordingly represents a more powerful and ecological stimulus for activating

social reward than non-direct skin-to-skin contact (Böhme et al., 2019). Furthermore, CT fibers are especially activated by touch at skin temperature (Ackerley et al., 2014).

A powder (*Maizena,* corn starch) was utilized to facilitate the stroking, to maximize pleasantness for the participant, and moreover, to ensure that the tactile sensation was comparable between subjects. In addition, the stimulating experimenter received extensive training and listened to the stimulation rhythms via headphones in each trial to perform the movement as smoothly and consistently as possible. The experimenter was further instructed to apply the same pressure while stroking for each of the three frequencies. To ensure that caressing was perceived and processed as a social rather than a sexual reward stimulus, only same-sex experimenters were assigned to each subject. For this reason, one requirement for the study was that the subjects defined themselves as heterosexual, and this way sexual associations should be limited. To exclude possible biases due to sympathy and for technical reasons, the subject could not see the experimenter while being stroked. Since the subject was in the scanner, she or he was able to perceive the touch detached and independently of any other environmental influences.

## Reward Task

A recently developed reward task (Korb et al., 2020a, 2020b) was optimized for functional neuroimaging and employed to assess brain and behavioral responses to social reward anticipation. For this task, participants were transferred to the MR center, located on the Medical University campus at the General Hospital of Vienna (AKH).

The reward task in total consisted of four experimental blocks, each with 16 trials. Each block comprised either Touch or Food trials. The order of Touch and Food blocks was alternating (ABAB or BABA). Randomization was used to determine which one to start with, ensuring a counterbalanced order across subjects. Within the food trials, participants received food stimuli (milk with different chocolate concentrations), but will not be analyzed here, as they are not the focus of the present thesis.

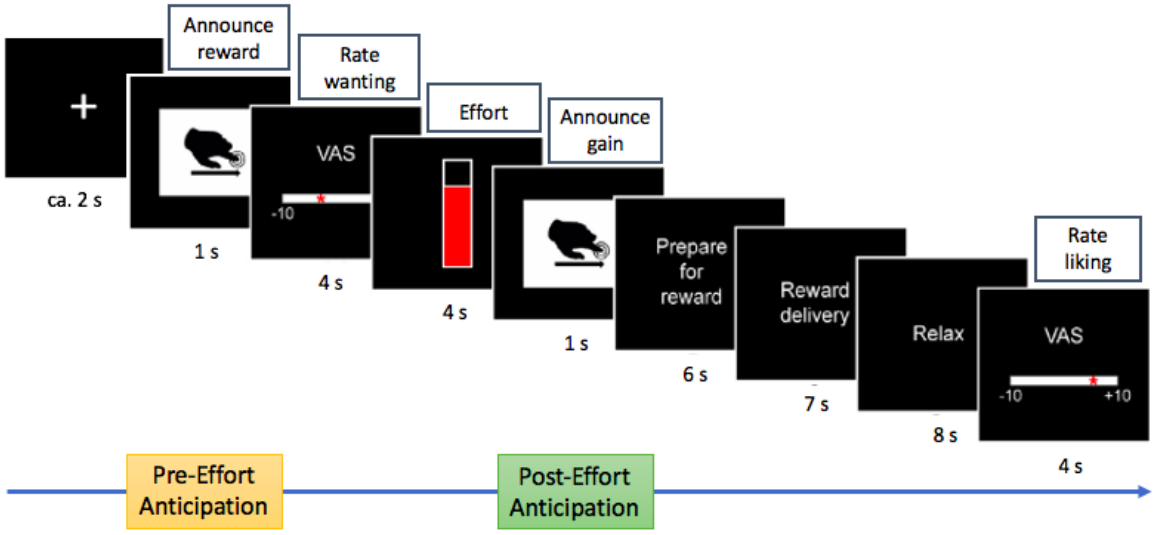
During the task, participants were lined on the scanner bed. The task was displayed on a screen that the subjects could see via a mirror implemented in the coil. The screen was located at the head end of the scanner.
The structure of one touch trial is exemplified in Figure 1. It included the following main steps:

First, a fix cross was presented (jittered between 2 and 4 sec), marking the beginning of each new trial. Second, a cue was displayed announcing the attainable highest reward in that trial (1 sec). This could be either the high or the low reward. This time window was analyzed and referred to as the *'pre-effort anticipation phase'*. Third, the subjective wanting ratings followed, asking the participants to rate how much they would like to receive the announced social reward (4 sec). The rating was expressed on a visual analogue scale (VAS) from "*not at all*" (-10) to "*very much*" (+10) by using the MRI-compatible button box with the right ring and index finger. The fourth step contained a 4-second period of physical effort, during which the probability of obtaining the announced reward was determined by the maximum amount of force exerted by pressing the dynamometer with the left hand. During this effort phase, subjects received visual feedback on a proportionally filling bar. The amount of force linearly predicted the likelihood of obtaining the announced reward, i.e., the greater the effort exerted by the participants, the higher the probability of receiving the announced reward. Depending on the pressure applied, the cue of the reward obtained was then presented (1 sec). This was either the announced option (high or low) if sufficient force was applied, or the lowest alternative, i.e., the very low reward (on all trials where not sufficient force was applied). This time window was additionally analyzed for exploratory reasons and termed the '*post-effort anticipation phase'*. Afterwards, a 6-sec period of preparation for the reward stimulus followed. Subsequently, the reward delivery phase took place, during which the touch was delivered to the participants' forearm (7 sec). Along with the following relaxation time of 8 sec, the reward consumption part comprised a total of 15 seconds. Finally, the subjects were requested to rate the liking of the received tactile stimulus (within 4 sec, using the button box with the right ring and index finger) on a VAS scale ranging again from "*not at all*" (-10) to "*very much*" (+10). The participants could take a short break after each block to rest until the next one started.

One touch trial (Figure 1) took a total of approximately 37 to 39 seconds and a whole block approximately 10.7 minutes. Overall, the entire scanning session lasted about 1 hour and 10 minutes, and 630 volumes were recorded for each touch block. The task was displayed on an LCD monitor with a resolution of 2560×1600 pixels and was implemented using MATLAB 2014b and the Cogent 2000 and Cogent Graphics toolboxes.

**Figure 1**

*Structure of one touch trial of the reward task*




## fMRI data acquisition

A 3.0 Tesla Siemens Prisma fit MRI scanner (Siemens, Erlangen, Germany) with a 64-channel head coil was used for signal reception. The structural T1-weighted mp2rage sequence was recorded with 1x1x1 mm slice thickness. The T2-weighted blood oxygen level-dependent (BOLD) sensitive functional imaging was performed using echo-planar imaging (EPI) sequence acquired with the following parameters: repetition time (TR) = 1 s, echo time (TE) = 35 ms, 3mm slice thickness, 2.3x2 mm, 3x3 mm Voxel size, 40 slices, multiband factor 4, field of view: 220x200 mm and interslice gap: 0.3 mm. 630 volumes were acquired within one run with a total duration of approximately 622 sec.

## Statistical analysis

The analysis of the data was composed of two parts: the behavioral and the neuroimaging analysis. The entire data analysis procedure is explained in detail below. For the behavioral analyses, an alpha level of 0.05 is used to determine if the statistical tests indicate that the results are significantly different from what would be expected if the null hypothesis were true. For the analysis of the neuroimaging data, the multiple comparison correction implemented in SPM12 will be applied using Random Gaussian Field Theory (familywise error rate (FWE) correction). In an added subsequent analysis, the uncorrected p-value threshold was used and lowered to $p < .001$.

### *Behavioral data*

To analyze the behavioral data of the reward task the statistics program IBM SPSS Statistics (Statistical Package for the Social Sciences) Version 27.0 for Mac was used. The graphs and figures were created in Microsoft Excel and Microsoft PowerPoint for Mac Version 16.43 (2020).

To investigate the effects of the dopamine antagonist on 'wanting' of social touch, I conducted two mixed design analysis of variance (mixed ANOVAs) with the between-subject factor Drug (Amisulpride, Placebo) and the within-subject factor Reward Level (high, low), one each with wanting ratings and exerted effort as the dependent variable. Significant main effects of Drug and Reward Level and interactions were analyzed.

Before conducting the ANOVAs, the following criteria were assessed: (1) the dependent variables (wanting ratings and effort) are at least interval scaled; (2) the between-subject factor (Drug) is independent and nominally scaled; (3) the within-subject factor (Reward Level) is independent and nominally scaled; (4) there are no severe outliers in the groups; (5) the residuals of the dependent variable are (approximately) normally distributed for each group; (6) the variances should be (approximately) equal (homoscedasticity); and (7) Sphericity should be given (Salkind, 2010).

Further, possible differences in the drug groups in mood, maximum voluntary contraction at rest, and possible drug side-effects were examined using independent two-sided t-tests.

### *Neuroimaging data*

The statistical analysis of the neuroimaging data was conducted using the Statistical Parametric Mapping software package (SPM12; Wellcome Trust Centre for Neuroimaging, UCL, London, UK) running in Matlab (Version R2019a; The MathWorks Inc., Natick, Massachusetts, USA). The procedure described below is based on the SPM12 manual published in 2021 by the Functional Imaging Laboratory (FIL) Method group.

**Preprocessing.** The first part of the analysis is the preprocessing of the neuroimaging data, which included the following five modules: (1) In the first step, the data were realigned to the mean image and unwarped. The realignment is used to correct for motion of the subject during the functional scans. It allows translations (moving the image in the x, y, or z-

direction) and rotations (over the x, y, and z-axis). In case of excessive movement artifacts (if movement is bigger than the Voxelsize (>3 mm)), the subject has to be consequently excluded from the analysis. The scans were registered to the resulting mean of the realigned functional images. Unwarping provides the supplementary correction required when image distortions occur in certain brain regions. After reviewing the realignment, four participants (Sub 17, 20, 50, 85; all in the Amisulpride group) were observed to show increased head movement in the scanner. However, as none of them counted as extensive movement artifacts, the decision was made to include them in the analysis nevertheless, so as to not reduce the sample size. Two subjects (Sub 4, 81, both Amisulpride) had to be excluded from the analysis because no fMRI data was available, due to an unplugged coil during testing (Sub 4) and a missing structural scan (Sub 4). For three subjects (Sub 20, 34, 38, again all of them were participants of the Amisulpride group), only the first block was defined within the first-level analysis, as the second block contained only low reward and no high reward trials, due to insufficient exerted force. In total, the fMRI analysis was based on data from 58 subjects (28 Placebo; 30 Amisulpride). (2) Secondly, the co-registration function was used to match scans of different modalities (alignment of functional and anatomical images of the same subject). (3) Next, the co-registered structural image was segmented to separate grey matter, white matter, and CSF in anatomical scans. (4) With normalization, the scans were put into standardized Montreal Neurological Institute (MNI) space. In addition to translations and rotations (i.e., the rigid body transformations that are also allowed in realign and coregister), normalization uses zooms and shears and nonlinear deformations, which allow for subtle corrections of anatomical differences between subjects. A $4^{th}$-degree B-Spline Interpolation was used. (5) As a final step, the normalized functional images were smoothed by convolution with a 6 mm full width at half maximum (FWHM) Gaussian Kernel. The reason to do this is to correct for slight remaining functional or anatomical differences between subjects. All these modules outlined are necessary in order to create comparable activation maps of the brain.

The pre-processed data was further analyzed as an event-related design within the GLM approach in a two-level procedure, including the first (individual) and second (group) level analysis. Subsequently, the analysis at the first and second level was also performed according to the standard approach.

**First-level analysis.** At the first level, the fMRI model specification was used at the single subject time-series level to design one matrix with the two touch sessions fitted for each subject. For each condition, the entire time period was modeled. For each run, the design

matrix included 11 regressors, one for each distinct phase of the trials (fix cross, pre-effort anticipation (divided into high and low rewards), rating wanting, effort, post-effort anticipation (divided into high and low rewards), preparation for delivery, delivery, relax, rating liking), as well as the six movement regressors: x-, y-, z-Translation and pitch-, roll-, yaw-Rotation. Thus, the design matrix contained also regressors of no interest (rating wanting, effort, preparation for delivery, delivery, relax, rating liking). As the focus of this thesis was to investigate brain activation in response to 'wanting' during the anticipation of a reward, the analysis focused on the pre-effort anticipation phase. Furthermore, the post-effort anticipation phase was also explored, even though this phase is also largely modulated by the anticipated 'liking' of the reward and therefore possible results are less precisely traceable to the theoretical construct of 'wanting'.

Resulting from these considerations, four comparisons of conditions were specified. The following contrast images were calculated for each subject: (i) pre-effort anticipation "high" vs. fix cross; (ii) pre-effort anticipation "low" vs. fix cross; (iii) post-effort anticipation "high" vs. fix cross; and (iv) post-effort anticipation "low" vs. fix cross. To examine group differences among the Amisulpride and Placebo groups in the processing of social rewards related to reward anticipation, the aforementioned contrast images were taken to the second-level analysis.

**Second-level analysis.** The goal of the second-level analysis is to generalize the results from the single subject level to the group level and therefore, the population that the sample was drawn from. The second-level analysis included the factors Drug (Amisulpride, Placebo) and Reward Level (high, low). Two mixed-model ANOVAs (full factorial design), one for pre-effort and one for post-effort anticipation, were specified and calculated. The main effects of Drug and Reward Level, as well as their interactions, were explored in this whole brain analysis.

Regarding the brain mapping, the automated anatomical atlas 3 (AAL3) supplied with the MRIcron software was used. I only reported coordinates that survived the uncorrected threshold of $p < .001$ with an extended cluster size of at least 15 voxels.

# Results

To investigate whether dopaminergic antagonism in healthy participants via administration of amisulpride leads to reduced 'wanting' of social rewards, data representing this motivational component was collected at explicit and implicit levels using behavioral as well as neuronal measures. The results of the respective data analyses are presented in the following.

## Behavioral results

At the behavioral level, two sets of data were analyzed, each measuring the wanting of the announced reward. First, the subjective self-reported wanting ratings and second, the physical effort as a self-executed intervention to influence the likelihood of receiving the announced stimulus.

### *Effect of amisulpride on subjective wanting ratings*

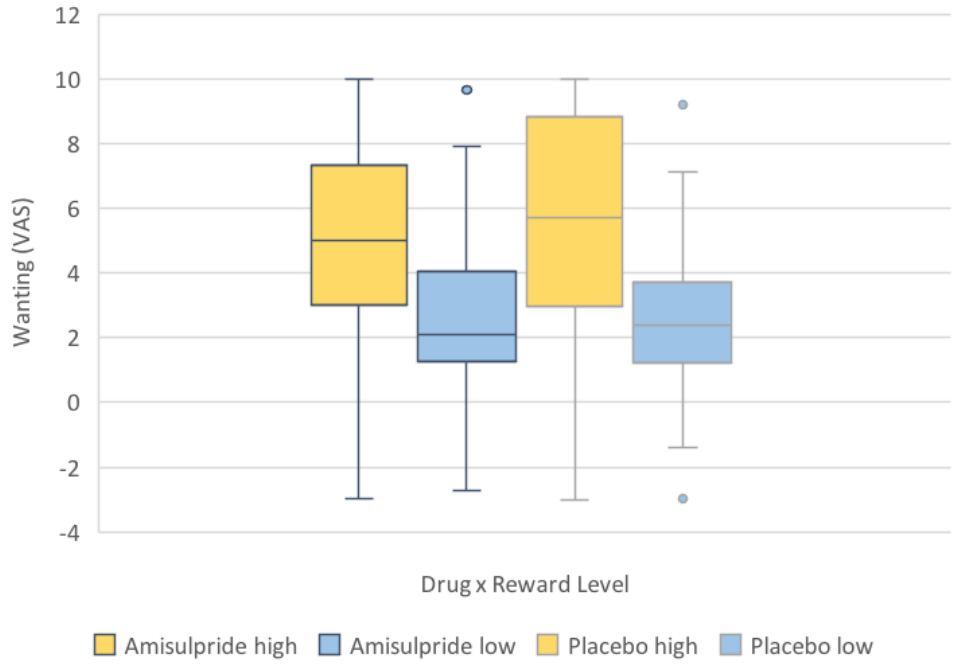
***H1a****:* selective blockade of postsynaptic striatal D2 and D3 receptors by amisulpride in healthy participants leads to *reduced subjective wanting ratings* a cued social reward

A mixed-design ANOVA was used to test the hypothesis that the selective blockade of postsynaptic striatal D2 and D3 receptors by amisulpride in healthy participants leads to reduced subjective wanting ratings in response to cues indicating social rewards, with wanting ratings as the dependent variable, Drug (Amisulpride, Placebo) as between-subject factor and Reward Level (high, low) as within-subject factor.

Behavioral analyses on wanting ratings revealed a significant main effect of Reward Level ($F(1, 58) = 32.929$, $p < .001$), due to higher wanting ratings for high ($M = 5.31$, $SD = 3.27$) in comparison to low rewards ($M = 2.68$, $SD = 2.62$). The main effect of Drug ($F(1, 58) = .128$, $p = .722$) as well as the interaction between Reward Level and Drug ($F(1, 58) = .171$, $p = .681$) were not significant. Figure 2 illustrates visually the wanting ratings boxplotted by Reward Level and Drug.

**Figure 2**

*Box plots of wanting ratings by Drug and Reward Level*




### *Effect of amisulpride on exerted effort*

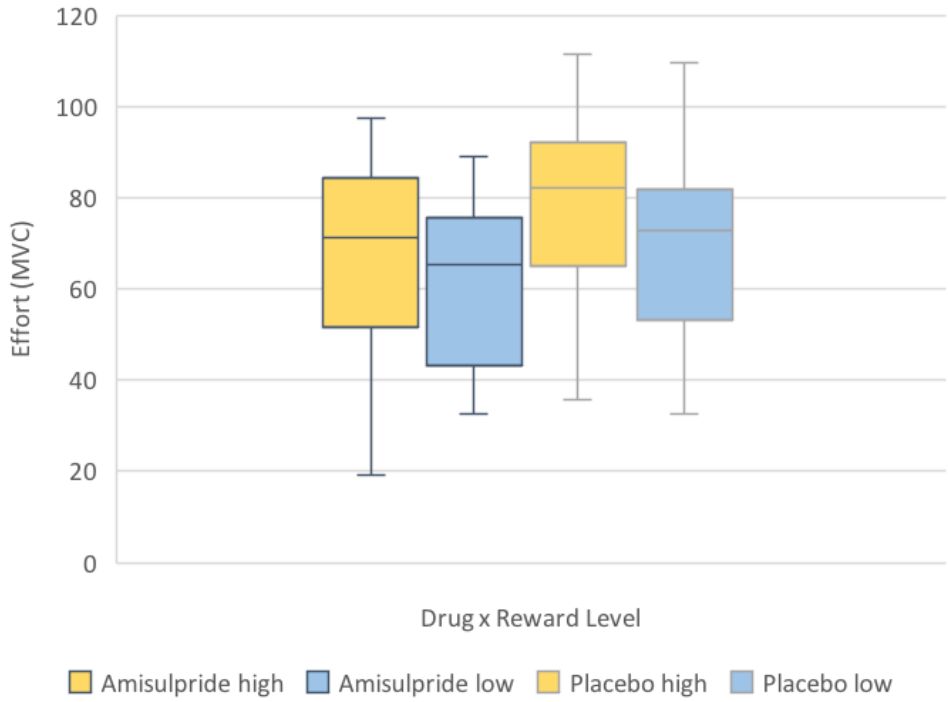
***H1b**:* selective blockade of postsynaptic striatal D2 and D3 receptors by amisulpride in healthy participants leads to *reduced exerted effort* to obtain a cued social reward

Another mixed-design ANOVA was conducted to test the hypothesis that the selective blockade of postsynaptic striatal D2 and D3 receptors by amisulpride in healthy participants leads to reduced exerted effort to obtain a cued social reward, with exerted effort as the dependent variable, Drug (Amisulpride, Placebo) as between-subject factor and Reward Level (high, low) as within-subject factor.

This analysis revealed a significant main effect of Reward Level, ($F(1, 58) = 13.5$, $p < .001$), due to greater effort exerted for high rewards ($M = 73.02$, $SD = 20.17$) compared to low rewards ($M = 65.58$, $SD = 18.58$). The analysis also showed marginally significant main effect of Drug ($F(1, 58) = 3.73$, $p = .058$), in the direction that the average effort exerted tended to be lower for the Amisulpride group ($M = 65.26$, $SD = 18.73$) than in the Placebo group ($M = 73.92$, $SD = 19.32$). The interaction between Reward Level and Drug was not statistically significant ($F(1, 58) = .35$, $p = .556$). Figure 3 illustrates visually the exerted effort values boxplotted by Reward Level and Drug.

**Figure 3**

*Box plots of effort by Drug and Reward Level*




***Prove of assumptions***

As outlined in the method chapter, seven assumptions had to be checked and fulfilled in advance for the mixed ANOVAS to be calculated (Salkind, 2010).

The first three requirements relating to the scale characteristics of the independent and dependent variables can be considered fulfilled after reviewing the data. These comprise: (1.) The two dependent variables (wanting ratings and effort) to be both interval scaled; (2.) The between-subject factor (Drug) is independent and nominally scaled; (3.) Furthermore, the within-subject factor (Reward Level) is also independent and nominally scaled. (4.) Potential outliers were analyzed visually by boxplotting the values. As illustrated in Figure 2 and 3 (see above), boxplots were created respectively for wanting ratings and exerted effort, divided into Drug (Amisulpride, Placebo) and Reward Level (high, low). The boxplots graphically illustrate the minimum and maximum value of the distribution as well as the first (1Q) and third quartile (3Q) of the data, corresponding to a $25^{th}$ and $75^{th}$ percentile respectively, represented as the lower and upper boundary of the box. The line inside the boxes indicates the median. The distance from the upper to the lower quartile is called the interquartile range (IQR). The length of the whiskers around the boxes amounts 1.5 times the IQR (Salkind, 2010). For a comprehensive overview of the corresponding values mentioned, see Table 1.

**Table 1**

*Descriptive statistics of boxplots for wanting ratings and effort*

| Drug | Reward Level | DV | *min* | *max* | *1Q* | *Mdn* | *3Q* | *IQR* |
|---|---|---|---|---|---|---|---|---|
| Amisulpride | High | Rating | -2.96 | 10.00 | 3.00 | 5.00 | 7.34 | 4.34 |
| | Low | Rating | -2.71 | 9.65 | 1.25 | 2.10 | 4.06 | 2.81 |
| Placebo | High | Rating | -3.01 | 9.98 | 2.95 | 5.73 | 8.83 | 5.88 |
| | Low | Rating | -2.99 | 9.20 | 1.24 | 2.37 | 3.70 | 2.46 |
| Amisulpride | High | Effort | 19.20 | 97.28 | 51.59 | 71.23 | 84.47 | 32.88 |
| | Low | Effort | 32.53 | 88.88 | 43.07 | 65.36 | 75.74 | 32.67 |
| Placebo | High | Effort | 35.84 | 111.58 | 64.94 | 82.19 | 92.27 | 27.33 |
| | Low | Effort | 32.50 | 109.47 | 53.16 | 72.88 | 81.88 | 28.72 |

*Note.* DV = Dependent Variable; min = minimum; max = maximum; 1Q = first quartile ($25^{th}$ percentile); Mdn = Median; 3Q = third quartile ($75^{th}$ percentile).

Values in the data set below 1Q - 1.5 IQR or above 3Q + 1.5 IQR are deemed as outliers. The wanting ratings show a total of three outliers (see Figure 2), each in the low reward category (two in the placebo (Sub 45 = 9.2; Sub19 = -2.99) and one (Sub63 = 9.65) in the Amisulpride group). However, since none of these outliers are statistically significant and can therefore be considered as not severe, the three subjects were included in the analysis. The boxplots for the effort exerted revealed any outliers (see figure 3). Accordingly, none of the 60 subjects in total (32 Amisulpride; 28 Placebo) were excluded from the behavioral analysis. In addition to the analysis of the outliers, the boxplots can also be used to provide information about the shape of the distributions of the values. The position of the median within the boxes is decisive for this. For the wanting ratings, the median lies relatively centrally in three of the four groups, which means that the distributions were symmetrical. For the Amisulpride group in the low reward category, however, it is shifted somewhat downwards. Therefore, it can be concluded that it is a right-skewed distribution. On the other hand, all medians of the effort data were slightly above the means. The underlying distributions are therefore rather left-skewed. (5.) Examination of the histograms of the distributions (divided into Drug and Reward Level, respectively for wanting ratings and effort) allow the conclusion that the residuals of the dependent variable are (approximately) normally distributed for each group. Additionally, the Shapiro-Wilk Test statistically confirms

this visual conclusion, since it is not significant (all $p > .05$) for every dependent variable split into groups, except for the Amisulpride group 'effort low' ($p = .026$). Nevertheless, minor deviations can be ignored, as some authors (e.g. Salkind, 2010) consider this assumption to be the least important, hence the mixed ANOVA is considered sufficiently robust to the violation or, in this case, minor deviations of this assumption. Therefore, the assumption of normality has been met. (6.) The sixth assumption, regarding the homogeneity of error variances for both wanting ratings and effort in the within-subject factor (Reward Level), was also proved, as assessed by Levene's test (with all $p > .05$). (7.) The seventh and last assumption of the sphericity could not be calculated because the within-subject factor Reward Level only has two levels. In this case, sphericity is always given.

Based on these considerations, it could be stated that all necessary assumptions for the statistical model of a mixed ANOVA were met. Consequently, two mixed ANOVAs (one each with wanting ratings or effort as the dependent variable) were subsequently calculated to answer the hypotheses *H1a* and *H1b*. Significant main effects of Drug and Reward Level as well as interactions were analyzed and presented below.

### *Group comparisons of current mood, strength, and drug side-effects*

Group differences in age, BMI, current mood, MVC, and drug side-effects were assessed using independent two-sided t-tests. For an overview of the participants' characteristics across groups and potential differences see Table 2 below.

#### *Mood*

The subjects' current mood before pill administration (T1) and after the reward-task (T2) was measured using the PANAS questionnaire (Watson et al., 1988), which include a 'positive mood' and a 'negative mood' subscale. The calculated t-tests did not reveal any significant group difference in positive and negative mood before (T1; positive: $t(57) = -.26$, $p = .81$; negative: $t(57) = 1.38$, $p = .17$) or (approximately) 250 min after pill administration (T2; positive: $t(57) = -1.42$, $p = .16$; negative: $t(43.79) = 1.71$, $p = .09$). The index (T2-T1) confirmed additionally that the groups did not differ significantly in their current mood changes over the time course of the main task (positive: $t(38.33) = -1.4$, $p = .17$; negative: $t(58) = .04$, $p = .97$).

*Maximum voluntary contraction at rest*

The MVC data collected at the end of the task are missing for five subjects (2 Amisulpride, 3 Placebo) due to technical issues. Therefore, the corresponding t-test was conducted with the remaining 55 subjects (30 Amisulpride, 25 Placebo).

The average MVC before the reward task were 120.1 N (*SD* = 38.01) for female participants and 174.52 N (*SD* = 51.92) for male participants. Interestingly, the mean MVC increased for females with an average of 139.41 N (*SD* = 43.2) and 201.49 N (*SD* = 45.45) for male participants, at the end of the main task.

The t-tests did not yield a significant difference in maximum strength either at the beginning ($t(58) = .93$, $p = .36$) or at the end ($t(53) = p = .56$) between the groups. This indicate that the drug did not alter participants' strength at rest. Furthermore, the change in maximum strength over the course of the experiment (T2-T1) due to muscle fatigue was not significantly different between the Amisulpride group (*M* = 20.29, *SD* = 36.38) and the Placebo group (*M* = 25.18, *SD* = 40.87) ($t(53) = .- 47$, $p = .64$).

*Drug side effects*

A number of known drug side effects were assessed using self-report questionnaires before (T1) and after (T2) the reward task. The responses were scored on a 4-point Likert scale (with the anchors 1 = "*not at all*" to 4 = "*very much*"). Selected side effects that would affect the interpretability of the results were assessed for group differences. No significant effects of Drug were observed in any of the ten side effects tested (nausea ($p = .96$), headache ($p = .37$), unrest ($p = .91$), nervousness ($p = .65$), tiredness ($p = .42$), weakness ($p = .15$), thirst ($p = .62$), skin rash ($p = .16$), dizziness ($p = .89$) or despondency ($p = .64$)). Importantly and in line with the findings above regarding the strength, the index (T2-T1) of the side-effect 'weakness' did not differ between the groups ($t(58) = 1.47$, $p = .15$) either, even though the subjects in the Amisulpride group felt slightly weaker (*M* = .31, *SD* = .78) after the testing than before, compared to a relatively unchanged mean (*M* = .07, *SD* = .47) in the Placebo group.

**Table 2**

*Participants´ characteristics across groups, as tested with t-tests for independent samples*

| | Amisulpride | Placebo | Group differences |
|---|---|---|---|
| N (female, male) | 32 (18, 14) | 28 (17,11) | |
| Age *M (SD)* | 24.03 (3.96) | 23.25 (3.61) | $t$ = .79, $p$ = .43 |
| BMI *M (SD)* | 23.03 (2.61) | 22.79 (2.15) | $t$ = .39, $p$ = .7 |
| PANAS pos (T2-T1) *M (SD)* | -5.72 (6.42) | -3.29 (7.02) | $t$ = -1.4, $p$ = .17 |
| PANAS neg (T2-T1) *M (SD)* | -.94 (3.59) | -.96 (1.17) | $t$ = .04, $p$ = .97 |
| MVC (end-beginning) *M (SD)* | 20.29 (36.38) | 25.18 (40.87) | $t$ = -.47, $p$ = .64 |
| Weakness (T2-T1) *M (SD)* | .31 (.78) | .07 (.47) | $t$ = 1,47, $p$ = .15 |
| Nausea (T2-T1) *M (SD)* | .03 (.4) | .04 (.33) | $t$ = -.05, $p$ = .96 |

*Note.* The $t$ and $p$ values refer to the main effect of group.
BMI = Body Mass Index; *M* = Mean; *SD* = Standard deviation; PANAS = Positive and Negative Affect Schedule; MVC = maximum voluntary contraction.

Since the groups did not differ significantly in any of the control variables examined, it is reasonable to conclude that the present results can be interpreted as a consequence of the experimental manipulation rather than being attributed to the influence of covariates.

The descriptive statistics for both wanting ratings and effort by Drug and Reward Levels are summarized in Table 3.

**Table 3**

*Means and standard deviations for wanting ratings and effort as a function of Drug and Reward Level*

| | | High rewards | | Low rewards | |
|---|---|---|---|---|---|
| | | *M* | *SD* | *M* | *SD* |
| Wanting ratings | Amisulpride | 5,12 | 3,06 | 2,67 | 2,56 |
| | Placebo | 5,53 | 3,53 | 2,7 | 2,73 |
| Effort | Amisulpride | 68,41 | 20,41 | 62,1 | 17,04 |
| | Placebo | 78,29 | 18,88 | 69,55 | 19,76 |

*Note.* The abbreviations *M* and *SD* stand for mean and standard deviation respectively.

## Neuroimaging results

***H1c*:** pharmacological blockade of dopaminergic receptors in healthy participants by amisulpride leads to *reduced brain activation* in areas associated with reward anticipation (such as VTA, VS, and vmPFC).

In order to investigate drug effects on brain activity during reward anticipation, brain activations (BOLD signal) during the announcement of the attainable social reward (pre-effort anticipation phase) were examined. In a more exploratory way, also brain activations during the announcement of the attained social reward (post-effort anticipation phase) were also assessed.

As a first whole brain analysis of the neuroimaging data, the multiple comparison correction, implemented in SPM12, was applied using Random Gaussian Field theory (FWE correction). All main effects and interactions of interest were examined for significant activation. In an additional, subsequent analysis, selected contrasts were calculated, using an uncorrected p-value threshold lowered to $p < .001$. Furthermore, a cluster extended threshold of $k > 15$ was chosen in this second run of analysis. The obtained results are presented below.

### *Pre-effort anticipation*

Testing for main effects and the interaction of Drug and Reward Level at the whole brain level ($p < .05$, FWE corrected), revealed no significant activation in the corresponding contrasts (see Table 4) in the pre-effort anticipation phase.

**Table 4**

*Whole brain analysis results ($p < .05$ (FWE Correction)) for main effects and interaction*

| | | | | | | MNI Coordinates | | |
|---|---|---|---|---|---|---|---|---|
| Region | dist | Hem | Cluster k | $p_{FWE\text{-}corr}$ | **T** | **x** | **y** | **z** |
| Interaction Drug*Reward Level (pla(high>low) > ami(high>low)) | | | | | | | | |
| No suprathreshold voxels | | | | | | | | |
| High > Low | | | | | | | | |
| No suprathreshold voxels | | | | | | | | |
| Low > High | | | | | | | | |
| No suprathreshold voxels | | | | | | | | |
| Placebo > Amisulpride | | | | | | | | |
| No suprathreshold voxels | | | | | | | | |
| Amisulpride > Placebo | | | | | | | | |
| No suprathreshold voxels | | | | | | | | |

*Note.* Brain regions activated during the anticipation of social rewards for the contrasts High > Low; Low > High; Placebo > Amisulpride; Amisulpride > Placebo (using a family wise error (FEW) correction, $p < .05$). Hem = Hemisphere (L = left, R = right); dist = distance (in mm) between coordinates and closest region; MNI = Montreal Neurological Institute.

Since at the conservative FWE $p < .05$ threshold no suprathreshold activations were found, I therefore also examined in an exploratory way activation at the less conservative threshold $p < .001$ uncorrected.

The main effect of Drug (Placebo > Amisulpride) did not yield any clusters of activation that survived the uncorrected p-value threshold ($p < .001$). Accordingly, reduced activation of reward-associated areas in the Amisulpride group during the anticipation of a social reward could not be demonstrated. However, the main effect of Reward Level and the interaction Drug by Reward Level showed significant activation, which will be presented in more detail hereafter. For a comprehensive overview, see Table 5, which provides a list of all clusters and corresponding MNI coordinates with the strongest activation in the respective regions.

**Table 5**

*Whole brain analysis results (p < .001 (unc.)) in the computed contrasts of interest*

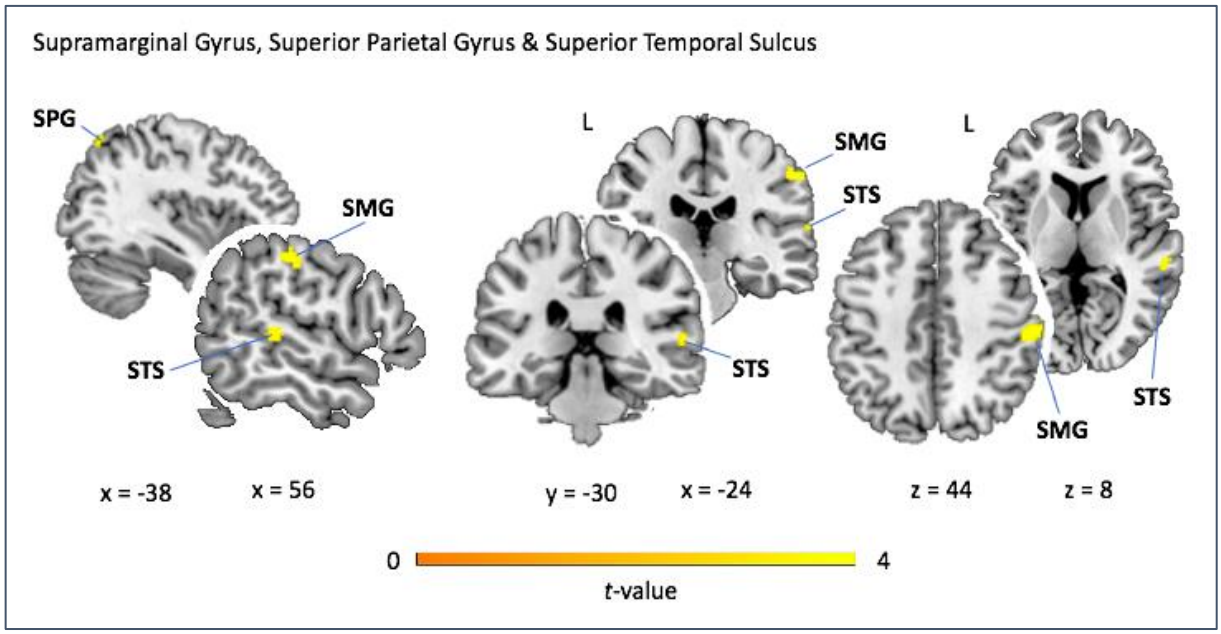
| | | | | | | MNI Coordinates | | |
|---|---|---|---|---|---|---|---|---|
| Region | dist | Hem | Cluster k | $p_{uncorrected}$ | **T** | **x** | **y** | **z** |
| High > Low | | | | | | | | |
| Supramarginal Gyrus | | R | 144 | .035 | 3.76 | 56 | -24 | 44 |
| Superior Parietal Gyrus | 2.00 | L | 18 | .431 | 3.58 | -38 | -68 | 56 |
| Superior Temporal Sulcus | | R | 47 | .203 | 3.53 | 58 | -30 | 8 |
| Interaction Drug*Reward Level (pla(high>low) > ami(high>low)) | | | | | | | | |
| Caudate | 6.00 | L | 114 | .056 | 4.71 | 0 | 2 | 12 |
| Insula | 3.46 | R | 196 | .016 | 4.53 | 32 | -2 | 18 |
| ACC superior | 2.83 | R | 159 | .028 | 4.32 | 16 | 22 | 24 |
| Cingulum Anterior | | R | 49 | .194 | 4.26 | 2 | 42 | 14 |
| SMA | 2.00 | L | 77 | .109 | 4.24 | -2 | 2 | 80 |
| SMA | | L | 231 | .010 | 4.13 | -8 | -6 | 64 |
| Supramarginal Gyrus | | R | 42 | .228 | 4.01 | 62 | -24 | 44 |
| Postcentral Gyrus | | L | 90 | .086 | 4.01 | -54 | -10 | 42 |
| Thalamus | | L | 29 | .315 | 3.94 | -14 | -24 | 8 |
| Caudate | 2.00 | L | 45 | .213 | 3.8 | -16 | 0 | 14 |
| Middle Frontal Gyrus | 6.00 | L | 26 | .342 | 3.62 | -22 | 26 | 24 |
| Temporal Pole Superior | | L | 26 | .342 | 3.62 | -50 | 10 | -18 |
| Insula | | R | 42 | .228 | 3.61 | 40 | 18 | -10 |
| Middle Cingulate Cortex | | L | 19 | .418 | 3.36 | -6 | -4 | 36 |
| Precuneus | | L | 37 | .257 | 3.34 | -2 | -66 | 24 |

*Note.* Brain regions activated during the anticipation of social rewards for the contrasts high > low rewards and the interaction Drug x Reward Level (using a voxel-wise uncorrected p-value threshold ($p < .001$) and a cluster extended threshold k > 15). Labeled with the automated anatomical atlas 3 (AAL3). Cluster size represents the total number of voxels in the clusters meeting the threshold criteria in the region. The coordinate values represent the cluster with the strongest activation within the region. Hem = Hemisphere (L = left, R = right); dist = distance (in mm) between coordinates and closest region; MNI = Montreal Neurological Institute. ACC, anterior cingulate cortex; SMA, supplementary motor area.

As already indicated, testing for main effects and interactions at the whole brain level using a voxel-wise uncorrected p-value threshold ($p < .001$) and a cluster extended threshold $k > 15$, revealed significant activation for the main effect of Reward Level (high > low) during the pre-effort anticipation phase. Specifically, the right supramarginal gyrus, the left superior parietal, and the right superior temporal sulcus (Table 5, Figure 4) were active during the anticipation of high social reward as compared to low social reward.

**Figure 4**

*Neuroimaging results for main effect of Reward Level (high > low), with p < .001 (unc.)*

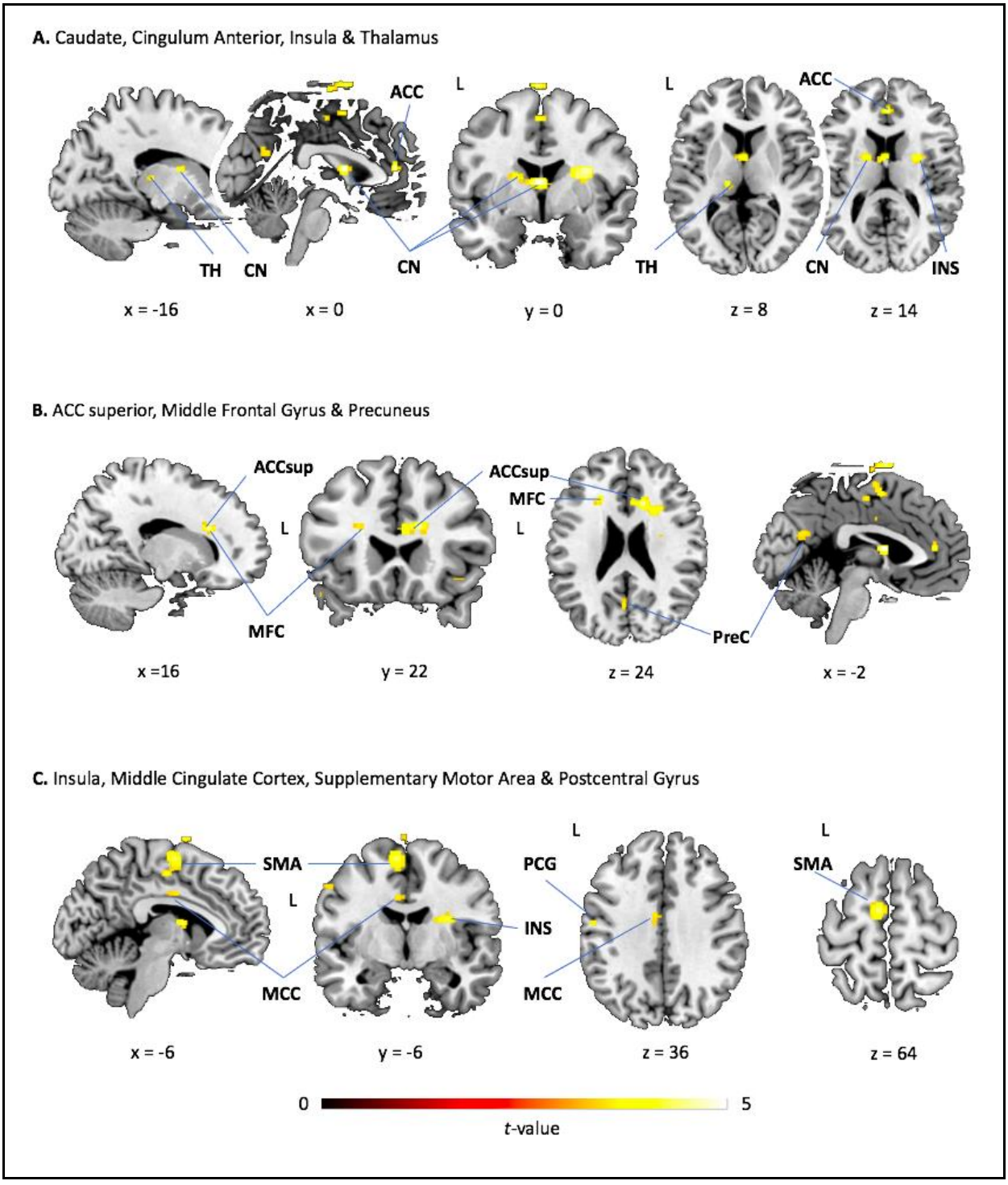



*Note.* Data is presented on a template (ch2bet.nii.gz) provided by MRIcron with an uncorrected threshold of $p < .001$ and a cluster extended threshold $k > 15$. (A.) Peak activations in the Supramarginal Gyrus (SMG), the Superior Parietal Gyrus (SPG) and the Superior Temporal Sulcus (STS) for high compared to low rewards.

Importantly, suprathreshold activation was observed in the Drug by Reward Level interaction (Pla(high>low) > Ami(high>low)). The interaction of Drug by Reward Level (with $p < .001$, uncorrected) showed significantly reduced activation for high rewards compared to low rewards in the Amisulpride group compared to the Placebo group in the following regions: the left caudate, right insula, left thalamus, right cingulum anterior (Figure 5A), right cingulum anterior superior, left precuneus, left middle frontal gyrus (Figure 5B), left middle cingulate cortex, right supramarginal gyrus, left postcentral gyrus and left supplementary motor area (Figure 5C).

**Figure 5**

*Neuroimaging results for the interaction of Drug by Reward Level during the pre-effort anticipation phase, with p < .001*

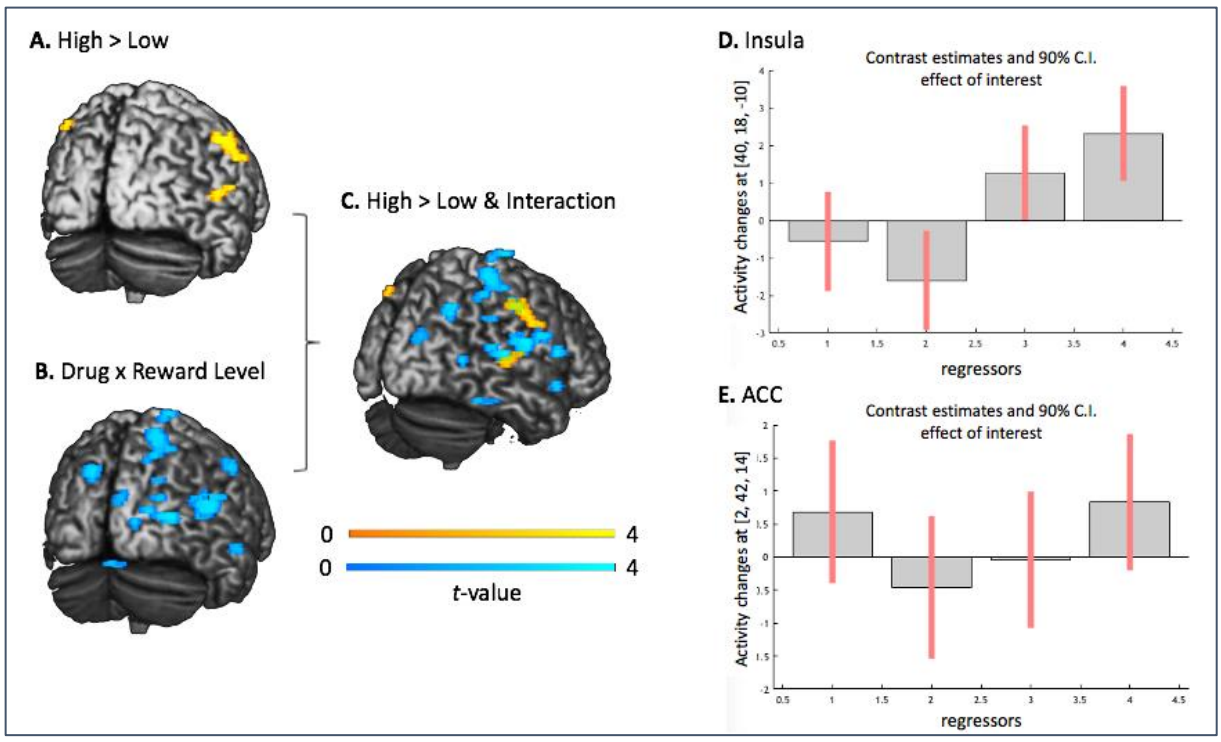



*Note*. Data is presented on a template (ch2bet.nii.gz) provided by MRIcron with an uncorrected threshold of $p < .001$ and a cluster extended threshold k > 15. L, left; Structure labels: (A) ACC, Anterior Cingulate Cortex; CN, Caudate Nucleus; INS, Insula; TH, Thalamus; (B) ACCsup, Superior Anterior Cingulate Cortex; MFC, Middle Frontal Cortex; PreC, Precuneus. (C) INS, Insula; MCC, Middle Cingulate Cortex; SMA, Supplementary Motor Area; PCG, Postcentral Gyrus.

The whole brain results for both significant contrasts (main effect Reward Level and interaction Drug by Reward Level) with an uncorrected p-value threshold ($p < .001$) during the pre-effort anticipation phase are summarized in Figure 6 below. Figure 6D and 6E clarify the signal difference for the interaction contrast in the voxels of the Insula and ACC, respectively, according to the four regressors (Placebo high, Placebo low, Amisulpride high, Amisulpride low). Figure 6D illustrates a decrease of activation in the Insula for the regressors Placebo high and Placebo low and an increase for Amisulpride. Figure 6E shows an increase of activation in the ACC for Placebo high and Amisulpride low and a decrease for Placebo low and Amisulpride high. The signal difference pattern of the Insula looks equivalent to the one in the Precuneus and Thalamus and is illustrated accordingly by representation. The activity change in the ACC corresponds in turn to that of the MCC. According to Sescousse and colleagues (2013), the Insula and ACC together with other subcortical structures were often referred to as the 'salience network' and were therefore chosen for illustration.

**Figure 6**

*Whole brain neuroimaging results and activity changes in insula and ACC*




*Note.* Neuroimaging results for main effect Reward Level and interaction, with $p < .001$. (A) Bold signal for main effect contrast High > Low reward; (B) Bold signal for interaction Drug x Reward Level; (C) combined activation of A. and B.; (D) Activity changes according to four regressors (Placebo high, Placebo low, Amisulpride high, Amisulpride low) in the

Insula for the interaction during the pre-effort anticipation phase; (E) Percent signal change analysis in the ACC during the pre-effort anticipation phase.

### *Post-effort anticipation*

The additional analysis of the post-effort anticipation phase yielded no significant results for the main effects of Drug or Reward Level at the conservative FWE threshold $p < .05$. The Drug by Reward Level interaction was also not significant. For the post-effort anticipation phase, no further analysis was performed with a reduced significance level to $p < .001$ uncorrected, as it was for exploratory purposes only.

# Discussion

## Summary

The goal of the present study was to investigate the functional role of mesocorticolimbic and striatal dopamine activity in 'wanting' social reward processing in healthy humans. To address this aim, a psychopharmacological experiment was designed using a recently developed reward task (Korb et al., 2020a, Korb et al., 2020b) in a fMRI environment. Subjects were randomly assigned to either an experimental (dopamine antagonist amisulpride administered) or a control (placebo administered) group. During the anticipation of social (affective touch) rewards, explicit (wanting ratings) and implicit (physical exerted effort and neuronal) measures of 'wanting' were recorded in 60 healthy adult participants. The hypotheses examined stated that the blockade of dopaminergic receptors by amisulpride leads to a decrease of 'wanting' to obtain a cued social reward, both in the brain and behavioral responses to social reward anticipation.

Contrary to expectations, at the behavioral level, neither the wanting ratings nor the exerted effort revealed a significant Drug effect, showing reduced 'wanting' in the Amisulpride group compared to the Placebo group to receive a cued social reward. Furthermore, the interaction of Drug by Reward Level was also not significant. Only the main effect of Reward Level for both dependent variables (wanting ratings and exerted effort) was significant, indicating a higher 'wanting' of high (slow stroking) compared to low (fast stroking) rewards.

At the neuronal level, no significant decrease of brain activation in the Amisulpride group compared to the Placebo group in corresponding areas associated with the anticipation of social rewards (such as the VTA, VS, and vmPFC) was found. Likewise, only the main effect of Reward Level was significant (on a low threshold level). During the anticipation of high social reward as compared to low social rewards the regions of the supramarginal gyrus, the superior parietal and the superior temporal sulcus were activated. In line with the literature (Boehme et al., 2019; Strauss et al., 2019), were these regions typically related to touch and particularly associated with slow touch. Furthermore, the superior temporal sulcus is important for numerous aspects of social cognition (Martins et al., 2021; Saitovitch et al., 2012; Sturm et al., 2016).

Additionally, the interaction of Drug by Reward Level was significant during the pre-effort anticipation phase. The activated clusters included indeed some of the hypothesized regions. Particularly noteworthy, the caudate as part of the striatum, represents one of the brain structures composing the reward system. Furthermore, other brain areas which are commonly involved in reward processing, such as the precuneus, the insula, and the thalamus showed also significantly reduced activation for high rewards compared to low rewards in the Amisulpride group compared to the Placebo group. The cingulum, moreover, is a structure expected to be associated in particular with reward anticipation (Vassena at al., 2014). In turn, the postcentral gyrus represents the primary somatosensory cortex (DiGuiseppi & Tadi, 2021), the most important sensory receptive area for discriminative (in contrast to affective) touch and tactile manipulations of the environment (Cascio et al., 2019).

## Possible interpretations

### *Behavioral results*

In general, the explicit (wanting ratings) and implicit (exerted effort) wanting were significantly higher for the high reward compared to the two low reward levels. This stands in line with previous studies using the same design (Korb et al., 2020a, 2020b) and the literature (Spreckelmeyer et al., 2009; Fareri & Delgado, 2014). These results suggest that the experimental intervention was successful and that the chosen stimuli were indeed experienced as rewarding to varying degrees. The significance of this main effect served as a manipulation check and is a necessary condition for further interpretation of the results. The revealed higher subjective ratings of slow touch, as well as the greater effort expended to obtain it, confirms the distinction between CT-optimal and non-optimal touch frequencies (Morrison et al., 2011; Pawling et al., 2017; Ree at al., 2019). Interestingly, this preference for stroking speeds in humans appears to be very stable over time (Luong et al., 2017). Furthermore, the results are coherent with previous studies highlighting the fact that humans and other social species are willing to exert additional effort to pursue social stimuli rated as higher (Ferari & Delgado, 2014; Deaner et al., 2005).

However, the two hypotheses *H1a* and *H1b*, which each assumed a reduction in wanting and ‘wanting’ at the behavioral level in the experimental group, could not be confirmed on the basis of the data collected. There was no evidence indicating that subjects in the Amilsulpride group were subjectively rating the rewarding stimuli as less wanted, nor was

there a significant difference in the effort they expended to obtain them. These results are inconsistent with expectations based on the theoretical background (Berridge & Robinson, 1998; Berridge et al., 2009). Previous studies that have likewise attempted to manipulate 'wanting' pharmacologically with dopamine antagonists have yielded contradictory results depending on the operationalization used (Soutschek et al., 2021; Weber et al., 2016).

Nevertheless, it is worth noting that the main effect of exerted effort (*H1b*) was marginally significant. It is arguable that with a larger sample size this might have reached significance. Notably, this effect goes in the expected direction with a decreased exerted effort to obtain the reward in the Amisulpride group. This measurement method elicited the implicit 'wanting' of the subjects. Accordingly, it can be cautiously interpreted that the trend of the effect could be an indication that the blockade of postsynaptic dopamine indeed leads to reduced incentive salience 'wanting'. Importantly, it is conceivable to discuss if the reduced mobilized effort which was not reflected in likewise reduced wanting ratings, might be an argument for the postulated theoretical distinction between implicit and explicit wanting to actually exist (Berridge & Robinson, 2003; Pool et al., 2016). Considered from this perspective, the results could be interpreted to imply that the wanting diverged at the conscious and unconscious levels. Possibly the subjects themselves assumed on a conscious level that they would like to receive the reward. Explanations could be the expectation or habit of evaluating rewards as attractive and desirable in general. For instance, Ree and colleagues (2019) described subjective reports as constructed assessments based on multiple processes, such as memory. The artificial test situation as well as social desirability effects could further have led to an influence on the subjective ratings. Possibly, both groups could have been equally rated to want the rewards because they did not want to be perceived as impolite. Since their ratings concerned a real, foreign person, they might not want to have them disappointed. This could be evaluated as a disadvantage of a real stimuli compared to showing pictures. In contrast, exerting force requires greater physical effort and, as a result, may only be expended when the participant is actually motivated to pursue the reward. Moreover, since it has the functional property of influencing which stimulus will be received, pressing the dynamometer may seem relevant to the subject only personally, but not in terms of the evaluation of others (like the rating). Accordingly, it may be less socially biased. Consequently, because of the unconscious component, it can be considered a suitable and representative method of measuring 'wanting'. This disparity in results across different methods of measuring wanting is reflected in previous research findings (Soutschek et al., 2021). In fact, several other studies using self-report wanting ratings could only reveal weak

or no effects of psychopharmacological manipulations, contrary to their hypotheses (Korb et al., 2020; Løseth et al., 2019). Whereas more objective methods were able to confirm effects (Weber et al., 2016)., indicating a higher sensitivity of these methods.

It is noteworthy that the experimental and control groups did not differ significantly concerning their current mood before or after testing, their general strength, or the side effects of the medications. Of particular importance is the fact that the groups did not differ significantly in terms of the side effect weakness. Otherwise, the results would not be interpretable if it had to be assumed that the Amisulpride group pressed less because the drug made them feel weaker. Accordingly, it can be assumed that the results were not influenced by these confounding variables. Moreover, fatigue or satiety effects can equally be ruled out as explanations for the present results. As already described, occurs adaptation to affective touch very slowly and satiety appears only after a longer period of time (Sailer et al., 2016).

***Neuroimaging results***

First, it is important to emphasize that the neural results did not reach significance at the conservative threshold for any of the relevant main effects and interactions. Consequently, hypothesis *H1c* cannot be confirmed with sufficient evidence based on the data collected and analyzed.

Nevertheless, it is arguable that the areas found at the lower significance level may provide some interesting indications for possible directions. However, these should be interpreted with caution, i.e., even if they might contain something meaningful, it is not powerful, due to the really low threshold applied. Overall, the majority of the regions identified in this study are compatible with the particular phase of the reward task. Noteworthy, they are to a broad extent in line with the results of the aforementioned meta-analysis of Martins and colleagues (2021) who reported the brain regions involved in the anticipation of social rewards compared to neutral feedback. I would like to discuss each of these structures for the respective contrasts in more detail in the following.

Regarding the main effect of Reward Level, it can be stated that, during the pre-effort anticipation of high compared to low social rewards, not much activation was found but at least some areas related to touch. Along the line of previous findings, the results supported the idea of ‘social-specific cognition’ additionally to the commonly shared reward circuits (Matyek et al., 2020). Particularly the STS is a region reported to be involved in several

aspects of social cognition (Martins et al., 2021) such as cognitive empathy, higher levels of prosocial behavior and perspective taking (Frith & Frith, 2006; Sturm et al., 2016). Interestingly, it is further essential for the detection of different types of social cues (Sabatinelli et al., 2011). Importantly, the STS is often found in the literature for slow compared to fast touch (Böhme et al., 2019; Strauss et al., 2019), which can be confirmed by the present results. Furthermore, in addition to the STS, the SMG is particularly associated with interpersonal touch. In a comprehensive study by Böhme and colleagues (2019), the researchers compared three different types of touch (other-touch, self- touch, and object-touch). Congruent with the present results, the researchers found increased activity in the other-touch condition in both aforementioned areas, whereas there was a decreased activity for self-touch and no changes for the object touch condition. It is important to underline that the described studies refer mostly to the consumption of rewards rather than anticipation. However, the present results suggest that the activity patterns in the anticipation phase might be similar in these regions to those activated during delivery. The third regions found, was the SPG. It plays a critical role in working memory (Koenigs et al., 2009), which is expectedly involved during cue presentation (holding the cue displayed in mind). Contrary to expectations, activation of the NAcc (as part of the ventral striatum), which is strongly associated with the anticipation of social rewards, was not found for any of the contrasts calculated (Izuma et al., 2008).

It is important to highlight once again that the decisive main effect of the group differences, similarly to the behavioral level, could not be confirmed neuronally either (not at the conservative threshold or the lower one). Nevertheless, the significant activity patterns of the interaction might provide some information about possible group differences. Remarkably, several areas related to the reward system were found, revealing significant reduced activation for high compared to low rewards in the Amisulpride compared to the Placebo group. These included the caudate, the anterior cingulate cortex, precuneus, thalamus, and the insula. Moreover, activation in the middle cingulate cortex, supramarginal gyrus, supplementary motor era, postcentral gyrus, middle frontal cortex, and temporal pole superior was additionally observed. Generally, according to Mow and colleagues (2020), several of these regions collectively comprise a ‘social interaction network’. While the STS, precuneus, and PFC, among others, constitute the mentalizing regions, the ACC, insula, and VS are considered the affective regions for processing social interaction. Again, the different regions identified, which were considered to play a role in incentive salience processing, will be discussed separately below.

The caudate is part of the striatum and it is known as one of the most important input nuclei of the basal ganglia and receives its information mainly from the cortex (Haber, 2016). The nuclei of the basal ganglia are essential for the execution of voluntary movements as well as the inhibition of involuntary ones (Drsicoll et al., 2021). Neuroimaging studies have shown that in addition to motor control, the caudate also plays an important role in the selection and evaluation of action schemas and goal-directed behavior that may lead to positive outcomes (Grahn et al., 2008). Furthermore, it is reported to be relevant for motivation and reward (Driscoll et al., 2021; Grahn et al., 2008). This is reflected in the comprehensive results of the meta-analysis mentioned before, by Clements and colleagues published in 2018, who investigated the social motivation hypothesis of ASD. Remarkably, they found a hypoactivation of the caudate in the ASD group, most likely due to the disrupted 'wanting' but not 'liking' in individuals with ASD. Subsequently, the present activation of the caudate in the pre-effort anticipation phase supports its previously reported role in the normal processing of 'wanting' social rewards (Izuma et al., 2008). This is further underlined by the fact that like in the current results, Knutson and colleagues (2001) similarly observed activation of the caudate instead of the NAcc for the encoding of reward anticipation.

From the caudate, efferent projections go (besides the hippocampus and globus pallidus) to the thalamus (Driscoll et al., 2021), which was another significantly activated area. One main function of the thalamus, that is particularly related to the present reward task, is to provide context-dependent salience encoding through associative learning (Zhu et al., 2018). From the thalamus information is further transferred to the ACC and OFC (Haber, 2011). This network is referred to as the 'cortico-ventral basal ganglia circuit' and is generally known to be central for different aspects of reward (Haber, 2011). Contrary to expectations, activity in the OFC could not be observed. However, the ACC as a key structure associated with the anticipation of reward (Vassena et al., 2014) was detected to be significantly involved. Furthermore, it seems to be important for assessing the value of a reward (Goerlich et al., 2017). This is especially in the pre-effort anticipation phase of the reward task a necessarily required ability since the displayed cue had to be provided with subjective value to subsequently evaluate how much it is wanted. Interestingly, the ACC was also reported to play a crucial role in focused problem-solving as well as emotional self-control, which is of critical relevance, particularly in addictive disorders (Allman et al., 2001). Moreover, previous studies suggested the ACC to be relevant whenever effort needs to be mobilized to carry out a task (Sescousse et al., 2013). Additionally, the ACC was also found to be strongly activated during skin-to-skin touch compared to touch by an object (Böhme et al., 2019). The

same applies to the insula, which also showed activation in the present study and is considered a target region for the CT afferent fibers (Björnsdotter et al., 2009; Morrison et al., 2011). However, again, this has more relevance to the consumption rather than the anticipation phase. In addition to sensory processing, the insula performs a variety of other functions in humans, ranging from affective processing to highly cognitive processes (Morrison, 2011; Uddin, 2017). Several neuroimaging studies indicated consistently the key role of the insula in social emotion, empathy and interoceptive awareness (Lamm & Singer, 2010; Zhao et al., 2021). It is further a key region for the detection of the salience of social stimuli (Chen et al., 2009). Accordingly, and in line with different studies, the insula's involvement during the anticipation of social rewards in the present task is compatible with its general role of processing salient cues that signal the probabilistic receipt of one of three potential social outcomes, depending on the effort subsequently applied (Martins et al., 2021; Schneider et al., 2018). As already mentioned, the ACC and insula combined were referred to as the ‘salience network’ (Sescousse et al., 2013). It is assumed that activation of this network likely triggers increased arousal to improve task performance (Schneider et al., 2018).

Besides the insula, a recent study examining brain networks for empathy of pain showed that the activation of the anterior middle cingulate cortex (aMCC) was also associated with affect sharing, while the right supramarginal gyrus (rSMG) was responsible for distinguishing self from others (Zhao et al., 2021). The involvement of the MCC and SMG in this study could indicate that the announcement of the stimulus reminds the subject that it is a shared social interaction and that the subject puts herself in the tester's place. However, since they cannot involve the tester in the upcoming decision of which stimulus to perform or receive, a distinction between self and other occurs at the same time.

Some of the present results contain indications for the clinical implications outlined above. Notably, regarding its role in addiction, the insula and ACC have been further reported to be involved in craving and disrupted impulse control respectively (Koob and Volkow, 2010; Kühn & Gallinat, 2011). Besides the disrupted function of the caudate in ASD, additional structures found in the current study, are especially important regarding their role in social reward processing in this disorder. Firstly, dysfunctional anterior insula connectivity was observed in individuals with ASD (Uddin & Menon, 2009). Secondly, as described initially, studies have demonstrated early neural developmental abnormalities of the STS in persons with ASD, leading to a deficit in the perception of socially relevant stimuli (Saitovitch et al., 2012). The role of the STS in the normal processing of those stimuli is

supported by the present results. Another characteristic of ASD is the dysfunction of the default mode network (DMN), which is usually activated during a state of resting consciousness, like daydreaming or mind-wandering (Palhano-Fontes et al., 2015). One region particularly involved in the DMN is the precuneus (Knyazev et al., 2011), being the third structure to mention in this context. A previous study demonstrated a positive correlation between an autism quotient (AQ) and the activation of the precuneus during the anticipation of social compared to monetary rewards (Barman et al., 2015). These results again suggest a lack of perception of the social stimuli in people with ASD (or healthy people with a higher AQ score), subsequently resulting in higher activation of the DMN. Interestingly, these results were reflected by the change patterns of the precuneus in the present study. In line with the hypothesis, the precuneus showed a decreased activation in the placebo group (for both high and low rewards), arguable due to higher 'wanting' and in turn, an increase in the Amisulpride group, indicating a higher activation of the DMN.

In addition to its function in the DMN, the precuneus seems to be further relevant to supplying emotion-related information for the episodic memory retrieval (Cavanna & Trimble, 2006). The activation of this structure could therefore also imply that memories about the presented cue were recruited to synchronize its rewarding value with the subjective experience related to it, to following decide how much it is wanted.

The supplementary motor area is located in front of the primary motor cortex mainly responsible for the planning and control of learned complex movements (Tanji, 1994). Its contribution during the anticipation phase stands also in line with previous studies (Martins et al., 2021). Even though it was initially rather surprising and counterintuitive since the subject was lying motionless in the scanner. Interestingly, however, a study using an oculomotor task showed that activity in SMA neurons actually represents reward expectancy. Thus, the neurons fire to facilitate the learning of a new, coordinated behavior between different body parts which will lead to a reward (Campos et al., 2005).

The postcentral gyrus is the target area for myelinated fibers (not CT-fibers) encoding particularly discriminative touch (Cascio et al., 2019). Interestingly, Morrison and colleagues (2011) showed activation of the postcentral gyrus in addition to the actual consumption of touch, also when subjects were shown only a video of a touch scene. The present results are consistent with these previous observations. Contrary to the present findings, the meta-analysis by Martins and colleagues (2021) found a decrease of activation both in the

postcentral and middle frontal gyrus during the anticipation of social rewards. This is reflected in several other studies that presented an activation of the postcentral gyrus for the monetary over the social condition (Goerlich et al., 2017; Kirsch et al., 2006). Finally, the middle frontal gyrus is commonly associated with computational processes (Gruber et al., 2001). A neuroimaging study examining the selection and anticipation of rewards in patients with major depressive disorders (MDD) found decreased activation of the middle frontal gyrus in these individuals (Gruber et al., 2009). The researchers argued that the lack of approach motivation typically associated with MDD may be due to this lack of information processing. The involvement of the MDD in healthy subjects could in turn play a role in the processing of the presented cue regarding its likelihood to perceive it, in order to subsequently initiate action in the right direction. However, it should be noted that the activity cluster found was six millimeters apart from the labeled area of the middle frontal gyrus and the results should be viewed with particular caution.

Finally, I would like to briefly discuss the post-effort anticipation phase. The non-significant results in this time window are partly in line with expectations. However, since no activity was found during the pre-effort anticipation phase with the same threshold either, interpretations regarding the participation of the ‘wanting’ component during the second presentation of the cue are inadmissible. This exploratory analysis only served to ensure that no relevant activity was overlooked. Thus, it can neither be confirmed nor rejected whether the component of ‘wanting’ overlaps with ‘liking’ in this time window or not.

In conclusion, it is expected that some of the structures identified may gain more informational weight in further studies with greater statistical power, examining the role of dopamine in ‘wanting’ social rewards. Below are some thoughts on possible limitations, insights, and future research.

## Limitations

Several limitations of the current study are worth mentioning. First, regarding the interpretability of the non-significant group differences, it should be taken into account that no baseline assessment of ‘wanting’ before drug administration has been conducted. Accordingly, there is no control for these possible baseline differences between the Amisulpride and Placebo group. Therefore, it cannot be excluded that the non-significant

effects of amisulpride on ‘wanting’ social reward stimuli may have been caused by just such pre-existing differences.

Second, in the case that actual group differences exist, the sample size was a bit under power and therefore may not have been sufficiently large to actually reveal those effects in this between-subjects design. On both behavioral and neuronal levels, the results showed a tendency in the expected direction, but the respective group size of about 30 participants might not have been powerful enough to yield statistical significance. Moreover, it should be considered that only two-thirds of the data collected were analyzed. The addition of those subjects administered the opioid antagonist naltrexone could provide more insight into whether dissociation of ‘wanting’ and ‘liking’ in healthy subjects and pharmacological manipulation of these processes succeeded.

Third, the sample is comprised of a homogeneous group of young individuals between 18-35 years of age. It is conceivable, for example, that younger people generally experience more physical or social proximity on a daily basis and thus perceive the announced stimuli as less salient because their desire for the reward is already more fulfilled. Possible differences in the processing of social reward stimuli across the lifespan are hence not reflected. In addition, the lack of cultural diversity is a strong point of criticism. The limited selection of origin regions of the subjects results in a biased perspective and does not reflect a large proportion of humanity with a great variety of cultures and socialization. This in turn leads to a lower representativity of the sample and a lack of generalizability to the general population.

Forth, another aspect that reduces remarkable the generalizability of the results is the artificial laboratory situation and the related lack of external validity. Social reward processing is far more complex than experiencing an isolated tactile stimulus and the valuation of the reward depends on several other factors, as described earlier. Even though care was taken in developing the design in a way that the stimulus administered had a high degree of naturalness (through actual skin-to-skin contact), the rewarding value might have been significantly affected by the unfamiliarity of the experimenter. Even more, the effect could be eliminated, if not reversed, if someone experiences it as unpleasant to be touched by a stranger. Generally, as described initially, is the positive effect of touch strongly context dependent. Consequently, it cannot be ruled out that the stimulus did not have a rewarding effect on the subject if they perceived the experimenter as unsympathetic. In addition, the fact that the subject is lying isolated in the scanner stands in contrast to the opposite atmosphere of

a typical social interaction which involves by definition others. The unfamiliar test situation as well as the loud, possibly irritating sounds of the scanner could lead to distractions and a further diminished rewarding sensation of the stimulus.

Finally, a few considerations are worth noting regarding the pharmacological manipulation by amisulpride. First, it was recently shown by Grimm and colleagues (2021) that the effects of amisulpride on BOLD signal changes during the anticipation phase, if any, could only be observed as weak in the reward system. The second limitation that should be considered in this regard addresses the dosage of amisulpride. As illustrated previously, high doses (≥400 mg) lead to a reduction in postsynaptic dopaminergic transmission, while smaller doses in turn increase dopaminergic activity via presynaptic mechanisms. At the same time, however, high doses may also increase D1-receptor signaling, which in turn may counteract the inhibitory effect of D2-transmissions (Schoemaker et al, 1997). Soutschek and colleagues (2021) argue that these presynaptic and postsynaptic effects of dopamine may have cancelled each other out between participants, as the effective dose may differ between individuals (Sescousse et al., 2016). This cancellation of effects could provide one explanation for the observed non-significant main effect of group on the behavioral as well as neuronal level. In addition, several researchers argued that low doses of amisulpride, usually used in studies with healthy participants have led to inconclusive results (Eisenegger et al., 2014; Kirsch et al., 2006; McCabe et al., 2011). Moreover, it has been suggested that these doses produce a stronger functional blockade of limbic and cortical dopamine receptors rather than of those located in the striatum (Eisenegger et al., 2014; Xiberas et al., 2001).

## Future directions

Deriving from the limitations presented previously, the following section provides some perspectives on possible future research. In the investigation of ‘wanting’ social reward stimuli in healthy individuals, some aspects could be changed or optimized in future studies using this design or approaching the topic.

As described above, interindividual baseline differences in the ‘wanting’ of social rewards should be determined prior to drug administration. One possibility would be to survey how satisfied or deprived of social rewards the subjects evaluate themselves in their personal history as well as generally on a daily basis. It would be important to examine

whether, in addition to the individual differences, there might be varying importance and salience of social rewards across the life span. For instance, it could possibly be hypothesized that elderly people have a stronger desire for social rewards compared to younger people (Rademacher et al., 2013). Moreover, particularly with regard to the consequences of the Covid-19 pandemic outlined, it would be interesting (if possible), to recruit the same subjects tested in this study in order to investigate possible changes in the perception of the rewarding value of touch in a longitudinal study by comparing measurements of 'wanting' prior and posterior to the time periods of social restrictions. Since the effects may decline again after the end of the restrictions, it would certainly be even more meaningful to conduct surveys in the acute and persistent situations of social deprivation (e.g., during the lockdowns). This possibility of extending data collection to everyday life situations, for example through ecological momentary assessments (Shiffman et al., 2008; Massaccesi et al., 2021), could also address the problem of the artificial laboratory situation. Another approach to increase the actual social reward value of the touch stimulus would be to choose close people instead of strangers as experimenters. This approach has already been used by Massaccesi and colleagues (2021) in a study with the same reward task. Subsequently, in future studies, attention should be paid to an emotional connection and familiarity between tester and subject.

Besides examining reward processing in healthy subjects, transferring the applied design to studies with subjects affected by different disorders could shed light on the atypical functioning of reward processing. For instance, two interesting focal points for subsequent studies could be in this regard, as outlined before, the investigation of 'wanting' social rewards in persons with ASD. This topic has in fact been addressed in a recent study by the same research unit under the direction of Silani and her colleagues. Furthermore, as previously mentioned, the number of people with social media dependencies is increasing (Kuss & Griffiths, 2011). To date, the research evidence in this field is very scarce. It would be interesting to explore if a similar sensitization process takes place among affected individuals as with other addictions such as substance use disorders. The design used in this thesis could be excellently transferred to examine whether, for example, the component of 'wanting' is increased in the absence of liking after consuming social media content in affected persons.

Finally, future research should additionally incorporate greater cultural diversity. This might increase the representativeness and generalizability of the results. Cross-cultural studies

could further be informative about different models of society (collective versus individualistic systems) in terms of satisfying access to social rewards in contrast to possibly perceived loneliness and disconnection.

## Conclusion

Finally, does the blockade of postsynaptic striatal D2 and D3 dopamine receptors reduce ‘wanting’ of social rewards in healthy humans? Although the present work was not able to successfully answer this question and further research in this area is clearly required, it nevertheless provides some insights into the processing of social rewards, as well as related practical implications.

In general, one conclusion that can be drawn from the considerations and findings presented is not to underestimate the essential importance of social rewards for a person's mental health and well-being. Subsequently, the thesis shed new light on the need to establish structures in society, at both the institutional and private levels, to ensure access to social rewards and thus counteract the widespread phenomenon of loneliness. More specifically, this knowledge (even if weak) may help us to better understand the dysfunctional processing of social stimuli, for example, in people with autism or various addictive disorders. The findings may have relevance to identify potential target circuits related to altered ‘wanting’, which can further improve therapeutic interventions and shape treatment success in the long term. Volkow and Morales (2015) described the stigma that addiction is often misinterpreted as a 'lifestyle choice' or 'biological vulnerability'. Understanding the relapsing mechanisms based on neural processes can relieve affected individuals of feelings of guilt and shame, mitigate personal responsibility for recidivism, and increase persistence in facing the chronic nature of the disease.

In conclusion, however, it must be noted that experimentally influencing ‘wanting’ in humans poses some difficulties. Since the present work has failed to show a pharmacological manipulation of ‘wanting’ social rewards, it further adds to the controversy as to whether the incentive salience theory can be applied to humans. Although the role of dopamine on wanting social rewards can neither be confirmed nor rejected on this basis, the work nevertheless makes a small contribution along the way.

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# Supplementary material

**Abstract (English)**

Social rewards are a powerful, motivating force for our behavior and of essential importance for human survival. Currently, the most influential theory of reward processing is the 'incentive-salience theory'. It distinguishes between an opioid-mediated hedonic component of 'liking' and a dopamine-mediated motivational component of 'wanting'. Previous research in this topic is largely based on food rewards in animals. However, there have been few studies to date regarding its transferability to humans. Therefore, the aim of the present thesis was to examine the functional role of mesolimbic and striatal dopamine activity in 'wanting' social rewards in healthy humans. To address this goal, a psychopharmacological experiment was conducted in an fMRI environment. Subjects (n = 60) were randomly assigned to an experimental or a control group. They were respectively administered either 400 mg of the dopamine antagonist amisulpride or a placebo. During the anticipation of social rewards (affective touch) of different reward levels (slow vs. fast stroking), explicit (ratings of wanting) and implicit (physical effort as well as neural) measures of 'wanting' were recorded. No significant effect of drug was found. The main effect of reward level, on the other hand, was significant for both subjective ratings and exerted effort, indicating a higher wanting for high rewards compared to low rewards. At the neural level, significant activity was only found at a low threshold ($p < .001$). During the anticipation of high compared to low social rewards, the SMG, SPG and STS were activated. The interaction of drug by reward level included significant activation in the caudate, insula, ACC, SMA, SMG, MFC, thalamus, and precuneus. In line with expectations, significant reduced activation for high compared to low rewards in the Amisulpride compared to the Placebo group was revealed in the ACC and MCC. Contrarily, the signal difference pattern of the insula, precuneus and thalamus showed decreased activation in the Placebo and increased activation in the Amisulpride group with stronger changes for high compared to low rewards respectively. The hypotheses could not be confirmed on the basis of the present results, even though they indicate a tendency in the expected direction. Nevertheless, the present work is of importance for the adaptation of the incentive salience theory to humans, the understanding of the negative consequences of the absence of social rewards as well as for the effective treatment of various motivational and addictive disorders.

*Keywords*: Incentive salience theory, wanting, social reward, dopamine, amisulpride, fMRI, social isolation, motivation and addictive disorders

## Abstract (German)

Soziale Belohnungen sind eine treibende Kraft für unser Verhalten und von essentieller Bedeutung für das menschliche Überleben. Die derzeit einflussreichste Theorie der Belohnungsverarbeitung ist die „Anreiz-Salienz Theorie“. Diese unterscheidet zwischen einer Opioid-vermittelten, hedonischen Komponente, des ‚Mögens‘ und einer Dopamin-vermittelten motivationalen Komponente des ‚Wollens‘. Sie basiert mehrheitlich auf der Erforschung von Nahrungsbelohnungen bei Tieren. Es gibt jedoch bisher nur wenige Studienergebnisse hinsichtlich ihrer Übertragbarkeit auf den Menschen. Ziel der vorliegenden Masterarbeit war es, die funktionelle Rolle der mesocorticolimbischen und striatalen Dopaminaktivität beim ‚Wollen‘ von sozialen Belohnungen bei gesunden Menschen zu untersuchen. Um dieses Ziel zu erreichen, wurde ein psychopharmakologisches Experiment in einer fMRI-Umgebung durchgeführt. Die ProbandInnen (n = 60) wurden nach dem Zufallsprinzip einer Experimental- oder einer Kontrollgruppe zugeteilt. Ihnen wurde jeweils entweder 400 mg des Dopamin-Antagonisten Amisulprid oder ein Placebo verabreicht. Während der Erwartung sozialer Belohnungen (affektive Berührungen) verschiedener Belohnungsniveaus (langsames vs. schnelles Streicheln) wurden explizite (Bewertungen des Wollens) und implizite (körperliche Anstrengung sowie neuronale) Maße des ‚Wollens‘ erfasst. Es wurde kein signifikanter Effekt des Medikamentes gefunden. Der Haupteffekt des Belohnungsniveaus hingegen war sowohl für die subjektiven Bewertungen als auch der ausgeübten Kraft signifikant, was auf ein höheres Verlangen nach hohen Belohnungen im Vergleich zu niedrigen Belohnungen in beiden Gruppen hinweist. Auf neuronaler Ebene wurde signifikante Aktivität nur bei einem niedrigen Schwellenwert festgestellt ($p < .001$). Während der Erwartung hoher im Vergleich zu niedrigen sozialen Belohnungen wurden der SMG, SPG und STS aktiviert. Die Interaktion von Medikament und Belohnungsniveau umfasste unteranderem eine signifikante Aktivierung im Caudate, der Insula, dem ACC, SMA, SMG, MFC, Thalamus und Precuneus. Im Einklang mit den Erwartungen zeigte sich in der Amisulprid-Gruppe im Vergleich zur Placebo-Gruppe eine signifikant geringere Aktivierung für hohe im Vergleich zu niedrigen Belohnungen im ACC und MCC. Konträr zu den Erwartungen zeigten sich in der Insula, dem Precuneus und dem Thalamus eine verringerte Aktivierung in der Placebo-Gruppe und eine erhöhte Aktivierung in der Amisulprid-Gruppe, jeweils mit stärkeren Signalunterschieden für hohe im Vergleich zu niedrigen Belohnungen. Die Hypothesen konnten auf Grundlage der vorliegenden Ergebnisse nicht bestätigt werden, weisen jedoch eine Tendenz in die erwartete Richtung auf. Dennoch ist die vorliegende Arbeit von Bedeutung für die Übertragbarkeit der Theorie der Anreiz-

Salienz auf den Menschen, das Verständnis für die negativen Folgen des Fehlens von sozialen Belohnungen sowie für die wirksame Behandlung verschiedener Motivations- und Suchterkrankungen.

*Schlüsselwörter*: Anreiz-Salienz Theorie, Wollen, soziale Belohnung, Dopamin, Amisulprid, fMRI, soziale Isolation, Motivationsstörungen, Suchterkrankungen

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## List of Abbreviations

| | |
|---|---|
| AAL3 | Automated anatomical atlas 3 |
| ACC | Anterior Cingulate Cortex |
| ACCsup | superior Anterior Cingulate Cortex |
| AIMS | Abnormal Involuntary Movement Scale |
| AKH | Allgemeines Krankenhaus |
| ANOVA | Analysis of Variance |
| ASD | Autism Spectrum Disorders |
| AQ | Autism Quotient |
| AQ-k | German Autism Spectrum Quotient |
| BARS | Barnes Akathisia Rating Scale |
| BMI | Body-Mass-Index |
| BOLD | Blood Oxygen Level Dependent |
| CN | Caudate Nucleus |
| CSNU | Clinical and Social Neuroscience Unit |
| CT | C tactile |
| DMN | Default Mode Network |
| DV | Dependent Variable |
| EPI | Echo-Planar Imaging |
| FEW | Familywise error rate |
| FIL | Functional Imaging Laboratory |
| fMRI | functional Magnetic Resonance Imaging |
| GLM | General Linear Model |
| HTAS | Health and Taste Attitudes Questionnaires |
| INS | Insula |
| IQR | Interquartile range |
| MCC | Middle Cingulate Cortex |
| MINI | Mini-International Neuropsychiatric Interview |
| MDD | Major Depressive Disorders |
| MFC | Middle Frontal Cortex |
| MNI | Montreal Neurological Institute |

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|---|---|
| MVC | Maximum Voluntary Contraction |
| NAcc | Nucleus Accumbens |
| OFC | Orbitofrontal Cortex |
| 6-OHDA | 6-Hydroxydopamine |
| PANAS | Positive and Negative Affect Schedule |
| PCG | Postcentral Gyrus |
| PreC | Precuneus |
| SMA | Supplementary Motor Area |
| SMG | Supramarginal Gyrus |
| SNc | Substantia Nigra |
| SPG | Superior Parietal Gyrus |
| SPM | Statistical Parametric Mapping |
| SPSS | Statistical Package for the Social Sciences |
| STS | Superior Temporal Sulcus |
| STQ | Social Touch Questionnaire |
| SUD | Substance Use Disorders |
| TAS-20 | Toronto Alexithymia Scale (20-item) |
| TE | Echo Time |
| TH | Thalamus |
| TR | Repetition Time |
| UNODC | United Nations Office on Drugs and Crime |
| VAS | Visual Analogue Scale |
| vmPFC | ventromedial Prefrontal Cortex |
| VS | Ventral Striatum |
| VTA | Ventral Tegmental Area |