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Introduction

Theoretical background

According to the World Health Organization, depression is one of the major causes of disability worldwide. On a global level about 280 million people suffer from depression, which makes 3.8 % of the world population (World Health Organization [WHO], 2021). Due to the COVID-19 pandemic the number of people suffering from anxiety and depression got even worse. In the first year after the outbreak, the prevalence increased by an alarming 25 % worldwide (WHO, 2022). Furthermore, in one third of patients suffering from major depression, conventional therapies such as pharmacological treatment or psychotherapy show no response (Voineskos, Daskalakis & Blumberger, 2020).

To diagnose depression, two main criteria have to be met. First, feeling depressed, and second, anhedonia, both of which must last for at least two weeks (DSM-5 – American Psychological Association, 2013). In regard to anhedonia, unlike the past, today's research looks at this phenomenon in a much more elaborate way (Rizvi et al., 2016). Anhedonia is basically defined by an inability to feel pleasure or interest in previously joyful activities and the extent of anhedonia severity is frequently assessed using specific scales and questionnaire-based methods (American Psychological Association, 2013; Rizvi et al., 2015). Here, one can distinguish between so-called first generation questionnaire-based methods, such as the Fawcett-Clark Pleasure Capacity Scale (FCPS), the Chapman Social Anhedonia Scale (CSAS) or the Snaith-Hamilton-Pleasure Scale (SHAPS) and second generation anhedonia scales such as the Temporal Experience of Pleasure Scale or the Dimensional Anhedonia Rating Scale (Chapman et al., 1976; Fawcett et al., 1983; Gard et al., 2006; Rizvi et al., 2015; Rizvi et al., 2016; Snaith et al., 1995). Although these scales offer several advantages as for example being less time-consuming and relatively cost-effective, certain disadvantages must also be considered (Silvia et al., 2021). The methods mentioned in this context differ to some extent in their definition of anhedonia, which makes it difficult to generalize the results across studies when different scales are used (Rizvi et al., 2015). As an example, while the Temporal Experience of Pleasure Scale and the Chapman Social Anhedonia Scale focus on both, consummatory pleasure and motivational aspects of pleasure, the Snaith-Hamilton-Pleasure Scale and Fawcett-Clark Pleasure Capacity Scale only concentrate on consummatory pleasure (Chapman et al., 1976; Fawcett et al., 1983; Gard et al., 2006; Snaith et al., 1995). In addition to this inconsistency in defining anhedonia, some of these scales exhibit a relatively strong cultural bias with respect to the wording of the individual questions, resulting in less generalizability across different populations. Furthermore, these methods are all based on self-

report, indicating that they lack objectivity of the data (Rizvi et al., 2015). Therefore, the growing scientific interest in a more comprehensive study of anhedonia and its relation to neural processes known to be involved in reward processing, shifts the focus from measuring anhedonia merely via subjective self-reports to more objective methods. This shift is also becoming increasingly important because pharmacological treatment such as tricyclic antidepressant, MAO inhibitors or serotonin reuptake inhibitors often do not have the promised effect, especially in severe forms of depression, and are additionally associated with various unpleasant side effects that jeopardize the willingness to take these medications on a regular basis (Brigitta, 2002). Therefore, gaining more knowledge about the underlying neural mechanisms of depression, or more specifically of anhedonia, broadens the possibilities of treating such disorders more efficiently, since one can rely on more objective data which might be more expressive compared to only rely on self-reported statements (Rømer Thomsen et al., 2015).

In this context, brain stimulation techniques such as deep brain stimulation (DBS), transcranial direct current stimulation (tDCS) or transcranial magnetic stimulation (TMS) are gaining more and more attention as potential tools for the treatment of particularly severe or treatment-resistant forms of neuropsychiatric disorders (Beszlej et al., 2019; Drobisz & Damborská, 2019; Temel et al., 2015; Mutz et al., 2019; Obeso et al., 2016). Although there are several studies investigating the possible use of these techniques in the treatment of disorders such as depression, what these methods have in common is that they are limited in their application. While deep brain stimulation requires surgical procedures to attach electrodes to specific target regions, transcranial direct current stimulation and transcranial magnetic stimulation have the advantage of being non-invasive, however, due to low spatial resolution it is not possible to target subcortical structures precisely, making it difficult to give specific impulses to deeper structures (Rezayat & Toostani, 2016). Therefore, the neuroscientific community is interested in a recently established stimulation method which seems to compensate for these drawbacks, since it is non-invasive and yet able to target subcortical brain structures precisely. This method is called low-intensity focused ultrasound stimulation and uses ultrasound waves in order to induce alternations in cortical activity (Bystritsky et al., 2011). Since both cortical and subcortical brain structures appear to play an important role in the emergence and onset of neuropsychiatric disorders such as depression, a better understanding of the underlying mechanisms could lead to enormous scientific advances in the development of promising treatments (Zhang et al., 2019).

For this purpose, the following thesis will first focus on anhedonia and in particular on its association to the brain's reward system to better understand the different mechanisms of reward processing and the underlying neural mechanisms. Secondly, common methods for treating depression will be discussed with a particular look at different brain stimulation techniques. Thirdly, an empirical part will follow analyzing a data set of 16 healthy participants who underwent low-intensity focused ultrasound stimulation combined with functional magnetic resonance imaging. This analysis should serve as a pilot study for investigating the general potential of low-intensity ultrasound stimulation in its capability to modify functional connectivity patterns. As mentioned earlier, low-intensity focused ultrasound appears to compensate for certain disadvantages of other common stimulation devices such as deep brain stimulation, transcranial direct current stimulation and transcranial magnetic stimulation and makes it thus possible to non-invasively target subcortical regions (Baeck et al., 2017).

Anhedonia as one aspect of depression

As mentioned above, anhedonia represents one of the two main symptoms for the diagnosis of depression and is characterized by an inability to feel pleasure or interest in previously joyful activities (American Psychological Association, 2013). Although other symptoms such as insomnia, poor concentration, or changes in appetite or weight also play an important role for the diagnosis (APA, 2013), anhedonia is gaining more and more attention in the scientific community for which there are several reasons.

First, studies provide evidence that anhedonia appears to be closely related to the strength of depression symptom severity (Pelizza & Ferrari, 2009; Vrieze et al., 2013). Moreover, researchers have shown that depending on the degree of anhedonia, conclusions can be drawn about the treatment outcome of depression. This means, that higher levels of anhedonia lead to a poorer treatment outcome in depression using conventional methods (Khazanov et al., 2022; McMakin et al., 2012; Uher et al., 2012). In addition to that, the presence of anhedonia seems to be associated with an increased risk for another depressive episode (Rawal et al., 2013) and furthermore, it has been found that even after treating depression using conventional methods, such as pharmacological medication or psychotherapeutic treatment, there is a chance that anhedonia persists in patients even though other symptoms seem to be disappeared (Alsayednasser et al., 2022; Clark, et al., 1984; Dunlop & Nemeroff, 2007; Schrader, 1997). Most importantly, studies have shown a strong relationship between the degree of anhedonic symptoms and suicidal ideation (Ducasse et al., 2018; Gillissie et al., 2023; Winer et al., 2014). In contrast to that, it has been observed that the amelioration of symptoms of anhedonia in

patients with major depression have led to an increase in general functioning (Llorca & Gourion, 2015).

Anhedonia thus seems to have an enormous influence on the course of depression which makes it even more necessary to study it more closely. In line with this, a major criticism regarding the prevailing clinical diagnosis of anhedonia is that it lacks a distinction between the different stages of reward behavior (Treadway & Zald, 2011; Rømer Thomsen et al., 2015). Therefore, a growing number of researchers are emphasizing the importance of studying this phenomenon in more detail, along with reward-related behavior, as the inability to feel pleasure or to engage in interesting activities appears to be closely associated with impaired reward processing (Der-Avakian & Markou, 2012).

Anhedonia and the reward system - A multistage process

When speaking of reward processing, science does not refer to only one single way by which reward-related stimuli are transferred into a feeling of pleasure, rather, it is considered a multistage process (Kring & Barch, 2014). Most commonly three different subtypes of reward processing are referred to, namely: reward liking, reward wanting and reward learning (Borsini et al., 2020; Höflich et al., 2019). Reward liking is related to the feeling of pleasure from the reward experience itself and is also described as hedonic experience. Reward wanting refers to the motivational aspect relevant to deciding whether it is worth making an effort to obtain the reward or not, as well as to the anticipatory aspect of looking forward to a future rewarding event (Der-Avakian & Markou, 2012). Reward learning consists primarily of the link between a stimulus and the reward-related outcome. This connection can then be used as a prediction for future situations in which similar cues are presented. It is the integration of feedback which allows learning from reward-related experiences and thus adapting future behavior to these experiences (Wang et al., 2021). Rømer Thomsen et al. (2015) summarized these aspects into a new perspective and transferred it to anhedonia. According to them, anhedonia is defined by “impairments in the ability to pursue, experience and/ or learn about pleasure” (Rømer Thomsen et al., 2015, p. 2).

Although this conceptualization of reward behavior is of course not always directly transferable to real-life reward processing, as the individual aspects may also occur in parallel, the distinction between the individual components is considered as crucial for a better understanding of anhedonic symptoms (Rizvi et al., 2016). Furthermore, given that depression, or more precisely anhedonia, is thought to be closely related to a disruption of the brain’s reward system, there have been a number of studies that have looked at this phenomenon in more detail.

In doing so, the results often refer to one type of the aforementioned forms of reward processing, rather than making general statements about reward behavior (Der-Avakian & Markou, 2012). In order to be able to empirically distinguish between these stages of reward processing, and thus generate more knowledge about them, different types of tasks are used in research. To provide a better overview of such tasks used for a closer examination of reward processing between healthy humans and depressed patients, in the following a choice of these tasks is introduced in some more detail. Thereby, the focus will lie on the first two types of reward processing mentioned above, namely reward liking and reward wanting.

Tasks for measuring reward processing

A common task for measuring the motivational aspect of reward processing, also described as reward wanting or reward anticipation, is called Effort Expenditure for Rewards Task (EEfRT) (Treadway et al., 2009). This method measures the effort a participant is willing to make to receive a monetary reward. At the beginning, participants can choose between two levels of task difficulty, low and high. Depending on the condition, effort is measured by the number of button presses during the task. While the task of low difficulty, performed with the dominant hand, requires a lower number of button presses to achieve the goal, the task with high difficulty must be performed with the non-dominant hand and requires more button presses. The higher the willingness to exert effort in order to obtain a certain reward, the higher the participants' motivation is estimated to be (Treadway et al., 2009). In their study, the researchers applied the EEfRT to participants with varying levels of anhedonia. They found that subjects with higher anhedonia scores showed less willingness to make effort to gain a reward and also a reduced willingness to receive rewards with a higher magnitude. In a more recent study, this task was tested in patients suffering from depression and their behavior was compared to a healthy control group. In line with the former study the results showed blunted willingness to work for a reward in depressed patients relative to the control group (Treadway et al., 2012). Furthermore, in another study it was observed that a decreased willingness of expending effort in depressed patients was predicted by the extent of anhedonia (Yang et al., 2014). A similar task was chosen in a study by Hershenberg et al. (2016). They used a Progressive Ratio Task (PRT), which also measures motivation by tracking the willingness to make an effort to obtain a monetary reward. At the beginning, two numbers are presented, along with the value of the monetary reward to be won. In addition, the number of trials needed to obtain the reward is also indicated on the display. For a successful trial, the participants have to pick out the larger number of the two numbers presented. With all this information, the

participants had to decide whether the effort is worth it or not. Effort was then measured by the number of correct answers in relation to the two stimuli. Their findings demonstrated a significantly lower motivation in the depressed group compared to the controls, as measured by lower effort to obtain the monetary reward (Heshenberg et al., 2016).

With respect to the assessment of hedonic experience itself, also defined as reward liking, the use of behavioral measurement methods has turned out to be more challenging (Rømer Thomsen, 2015). To measure this subdomain, in some cases, researchers rely on facial expressions during the consumption of a pleasant stimulus, either by coding facial movements or using methods such as electromyography (EMG) (Mauss & Robinson, 2009; Sato et al., 2020). Originally, orofacial expressions are used in animal studies as well as in studies with infants, as they are not able to give subjective ratings and therefore other parameters are needed to estimate their hedonic experiences (Steiner, 1973; Steiner et al., 2001). However, in studies with humans, this approach is often viewed critically. Solely relying on such measurements when studying the ability to feel pleasure in humans can be quite misleading. This method appears to be too simplistic considering all the cognitive processes which come into play when evaluating a taste stimulus and therefore applying the results of such studies to a human's general ability to feel pleasure appears to be questionable (Sander & Nummenmaa, 2021). In this regard, another frequently used method in human experiments is to collect subjective pleasure ratings via self-report while or after a pleasant stimulus was presented (Craske et al., 2016). Interestingly, in many cases no significant differences were found between depressed subjects and healthy controls. For example, Dichter et al. (2010) have used the Sweet Taste Test to assess the hedonic response towards a pleasant, sweet taste in depressed patients. This task was combined with a scale on which the participants had to indicate how much pleasure they felt when tasting. Compared to a non-depressed control group, the researchers could not find any significant differences in the subjective rating profile of these two groups (Dichter et al., 2010). This finding is in line with another study that examined both the hedonic evaluation of gustatory and olfactory stimuli of depressed patients. No significant differences in the hedonic evaluation were found compared to healthy participants (Swiecicki et al., 2009). In a study by McCabe et al. (2009), the authors examined subjective evaluation of a pleasant taste stimulus as well as neural activation of a specific reward related brain area, namely the ventral striatum, in recovered depressed patients relative to healthy controls. No differences were detected regarding the subjective ratings, however, with respect to the neural activation pattern of the ventral striatum, the authors observed lower activity in the depressed patients than in the healthy control subjects (McCabe et al., 2009). This finding may suggest that although the

subjective feeling appears to be restored in patients who are recovered from depression, the neural activation pattern is still in an altered state, which in turn may be an important indication that formerly depressed patients may have a persistently impaired reward system that is not observable on the behavioral level but at a neural level of reward processing. In addition, it must be emphasized once again that although the use of subjective rating scales seems to be a more appropriate method for assessing liking behavior (Craske et al., 2016), all the methods mentioned so far for measuring the ability to feel pleasure referred exclusively to the evaluation of taste stimuli, but not to more complex reward situations. Against this approach, it should be noted that taste stimuli by no means reflect complex hedonic experiences of everyday human life. For example, listening to one's favorite music, feeling the beat and perceiving the melody with pure joy and enthusiasm, as well as spending time in a pleasant social environment, having good conversations, and feeling the presence of a beloved community, could be considered much more relevant to a person's well-being than enjoying a piece of chocolate. In particular, when generalizing to people who have problems experiencing hedonic responses in formerly rewarding situations, such as depressed individuals, the question arises whether the use of taste stimuli can be considered a valid measurement to draw any conclusions or whether other tasks should be taken into account that relate more to human hedonic experiences.

Therefore, rather than relying solely on subjective and behavioral measures, more objective data, such as the neural mechanisms underlying reward processing, should also be considered, ideally together with more complex reward situations. This could provide a valuable additional perspective to better understand how disruptions in reward processing are related to the occurrence of anhedonia in humans. In other words, finding methods that take a causal rather than correlative approach to measuring reward behavior could raise the study of anhedonia to a new level.

Neurobiology of the reward system

In general, brain structures related to reward behavior are found in both, cortical and subcortical areas (Berridge & Kringelbach, 2013). Cortical structures that appear to play an important role in this relation are the medial prefrontal cortex, the orbitofrontal cortex, the insula and the anterior cingulate cortex, whereas the nucleus accumbens, the nucleus caudatus, the ventral pallidum and the amygdala are referred to as crucial subcortical reward regions (Berridge & Kringelbach, 2008; Höflich et al., 2019). Also of great importance for reward behavior is the ventral tegmental area, a brain area located in the midbrain (Ranaldi, 2014). Since these structures are embedded within circuit systems it is reasonable that they interact

with each other and do not function separate from each other. This is especially important to emphasize because what drives behavior is a network of several brain structures as a whole rather than individual brain structures themselves (Blanken et al., 2021).

The pathway most often associated with reward is the so-called mesocorticolimbic dopaminergic pathway that consists of several brain structures which have been observed to be activated in the context of rewarding situations (Dunlop & Nemeroff, 2007). It can be divided into two subordinated paths which are the mesolimbic dopamine path and the mesocortical dopamine path (Wang et al., 2021). In both pathways the ventral tegmental area builds the starting point but in regard to the mesocortical dopamine pathway dopaminergic neurons are projected from the ventral tegmental area to brain regions of the prefrontal cortex whereas in the mesolimbic dopamine pathway, dopaminergic neurons are projected to the nucleus accumbens when confronted with a rewarding stimulus or a cue which predicts an upcoming rewarding situation (Berridge & Kringelbach, 2015; Wang et al., 2021). According to literature, the nucleus accumbens is considered to play a central part within the reward system (Heshmati & Russo, 2015). It belongs to the ventral striatum and the connection between the ventral tegmental area to the nucleus accumbens is described as critical for the recognition of rewards as well as for the initiation of their consumption (Koob & Le Moal, 2008).

The nucleus accumbens as a critical part of reward behavior

With a closer focus on the two reward processing domains reward wanting and reward liking, the nucleus accumbens seems to have a crucial role for both, but with regard to reward liking, studies refer to only one specific area that seems to be connected to this kind of reward processing, whereas reward wanting appears to be connected to a broader, less specific area of the nucleus accumbens (Castro & Berridge, 2014b). Furthermore, while reward wanting seems to be strongly associated with the dopaminergic reward system mentioned above, numerous studies have reported the opioid system to be crucial for reward liking but not the dopaminergic system (Pardo et al., 2015; Salamone et al., 2016; Smith et al., 2011). For example, in a study with hyperdopaminergic mice, researchers reported an increase in wanting behavior to a sweet rewarding stimulus but no increase in the actual liking behavior measured by orofacial expressions (Peciña et al., 2003). This was also observed in a study, in which dopaminergic agents showed no changes in taste reaction behavior of rats but appeared to be associated with the regulation of food intake which can be further related to reward wanting (Treit & Berridge, 1990). In accordance with that, in a review by Castro and Berridge (2014a) the authors summarized that dopamine manipulations of the nucleus accumbens are considered to have an

effect on the subdomain of reward wanting in terms of an increase in food wanting but no effect on the subdomain of reward liking. In contrast to the previous results, the manipulation of the opioid system seems to affect the liking behavior in animals. For example, by stimulating opioid receptors in a specific area of the nucleus accumbens in rodents with an agonist microinjection, it has been observed an enormous increase in the liking response to a sweet taste of these animals compared to a control group. Furthermore, in another area of the nucleus accumbens, the same stimulation triggered a suppression of the liking reaction (Castro & Berridge, 2014b). This pattern was also demonstrated by studies which administered microinjections of an endogenous brain cannabinoid in rats (Mahler et al., 2007). In general, it seems to be a great concordance in literature that supports the impact of the opioid system on liking behavior and denies the involvement of the dopaminergic mesocorticolimbic system mentioned above (Peciña et al., 2006).

However, it should be noted, that all experiments used in these studies were, first, conducted with animals and not with humans, and second, only taste stimuli were used as rewards and not more complex stimulations. This once again raises the question of whether these studies can be regarded as suitable for applying their results to the human ability to experience pleasure. In contrast to the studies just presented, research related to music listening has provided evidence that the dopaminergic system is very well involved in the hedonic experience itself, not just in anticipation (Ferreri et al., 2019). For example, in a study by Salimpoor et al. (2011) it was demonstrated that listening to self-selected highly pleasurable music has been shown to activate the mesolimbic reward system. The authors reported that the deep feeling of pleasure as a response to music is related to both the nucleus accumbens and the nucleus caudatus, both of which are part of the striatum. While the nucleus caudatus appears to be more involved in the anticipation phase, the nucleus accumbens appears more prominent in the moments of highest pleasure with music. This pattern of activation of the mesolimbic reward system was also demonstrated in a study, in which participants were exposed to unfamiliar music (Salimpoor et al., 2013). The authors reported that, similar to other reward related stimuli, when listening to unfamiliar music, striatal dopaminergic activity was associated with the reward value of the music. In other words, the higher the reward value of the unfamiliar music, the more neural activation was observed in the striatum.

This insight into the diversity of findings on the relationship between reward behavior and the underlying behavioral and neural patterns in depressed subjects and healthy subjects is, of course, only a small and rather superficial excerpt from the entire existing literature. However, there seems to be a strong lack of consistency between these results, which further highlights

the importance for future research of gaining more knowledge about the specific processes that underlie reward behavior, and even more so, gaining knowledge about causal approaches in order to be able to treat neuropsychiatric disorders such as depression in a more targeted way.

Brain stimulation techniques

In this context, brain stimulation techniques are gaining more and more attention in the neuroscience community. As mentioned, the methods presented so far to measure differences between depressed subjects and healthy subjects in reward processing, such as the EEFRT or the Sweet Taste Test, are correlative rather than causal in nature (Crask et al., 2016). However, to be able to develop adequate treatment approaches for neuropsychiatric disorders, it is of great importance to find methods by which it is possible to draw causal conclusions. As for example in the case of anhedonia, it would be of great benefit to better understand how specifically set changes within a brain structure belonging to the reward circuit affect other structures as well as the behavior in relation to reward processing.

Transcranial magnetic stimulation, transcranial direct current stimulation, and deep brain stimulation

Brain stimulation techniques, such as repetitive transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), or deep brain stimulation (DBS) are gaining more and more attention as potential tools for the treatment of particularly severe or treatment-resistant forms of neuropsychiatric disorders, due to their ability to alter cortical activity locally (Beszlej et al., 2019; Drobisz & Damborská, 2019; Temel et al., 2015; Mutz et al., 2019). Regarding TMS and tDCS, both methods are non-invasive, which means that no surgical intervention is required for their application (Obeso et al., 2016). Transcranial magnetic stimulation (TMS) works with a magnetic field generated by current flowing through an electromagnetic coil placed on the scalp (George et al., 1999). This magnetic field is able to elicit excitability alternations within the cortex (Klompai et al., 2015). A modification of this method is the so-called repetitive transcranial magnetic stimulation (rTMS). It follows the same principle as TMS with the additional feature to be able to adapt cortical activity beyond the actual stimulation time span, which makes it an attractive potential tool for treating neuropsychiatric disorders (Davis & van Koningsbruggen, 2013). In comparison to rTMS, tDCS uses low direct current, which is delivered via two electrodes placed on the scalp. Just like TMS, it has the ability to alter cortical activity in a wide range of motor and cognitive processes (Schulz et al., 2013). Since the two non-invasive techniques are not able to target

deep brain structures precisely, a frequently used target region for both types is the dorsolateral prefrontal cortex (Mutz et al., 2018; Noda et al., 2015). While several studies have reported success in improving depressive symptoms (Luber et al., 2017; McGirr et al., 2016; Mutz et al., 2018; Ren et al., 2014), other research groups that have investigated the effect of rTMS in patients suffering from treatment-resistant depression concluded that there was no significant difference between the stimulation method and the administration of an antidepressant (Bares et al., 2009; Brunelin et al., 2014). This pattern was also shown in a study by Brunoni et al. (2013) in which the efficacy of tDCS applied to the prefrontal cortex was compared with the administration of an antidepressant in patients with moderate to severe depression. The authors found no significant difference between these treatment options. In addition, the results of these studies all referred to depressive symptoms in general and did not specify them. With consideration to the treatment effectiveness of these methods in relation to anhedonia, studies are quite scarce and due to very heterogeneous results, further research is needed to be able to make more concrete statements (Spano et al., 2019). Another non-negligible disadvantage of these methods refers to their inability to target subcortical brain structures precisely or even at all (Brunoni et al., 2019). As shown in the previous section, subcortical structures such as the nucleus accumbens play an important role in terms of hedonic experiences and reward processing in general (Rezayat & Toostani, 2016). Therefore, to understand more reliably how a given kind of stimulation affects the pattern of activation in a particular brain structure and those surrounding them, it may be helpful to look more closely at methods that have the advantage of targeting brain regions more accurately, even if they are located deep in the brain.

In light of this, deep brain stimulation as an invasive technique comes into play. Here, electrodes are implanted in specific brain regions through a surgical procedure, which are then connected to a power source that is placed under the skin in the upper chest area. This generator controls stimulation and serves as power source (Dougherty, 2018). Therefore, deep brain stimulation has the ability to reach subcortical structures very precisely and can be regarded as a potential alternative to the two stimulation methods mentioned before (Oluigbo et al., 2012). In fact, studies exist where the effect of deep brain stimulation was specifically investigated with the focus on anhedonia, rather than depressive symptoms in general. According to literature, among others, the nucleus accumbens appears to be a promising target region in terms of the improvement of anhedonic symptoms in depression (Hauptman et al., 2008; Drobisz & Damborská, 2019). In a preliminary study by Schlaepfer et al. (2008), three patients suffering from severe treatment resistant depression underwent deep brain stimulation. Due to its present role within the reward system, the authors decided to take the nucleus accumbens as target

region and implanted electrodes bilaterally. As a result, they reported an immediate improvement in regard to the clinical ratings in phases where stimulation was active compared to phases where stimulation was inactive. Similar results were also shown in other studies in which the nucleus accumbens and the ventral striatum were stimulated by deep brain stimulation, respectively and about half of the participants suffering from treatment-resistant depression reported a reduction in depressive symptoms by about fifty percent (Malone et al., 2009; Bewernick et al., 2010). Nevertheless, despite this great advantage of deep brain stimulation to be able to reach subcortical structures and thus follow rather hypothetical approaches, there are nevertheless aspects that should be regarded with caution. Considering the ethical aspects related to its invasiveness and the high financial costs of its application, the use of this method has so far been justified only in clinical cases where all other treatment approaches showed no success (Delaloye & Holtzheimer, 2014). However, as the setting of the studies presented, is either preclinical or in clinical, the problem arises of not having a status quo in healthy participants. For a general study of causality in relation to brain reward processing mechanisms, non-clinical settings with healthy participants would be of great benefit, as conducting studies with clinical subjects is much more complex, especially in terms of interpretation of the results (Specht, 2020). Thus, gaining insights from basic research studies may be an essential first step to further be able to draw conclusions based on such a frame of reference to other population groups, such as depressive persons.

Low-intensity focused ultrasound stimulation

In consideration of all the difficulties associated with the stimulation methods presented so far, the neuroscientific community has become increasingly interested in a stimulation technique which seems to compensate for these drawbacks. This method is called focused ultrasound stimulation and, as the name implies, uses ultrasound in order to induce alternations in cortical activity (Bystritsky & Korb, 2015). The ultrasound waves in the form of acoustic energy, whose frequency is beyond the audible range, make it possible to reversibly modulate small subcortical brain regions of interest in a very precise manner and without damaging the skull bone (Baek et al., 2017). Depending on the stimulation parameters, focused ultrasound stimulation can induce both, inhibition and excitation of cellular activity (Plaksin et al., 2016). In addition to its noninvasiveness and the ability to address subcortical brain structures, this technique has another tremendous benefit in its application compared to the methods mentioned in the previous section. Because focused ultrasound stimulation acts mainly mechanically on nerve activity, it can be combined simultaneously with imaging techniques such as functional

magnetic resonance imaging. This simultaneous application of the stimulation and the neuroimaging technique allows monitoring the stimulation and thus more reliable conclusions about its effectiveness (Bystritsky et al., 2011). Concerning the device itself, one can distinguish between two types of focused ultrasound stimulation, which are high-intensity focused ultrasound stimulation and low-intensity focused ultrasound stimulation (Rezayat & Toostani, 2016). While high-intensity focused ultrasound is often investigated in the context of neurosurgical studies, as this type of ultrasound stimulation has the property of ablating degenerated tissue, due to its high intensity parameters (Martin et al., 2009; Elias et al., 2013), low-intensity focused ultrasound is more related to its effect on neuromodulation (Blackmore et al., 2018). This property at low intensities was shown in a study by Yoo et al. (2011), who investigated focused ultrasound stimulation in vivo in rabbits in motor and visual brain areas and found bimodal modulatory effects, which means both an increase of brain activity and a decrease of brain activity. Subsequent histological examinations of the brain tissue did not reveal any damage (Yoo et al., 2011). Min et al. (2011) investigated the question of whether the neurotransmitter level changes as a result of ultrasound. By stimulating the thalamic areas of rats with low-intensity focused ultrasound, the authors reported a significant increase of extracellular dopamine and serotonin levels in the sonication group compared to the group with no sonication (Min et al., 2011). While these two examples referred to studies with animals, there also exist studies in which the modulatory effect of ultrasound stimulation was tested in humans. For example, in a study by Lee et al. (2015), the authors showed that stimulation of the somatosensory cortex in humans with focused ultrasound evoked both somatosensory sensations with high anatomical precision contralateral to the stimulated brain area and cortical potentials which resembled the classical somatosensory evoked potentials produced by median nerve stimulation (Lee et al., 2015). Furthermore, similar to the previous studies, the modulatory effect was reversible, and no side effects were reported by participants or physicians even weeks after the stimulation. In another study, in which focused ultrasound stimulation and functional magnetic resonance imaging were used simultaneously, the stimulation effect was investigated in relation to the human primary visual cortex. In doing so, the researchers reported an increase in neural activation during the stimulation both in the stimulated brain area and in brain areas connected to the primary visual cortex (Lee et al., 2016). Regarding deeper brain structures, Folloni et al. (2019) conducted a study with primates in which the authors focused on two stimulation targets that differed in terms of the depth of their location. First, they stimulated the amygdala, which they defined as subcortical brain region, and second, they chose the anterior cingulate cortex as a deep cortical region. During the

stimulation, neuronal activation patterns were recorded by using functional magnetic resonance imaging. The authors demonstrated that focused ultrasound stimulation is able to affect neuronal activation in a relatively focused and confined manner. Furthermore, they provided evidence that ultrasound stimulation is able to induce longer-lasting effects over several hours, even with short stimulation durations (Folloni et al., 2019).

The presentation of the individual studies is intended to illustrate the versatility of this type of stimulation. Especially its capability to modulate both cortical and subcortical brain structures in a very precise way, which can be monitored by functional magnetic resonance imaging, together with its ability to evoke changes in the extracellular concentration of neurotransmitters makes it a potential tool with respect to treatment of neuropsychiatric disorders (Kubaneck, 2018; Zhang et al., 2019). Moreover, by considering the correct stimulation parameters, the studies also demonstrate the possibility to use focused ultrasound stimulation even in healthy participants (Arulpragasam et al., 2022). Therefore, using ultrasound stimulation in studies with healthy subjects, together with its beneficial features mentioned above brings an enormous advantage. Performing ultrasound studies in healthy participants before applying it to clinical subjects opens the possibility to create a more stable basis regarding reward behavior and its underlying neural mechanisms. As mentioned earlier, the interpretation of results arising from clinical studies are much more difficult to interpret compared to results arising from studies conducted with healthy participant (Specht, 2020). Because of that, studying the underlying neural mechanisms of reward processing in healthy participants by using low-intensity ultrasound stimulation might bring a certain base which facilitates the general understanding of anhedonia and therefore might be much more useful in regard to clinical subjects compared to the direct application of this method to them.

Since this thesis is interested in finding a method that allows to draw causal conclusions about different types of reward processing and the underlying neural mechanisms to better understand the concept of anhedonia, low-intensity focused ultrasound appears to be highly promising tool.

Present study

In summary, the literature reviewed above supports the notion that there exists a strong relationship between symptoms of anhedonia and a disruption in reward processing. However, as also shown in the previous sections, so far, the underlying mechanisms of this relationship are still poorly understood. Since anhedonia is one of the two main criteria for the diagnosis of depression and also plays an important role in several other neuropsychiatric disorders (Der-

Avakian & Markou, 2012), there is a need to understand this relationship in more detail in order to improve treatment. Many studies have addressed this issue more thoroughly by investigating reward behavior at different levels in both healthy participants and depressed subjects. Although research has found differences between those subject groups using behavioral tasks as well as neural activation data, there are still ambiguities in many respects. In particular, a casual understanding of the neural mechanisms of reward processing is lacking. The development of a new brain stimulation technique, called low-intensity focused ultrasound stimulation, offers the possibility to discover more about casual relationships between different brain structures involved in reward processing due to its non-invasiveness and the ability to reach subcortical brain regions.

Given that subcortical structures such as the nucleus accumbens and the nucleus caudatus appear to be particularly important for reward processing and given that studies have shown that low-intensity ultrasound stimulation can be considered as a safe method if all regulations are followed, this technique represents a promising opportunity for researchers to study reward processing in healthy subjects to gain deeper insights into the specific neural mechanisms of reward processing.

Therefore, the here presented study is intended to serve as a pilot study, focusing primarily on examining the effect of low-intensity focused ultrasound stimulation when stimulating a subcortically located brain region in healthy subjects. The investigation arises from the unique opportunity to have been provided data from a study in which this type of stimulation was performed on healthy participants (Cain et al., 2021). In this study, the left globus pallidus was chosen to be the target region to be stimulated. Although this subcortical structure is not considered to be associated with a direct part of the reward system, such as nucleus accumbens or nucleus caudatus, it is still part of a superordinated network system called the cortico-basal ganglia circuitry. This circuit has for a long time been mainly associated with the regulation and modulation of motor behavior. Today, it is undeniable that this circuit is responsible for the regulation and control of several facets of behavior, such as cognitive/affective behavior, the emotional behavior, and the sensorimotor behavior (Pierce & Péron, 2020). It includes subcortically located nuclei of the basal ganglia as well as regions of the cerebral cortex that are functionally and structurally intertwined in multiple ways and thus comprises central reward related brain structures (Gunaydin & Kreitzer, 2016). To give a brief overview of this superordinated system: In general, the basal ganglia can be divided into several structural main components, namely the striatum, the substantia nigra, the globus pallidus and the subthalamic nucleus, which further comprise substructures with specific functions

(Simonyan, 2019). The largest structure of the basal ganglia is the striatum. It consists of the dorsal striatum including the nucleus caudatus and putamen, and the ventral striatum, including the nucleus accumbens. It is considered the central input structure to the basal ganglia as it receives projections from the cerebral cortex, thalamus, and brainstem (Haber, 2003; Nambu, 2002). While the dorsal striatum mainly receives afferent projections from frontal- and parietal-related cortices as well as sensorimotor cortices and is associated with the regulation of motor and executive functions, the ventral striatum plays an important role in the surveillance of reinforcement learning, emotion regulation, as well as motivated behavior and receives information from limbic structures, such as the hippocampus, the amygdala and the medial prefrontal and anterior cingulate cortices (Haber, 2003; Haber & Knutson, 2010; Macpherson & Hikida, 2019; Rusu & Pennartz, 2020). The substantia nigra, which is located in the ventral mesencephalon, receives corticostriatal signals (Calabresi et al., 2014). It can be split into the pars compacta and the pars reticulata. While the substantia nigra pars compacta is considered to be engaged in motor control due to its efferent connections to the striatum, the substantia nigra pars reticulata, together with the globus pallidus internus, is mostly associated with its involvement in the final information processing step before the information is transmitted to cortical motor areas via the thalamus (Deniau et al., 2007). This connection is also referred to as the direct pathway and is related to the execution of movements (Calabresi et al., 2014). Lastly, the globus pallidus can be subdivided into the globus pallidus internus and the globus pallidus externus. As mentioned before, the globus pallidus internus is thought to interact with the substantia nigra pars reticulata and seems to be responsible for the information forwarding to the thalamus to adjust motor control. The globus pallidus externus provides input for the subthalamic nucleus and thus indirectly for substantia nigra pars reticulata. It is therefore able to indirectly modulate motor control through (dis-) inhibition of these two target regions and is thus part of the so-called indirect pathway (Calabresi et al., 2014).

The aim of this thesis is to lay the groundwork to implement causal inference in understanding anhedonia by verifying in a first step whether the stimulation of subcortical regions with low-intensity focused ultrasound is able to modulate interaction of a whole network system in which we know the stimulated region is embedded. In a second step, further implications and future directions are discussed. Based on the specific data available, the following hypothesis is tested:

H1: Low-intensity focused ultrasound stimulation is able to induce changes in the functional connectivity pattern between the left globus pallidus as the target region and the

structures involved in the cortico-basal ganglia circuitry, measured by blood oxygen level dependent (BOLD) signal.

Methods

Participants

The original study from which the data was taken comprised 16 healthy participants (15 male; age = 18-44 years ($M = 25.25$; $SD = 7.78$)) with no history of either neurological nor psychiatric disorders and with no medical condition. To administrate the ultrasound transducer properly, the participants were asked to shave their hair around their left temple below 0.5 inches during the time of the study. This provision was made to eliminate the potential risk of enclosing air bubbles which might reduce the strength of the ultrasound application. Written informed consent was provided by each subject following procedures approved by the UCLA Institutional Review Board. Furthermore, all procedures were carried out in line with the respective guidelines and regulations, and informed consent was received for the publication of the participants' identifying information and images. As a compensation for participating in the study, each participant received \$150. After the data was collected, no subject was excluded.

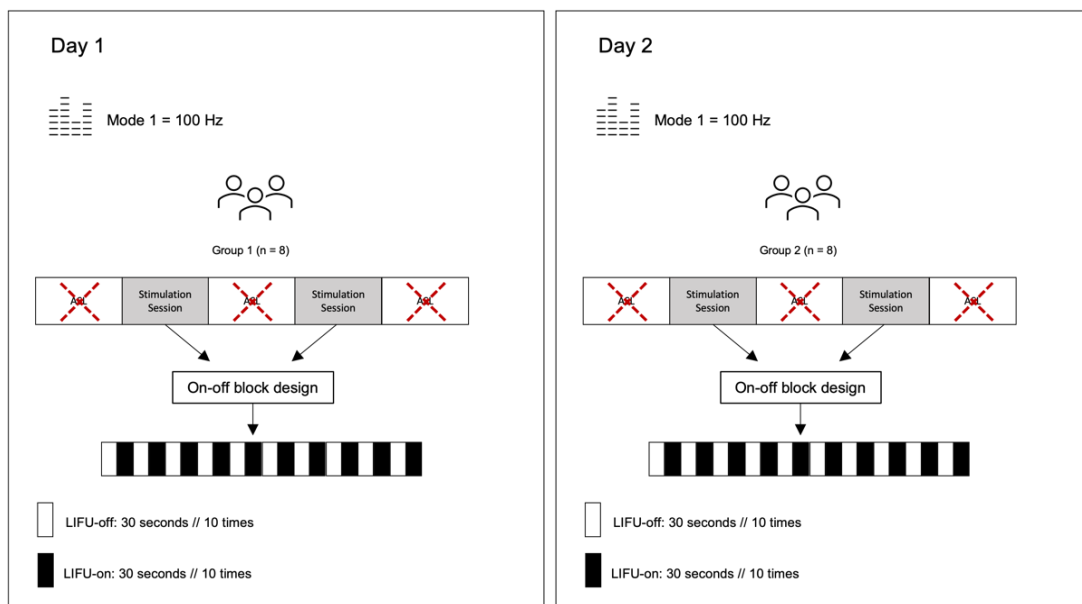
Experimental Procedure

The main study took place within a period of two days. In this time, three individual sessions were conducted. Using functional magnetic resonance imaging, the first session was designed to collect baseline data from the participants, both structural and functional. The other two sessions focused then on the recording of brain activation while simultaneously using ultrasound stimulation. These two sessions in which ultrasound stimulation was applied differed in their sonication parameters, namely 100 Hz (Mode 1) and 10 Hz (Mode 2), however beside this difference, the general procedure of those sessions was the same. More specifically, both sessions were embedded in an on off block design and each session consisted of 10 "LIFU-off" blocks and 10 "LIFU-on"-blocks alternating, with each block lasting 30 seconds. Therefore, the participants were divided into two groups of eight subjects each. On the first day, half of the participants received two sessions of 100-Hz ultrasound stimulation, while the other half received 10-Hz ultrasound stimulation. On the second day, the same procedure was performed in reverse order.

The reason why two sessions of each stimulation condition were conducted in the original study is related to the fact, that this study was designed to investigate not only the online effect of stimulation but also the offline effect measured by arterial spin labeling (ASL).

This means, functional magnetic resonance imaging data were recorded both between the two sessions as well as at the beginning and at the end to assess the effect of the stimulation after a certain period of time. However, since this study is only concentrating on online effects of the stimulation condition by analyzing the blood oxygen level dependent (BOLD) signal, this information does not need to be considered further. In addition, as this would exceed the scope of this master thesis, the present study only focuses on the analysis of 100-Hz stimulation condition. For this reason, Figure 1 shows the specific experimental procedure that will be focused on in the remainder of this study.

Figure 1 *Experimental design*



Ultrasound waveform and positioning

The device used in the original study for the stimulation was a BXPulsar 1001, Brainsonix Inc. ultrasound device. The high pulse repetition frequency (PRF) of 100 Hz (Mode 1) using a low Pulse Width of 0.5 ms. Other parameters to be considered are the Carrier wave frequency of 650 kHz, Duty Cycle of 5% as well as intensity values of $I_{spta.3} = 720 \text{ mW/cm}^2$ and $I_{sppa.3} = 14.40 \text{ W/cm}^2$. All parameters fit within the FDA safety guidelines for ultrasound imaging of the cranium (Duck, 2007).

For each participant, the ultrasound transducer was placed so that its center was located on the left temple. More specifically, the transducer was placed about one-third of the distance from the corner of the left eye to the left and 2 cm above. Ultrasound gel was applied to this area in the diameter of the transducer. To keep the risk of the formation of air bubbles as low as possible and to provide an even surface for attachment, the gel was additionally rubbed into

the surrounding hair. After applying a thin layer of gel to the transducer, it was attached to the head, with the gel covering all the voids that existed between the transducer membrane and the scalp. As already mentioned in the previous section, in order to make sure that the transducer is in the correct position, a rapid lower-resolution T1-weighted image (TR = 1900 ms, TE = 2.2 ms, voxel size 2 mm³) was performed after each sonication session to ensure that the position did not change unintentionally. Additionally, a vertical and a horizontal strap helped to secure the ultrasound device to the participant. Fortunately, none of the recordings had to be repeated as there were no noteworthy movement of the transducer during the sonication. With the help of a circular MR reference point together with the visible center of the transducer, reference lines were traced in the transverse and coronal planes using the scanner console to visually localize the seed region, namely the left globus pallidus, of the LIFU beam in three dimensions. This localization was followed by a stepwise positioning of the transducer. The adjustment of the transducer was regarded as successful if the path of the ultrasound beam passed through the temporal bone and the anterior dorsal aspect of the left globus pallidus in a transverse and coronal direction and terminated in the left thalamus.

Data acquisition

Functional magnetic resonance imaging

For data acquisition a 3 T Siemens Prisma Magnetic Resonance Imaging (MRI) scanner was used at the Staglin IMHRO Center for Cognitive Neuroscience at UCLA. Due to the simultaneous application of MRI and ultrasound stimulation, a 20-channel siemens Prisma head coil was used so that there is sufficient space for the ultrasound device.

As a first step, both baseline structural data as well as baseline functional data were acquired. Once these steps were completed, the actual acquisition began. As mentioned in the last section, although the main part of the original study consisted of five functional acquisitions, comprising offline effects of low-intensity focused ultrasound stimulation as well as online effects of the stimulation, this study is only interested in the two acquisitions in which functional imaging data were recorded during the online mode while using the 100 Hz stimulation condition. For this purpose, a T1-weighted structural sequence (MPRAGE, TR= 2300 ms, TE= 2.98, voxel size = 1mm³) was acquired for each participant with the transducer already in place. For the functional imaging, a T2*-weighted BOLD sequence (TR = 700ms, TE = 33ms, voxel size = 2.5mm³, 1000 volumes) was acquired for each participant and each of the two sessions concurrently with LIFU sonication. After each sonication, a lower-resolution T1-weighted

image (TR = 1900 ms, TE = 2.2 ms, voxel size 2 mm³) was recorded to make sure that the ultrasound transducer is in the correct position.

Preprocessing of functional magnetic resonance imaging data

Since the initially recorded data may contain a relatively large amount of noisy and interfering signals caused by head movements, random drifts, or other uncontrollable technical or physiological factors, as well as parts of the skull, the raw data must be preprocessed before the actual analysis can be conducted. First, brain extraction on the T1 anatomical images was performed using FSL optiBET with a default fractional threshold of 0.07. Through this process it is possible to remove skull tissue which is not relevant for the analysis. The brain extraction algorithm comprises four steps for removing skull from brain tissue and is originally invented as a brain extraction tool for data from patients suffering from severe brain pathology, which makes it an even more valuable tool for brain data from healthy patients, due to its high precision (Lutkenhoff et al., 2014). To assure that the extraction was successful for each participant, a visual check of the results was performed, and no manual editing was needed afterwards. Subsequently, FSL FAST was used for the segmentation of the brain extracted structural images, which means the extraction of gray matter, white matter, CSF and other tissue classes. FSL FAST, or more specifically the command `run_first_all`, was also used for the segmentation of subcortical regions, which will be described in more detail in the following section. When proceeding to the preparation of the functional T2* images, the first four time-points (volumes) of each dataset were discarded. This is necessary because the scanner often needs some time to set up (e.g.: magnetization stabilization) and the functional images were not “dummy-scanned” automatically. As a next step, motion parameters of the trimmed functional T2* images were checked to mitigate motion-related artefacts. This was done by using FSL MCFLIRT which loads the entire time series and selects the middle volume of the T2* image as the initial template image. It comprises three subsequent steps and starts with the performance on data which is sub-sampled to 8mm isotropic voxels. This subsampling allows the coarse intensity patterns in the images to guide the registration, and the optimization during this stage is performed using trilinear interpolation with a relatively large level of tolerance. After this, a second step is performed on 4mm isotropic voxels, using trilinear interpolation and the same tolerance level as it was specified in the first step. In a third step, the voxel size remains at 4mm but the tolerance level in this last step is set down to the default values, which are tighter compared to the former tolerance values. When all these steps are conducted and all transformation parameters are estimated, a transformation is applied to the image using again

trilinear interpolation (Jenkinson et al., 2002). Exclusion criteria were based on Parkes et al. (2018), meaning that subjects with either a mean framewise displacement greater than 0.2 mm, more than 20 percent framewise displacement above 0.2 mm and/ or any framewise displacement greater than 5 mm were marked as excluded. In regard to the calculation of the framewise displacement, it was also referred to Jenkinson et al. (2002). However, after checking these two cases separately, no participant needs to be excluded, since the thresholds of the exclusion parameters were set very conservatively, and the specific values were only slightly above the specified thresholds. After this step, a non-aggressive denoising was performed using ICA-AROMA, to which high-pass temporal filtering was subsequently applied using FSL, selecting a sigma value of 43. Due to multiband acquisition in all images, no slice time correction was performed. Spatial smoothing was performed using FSL SUSAN in FEAT with a Gaussian kernel of 6 mm full-width half-max. To achieve intra-subject matching, co-registration was performed between the structural and functional images for each individual due to the superior anatomical localization of the structural image which leads to an improved translation into MNI (standard) space (MNI152_T1_2mm_brain.nii.gz) later on. For this purpose, FSL FLIRT with a normal search was used. By completing the co-registration, spatial normalization and intrasubject registration was conducted using FSL FLIRT and FSL FNIRT with a non-linear warp-resolution of 10 mm. While spatial normalization refers to the normalization of the structural images from each participant to the standard space, intrasubject registration means the registration of the functional images to the normalized structural images. Those steps are important for ICA-AROMA as well as for the aim of analyzing functional magnetic resonance imaging data at the higher-level analysis as it transforms the structural brain images from each subject into standard space in order to reduce the variability between individuals and thus allow meaningful group analyses to be successfully performed. In addition to that, it improves the statistical power of the analysis. No intensity correction or volume censoring was conducted.

Data analysis

Psychophysiological interactions (PPI) analysis

To pursue the research question of this thesis, a psychophysiological interactions (PPI) analysis was conducted. This type of analysis was first introduced by Friston and colleagues and is described as a method which is capable to study modifications in functional connectivity patterns between different brain areas, which are induced by experimental conditions (Friston et al., 1997). In contrast to bivariate, correlation-based analysis of functional connectivity, the

PPI focuses specifically on the context-induced modifications of functional connectivity, rather than solely measure the degree of correlation between the activity in two regions in resting state (Harrison et al., 2017).

In order to conduct the analysis, several steps have to be done in advance. First, as in this study the left globus pallidus is chosen as the region of interest, it is necessary to create a mask of this specific area out of each participant's structural T1 brain image. For this purpose, the FSL command `run_first_all` was used which is an automated segmentation script for subcortical structures. Although this tool is also segmenting several other subcortical regions such as the amygdala, the nucleus caudatus, etc. simultaneously, for the purpose of this thesis, it is only focused on the left globus pallidus since this structure was chosen to be the target region of the stimulation condition in the original study. After the binarization of the created masks, a visual quality check of the results was performed to assure that the segmentation as well as the binarization were successful. As a next step, the extraction of the time series of this specific region followed by using the FSL command `fslmeants`. This command extracts the average time series of all voxels of the predefined region of interest out of the functional T2* brain image. This procedure was also conducted for each participant. After completing this step, for all further analysis, these activity time courses are defined as the physiological regressors, while the time course that was taken from the stimulation condition is used as the psychological regressor. These two regressors can then be used to create the so-called psychophysiological interaction (PPI) regressor, which is crucial for identifying stimulation-specific changes in functional connectivity. To be able to create this interaction regressor, the time course of the stimulation condition (psychological regressor) needs to be convolved by a certain hemodynamic response function (HRF). This is because the time course of the stimulation condition is modeled in real time while the time series taken from the region of interest already includes the HRF since it represents brain activity. The interaction regressor is then created from the (mean-centered) time course of the experimental condition time and the (demeaned) time course of the seed ROI. All these steps are performed for each subject and each session within a first-level analysis, using FSL FEAT as the analysis tool of choice.

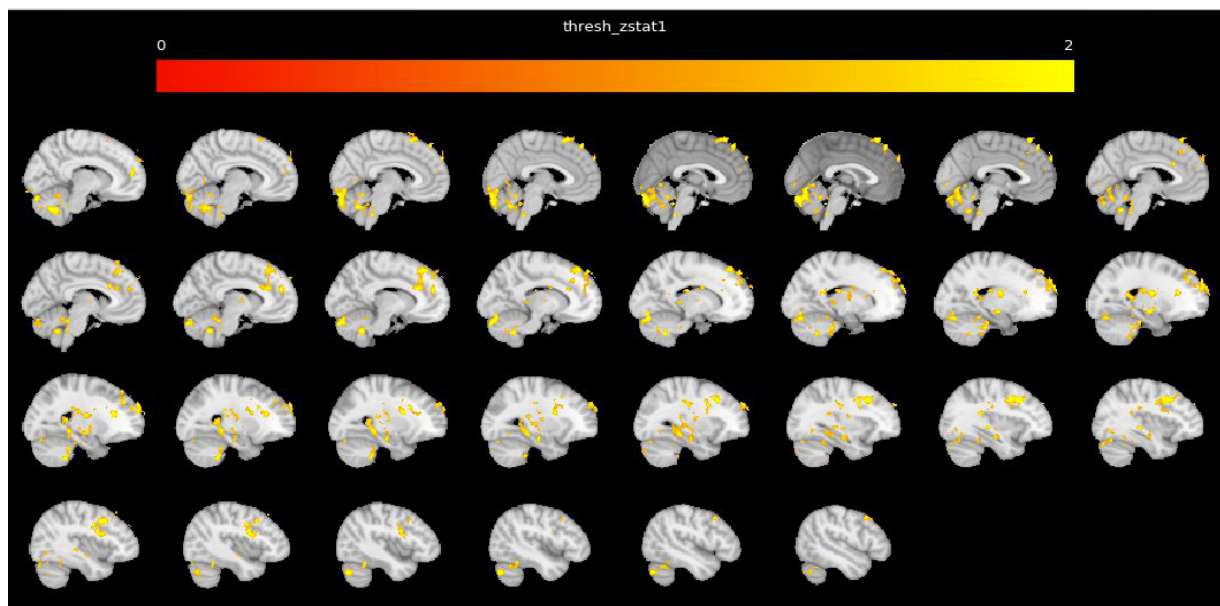
In order to be able to run the analysis at the group level, on a second level, the individual sessions of the participants have to be concatenated. This is also done by FSL FEAT, by combining the beta coefficients of the two sessions per participant. By finishing this step, the third level or rather the final group-analysis can be conducted in which the results stemming from the second level for all subjects are merged. In this analysis, we started with a z-value of 1.8 and chose 0.05 as the level of significance. As a result, cluster of voxels were identified

across all participants that are more strongly correlated with the seed region during the stimulation condition than during non-stimulation condition, shown by a positive correlation with the PPI regressor.

Results

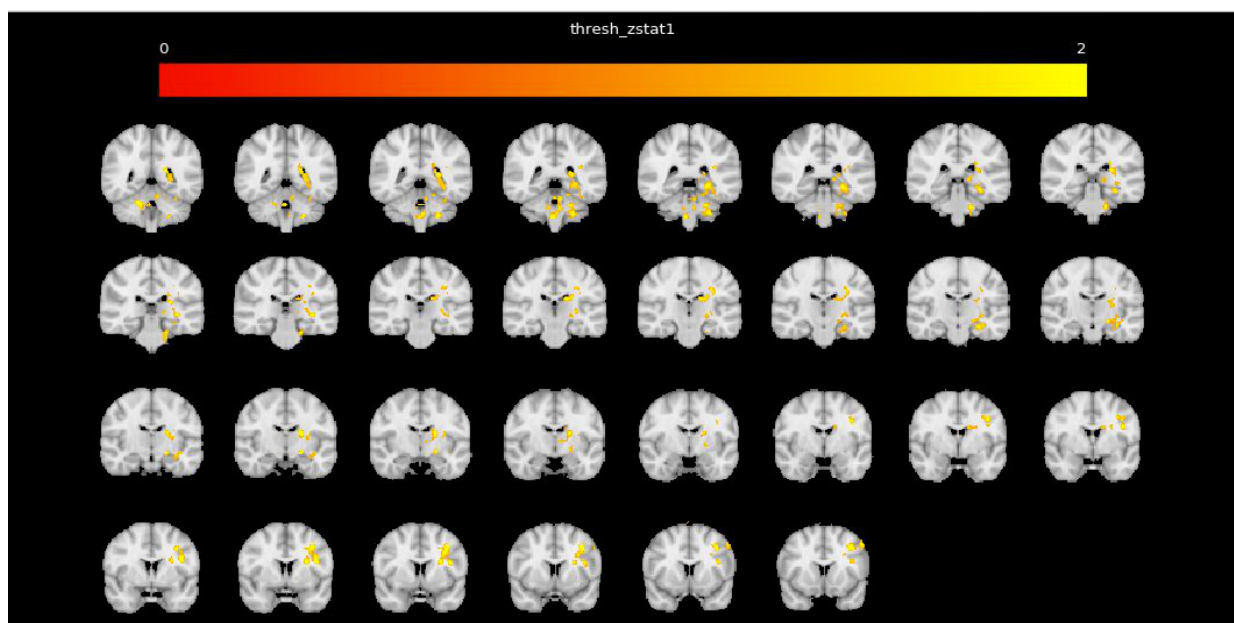
As mentioned in the previous section, at the beginning of the analysis, we started with a z-value of 1.8 and a level of significance of 0.05, but no significant results were observed. Therefore, we decided to lower the threshold and ended with a threshold of 1.2. Looking at the results of the analysis performed, corrected at cluster level ($z = 1.2$, $p < .05$), a rather strict lateralization of the activation patterns can be observed. This means that almost all changes in functional activity within the group analysis refer to structures located in the left hemisphere which is consistent with the selected target seed region, the left globus pallidus (Figure 2 and Figure 3). Furthermore, on closer examination and as demonstrated in Figure 4, during the LIFU-on condition, there was an increase in functional connectivity in cortical structures such as the dorsolateral prefrontal cortex, the medial prefrontal cortex, and the anterior cingulate cortex. As for the more subcortical structures, an increase in functional connectivity during the LIFU-on condition was observed in the left striatum, namely in the left nucleus caudatus as well as in the left putamen. Furthermore, the left hippocampus, the left amygdala, the left thalamus as well as part of the left globus pallidus also showed an increase in functional connectivity. Greater functional connectivity was also observed in parts of the cerebellum during periods of stimulation compared to periods of no stimulation.

Figure 2 Results of the PPI analysis LIFU-on > LIFU-off in sagittal view



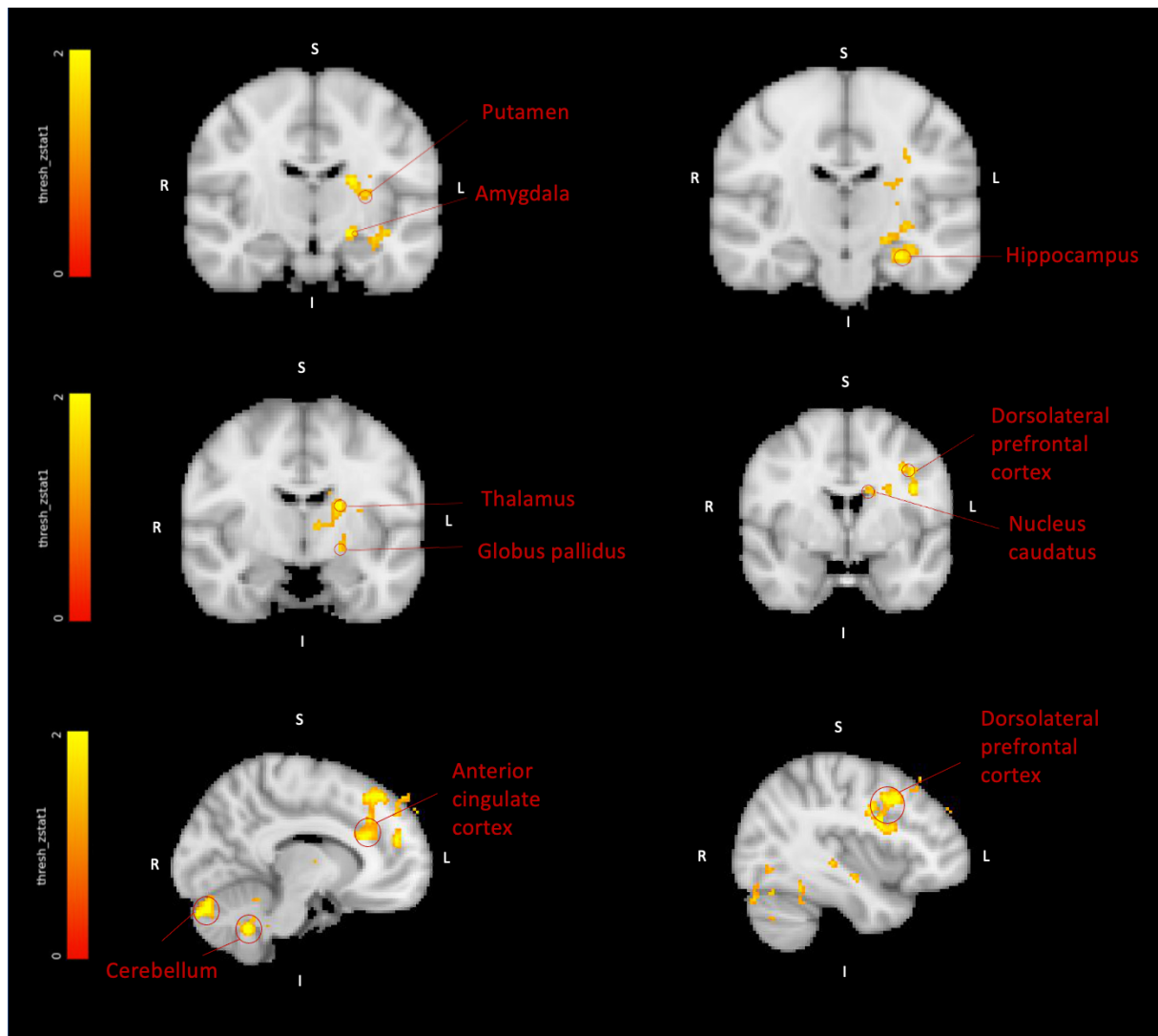
Note. The color bar represents z values.

Figure 3 Results of the PPI analysis LIFU-on > LIFU-off in coronal view



Note. Data are presented in radiological convention (R=L). The color bar represents z values.

Figure 4 Results of the PPI analysis LIFU-on > LIFU-off



Note. Closer examination of changes in functional connectivity in structures involved in the cortico-basal ganglia circuit induced by stimulation the left globus pallidus with low-intensity focused ultrasound. The color bar represents z values.

Discussion

In light of the overall research aim of this thesis, to lay the groundwork to implement causal inference in understanding anhedonia, the results of the pilot study conducted provide a valuable first insight. In this study, it was followed the question of whether low-intensity focused ultrasound stimulation has the potential to modify functional connectivity patterns within a specific brain network system when stimulating a subcortical brain region which is also part of this system. More specifically, in the pilot study it was examined, whether low-intensity focused ultrasound stimulation is able to induce changes in functional connectivity

within the so-called cortico-basal ganglia circuit when stimulating the left globus pallidus, a subcortical region that is also integrated into this larger circuit system (Marchand, 2010).

First, the findings of the analysis suggest that stimulation of a specific subcortical brain structure, such as the left globus pallidus, with low-intensity focused ultrasound does not result in a random distribution of activation throughout the brain. Rather, changes in functional connectivity patterns are elicited within brain structures belonging to the same hemisphere as the selected region of interest. This observation could be interpreted as an indication that stimulation with low-intensity focused ultrasound produces lateralized effects, which in turn may be considered as an important implication regarding the credibility of these preliminary results. Furthermore, given that the number of brain regions mentioned in the previous section, including the dorsolateral prefrontal cortex, the medial prefrontal cortex, the anterior cingulate cortex as well as the insula cortex, the nucleus caudatus, the putamen etc., showed a change in their functional connectivity by stimulating only one specific subcortical brain structure, it can be assumed that this stimulation method is likely to produce effects in a precise manner involving both subcortical and cortical regions. In accordance with that, all structures that showed changes due to the stimulation of the left globus pallidus are part of the superordinated cortico-basal ganglia circuitry (Bostan & Strick, 2010; Marchand, 2010). This is also true for the cerebellum. Although it has been long assumed that this structure and the basal ganglia function independently at the subcortical level and are only connected via cerebral areas, recent studies have demonstrated that the cerebellum has both efferent and afferent connections to the basal ganglia (Caligiore et al., 2017; Bostan & Strick, 2019). Interestingly, as shown in the results section, an increase in functional connectivity was also shown in parts of the left globus pallidus, which was the target region of the stimulation. This observation may suggest that by precisely targeting a specific area of the globus pallidus, an adjacent area of this structure was not exposed to direct stimulation and therefore an increase in its functional connectivity may be observed as well.

All in all, the observations just mentioned are particularly noteworthy, as they can be evaluated as further decisive indicators for a systematic approach to this stimulation technique. Especially in comparison to other non-invasive stimulation methods such as TMS or tDCS, which have already been discussed in the course of this thesis, this observed circuit-specific change in functional connectivity pattern of ultrasound stimulation can be seen as a tremendous benefit of this technique. Although TMS and tDCS are already being considered in the clinical setting as a method for treating depression, as demonstrated throughout this thesis, their overall stimulation effects appear to occur randomly rather than in a specific manner, making it difficult

to accurately understand their mechanisms of action (Arulpragasam et al., 2022). Furthermore, when placing these aspects into the theoretical context of the present thesis, the findings provide a valuable first step towards a better understanding of the brain's reward circuit, its various types of reward processing, and its association with the occurrence of anhedonia. The results of the analysis illustrate the efficacy of using low-intensity focused ultrasound to induce change in the functional connectivity of brain structures connected to a higher-level circuit by the stimulation of a subcortical brain structure that is also part of this circuit. This observation can be used as a foundation for future studies to investigate the introduced reward circuit or mesocorticolimbic circuit more specifically.

Therefore, in order to be able to gain more knowledge about how reward processing occurs in the brains of healthy participants, further studies must be conducted. By finding out more about the basic principles of reward processing in the brains of healthy subjects, these findings can also help to identify more precisely the underlying mechanisms of a disturbed reward system and thus get closer to certain patterns of the development of anhedonic symptoms.

Limitations

In this section, limitations regarding the current study will be discussed as this will be relevant for future research.

First of all, the data used for this study was originated for the purpose of another study, which did not focus on anhedonia, or rather the reward circuit, which makes it relevant to emphasize that this study here can only be regarded as a first step. In the original study, the globus pallidus was taken as the region of interest. This subcortical brain structure is not directly associated with the reward circuit as for example the nucleus accumbens or the nucleus caudatus, which makes it difficult to transfer the results specifically to implications concerning reward behavior or rather anhedonia. However, as discussed in the course of the paper, the globus pallidus is part of a superordinated brain circuit system, called the cortico-basal ganglia circuitry which, among others, comprises structures of the brains' reward circuit. For this reason, the given data set was suitable to pursue the research question relevant for this study. It provides a kind of proof of concept for the ability of low-intensity focused ultrasound stimulation to modify functional connectivity in a specific manner and therefore represents an important first step for future research. Second, the results cannot be considered significant when an appropriate cluster correction is applied. Due to the small sample size, we decided to lower the threshold of the z-value to 1.2, although we were aware of the fact that this reduces the overall expressiveness of the results, as it leads to an increase in the risk of false positives.

However, despite the lowering of the threshold, we observed changes in functional connectivity in a very specific way involving brain regions that are part of the cortico-basal ganglia circuit and the results were not randomly distributed, making it very unlikely to state that the results were caused only by false positives. Nevertheless, for future studies it is important to aim for a larger number of participants, as this will increase the statistical power and thus true effects would be represented more clearly. Furthermore, and related to the sample size, out of the 16 participants, 15 subjects were male. As differences due to the participants' sex could be relevant to the results, ideally, an even distribution of sexes should be also taken into consideration for future research. Fourth, with respect to the application of the transducer to the region of interest, it is important to keep in mind that due to the small size of the globus pallidus, there is a chance that neighboring structures might be also responsible for the final results. This is especially an issue concerning single-element transducer as it was used in the original study. In contrast to multi-unit arrays, single-element transducers are considered to be limited in terms of their focal precision (Cain et al., 2021; Izadifar, et al. 2020). As low-intensity focused ultrasound stimulation can be regarded as a quite novel stimulation technique, future research is needed to develop certain guidelines which ensure a high standard of precision in terms of placing a single-element transducer to small brain structures. As there already exist literature about methods involving computational simulation which aim to achieve the correct target region precisely, this might be a promising direction in terms of solving this limitation (Park et al., 2019; Samoudi et al., 2019). Fifth, research has shown that there exist a wide range of possible values with respect to the intensity levels that far exceed those chosen for this study, but still considered safe. For example, in a study by Gaur et al. (2020), a value of 25 W/cm² Ispta was proven for its safety in two large animal models and according to them, this value did not have a negative impact and therefore can be regarded as safe. As indicated in the methods section, in the current study, 0.72 W/cm² Ispta and 14.40 W/cm² Isppa were used as intensity parameters, which is notably lower than the value reported in this study. Therefore, for future studies it might be interesting to investigate whether higher values in intensity might lead to more expressive results. For example, as a first safe step, values of 1.5 W/cm² Ispta and 30 W/cm² Isppa could be tried out in future studies.

Implications for future research

As this study was intended to serve as a kind of proof of concept, in this part, a rough procedure is presented as a recommendation for future research purposes to investigate the question of whether low-intensity focused ultrasound stimulation is also able to induce changes

in the brain's reward circuitry in healthy subjects, and whether this manipulation succeeds in modifying hedonic experiences. In this context, the outlook will focus on the investigation of reward liking as one of the three subdomains of reward processing, as it appears that this specific type is still less understood in the scientific community compared to the subdomain of reward wanting.

As discussed in the course of the paper, using Sweet Taste Tests for assessing one's ability to feel pleasure appears to be too simplistic and far away with regard to humans' capacity to experience pleasure (Rizvi et al., 2016). Therefore, in a first step, a study could be designed in which participants are confronted with a reward task that is related to more complex hedonic experiences while lying in a functional magnetic resonance imaging scanner. Thus, instead of using the Sweet Taste Task, the study could include listening to one's favorite music as a reward stimulus, since the experience of listening to one's preferred music can be considered much closer to one's genuine hedonic experiences (Salimpoor et al., 2009). Therefore, the experimenters could invite the participants in advance to send them their favorite and most pleasurable music that they know can elicit positive emotional responses such as chills or musical frissons, in a similar way as it has been done in previous studies (Salimpoor, et al., 2011). In addition, the experimenters could also ask the participants to send them music, that they like less, i.e., music that does evoke negative feelings when listened to. While in the scanner and listening to the music, the participants could then be asked to rate their perception of the music's pleasure intensity on a scale displayed on a monitor in the scanner. This would bring the benefit to be able to observe the behavioral aspect of reward processing and at the same time brain activation can be monitored. Following this approach, in addition to the behavioral observations, a comparison of neural activation could be made between phases of low perceived intensity of the music and high perceived intensity. In the event that a change in neural activation can be observed between low levels of pleasure intensity and high levels of pleasure intensity in the brain structures related to reward processing, a third step could follow. In this step, the same study design could be applied with the additional feature using ultrasound stimulation in a block design. A specific stimulation by ultrasound of either the nucleus accumbens or the nucleus caudatus (Salimpoor et al., 2013) in healthy participants would allow a deeper insight into network-wide activation patterns related to the whole reward system, as phases with stimulation and phases without stimulation could be compared in order to pursue the question whether or not the stimulation leads to an increase in the participant's perceived intensity of the music as well as in the neural activation pattern of the mesocorticolimbic circuit. A placebo group could be used as a control, not receiving any active stimulation. The

results obtained from these studies, may serve as a valuable preparation for the use of low-intensity focused ultrasound stimulation in depressed patients with the goal of reducing anhedonic symptoms or rather to increase the ability to feel pleasure as well as motivation in patients suffering from severe forms of anhedonia in everyday life activities.

Conclusion

All in all, even though this study used data which cannot be associated with reward-related behavior or brain networks, the findings can be regarded as a highly promising first step in terms of the potential of low-intensity focused ultrasound stimulation and its neuromodulatory ability in healthy human subjects. As mentioned earlier, the purpose of this study was primarily conceptualized as a kind of proof of concept concerning the overall research aim of this thesis. It paves the way for future research focusing specifically on anhedonia and its connection to the mesocorticolimbic circuit, while also providing a valuable new perspective on the possibilities of using low-intensity focused ultrasound stimulation in both basic research and clinical trials. Taken together, all of these aspects may lead to a more informed future treatment of neuropsychiatric disorders, such as depression.

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Appendices

A. Abstract

Background: For the diagnosis of depression, anhedonia is described as one of the two main symptoms required. According to various studies, this symptom seems to be of particular importance with regard to the overall course of depression. Research has also shown that anhedonia appears to be strongly associated with a disturbance in the brain's reward circuit, also known as the mesocorticolimbic circuit. Since the underlying mechanisms of reward processing are generally poorly understood, there is a great need for a deeper understanding in order to subsequently extend this knowledge to anhedonia. A recently established stimulation method called low-intensity focused ultrasound (LIFU) is gaining more and more attention in regard to causal inference in general when targeting deep brain structures.

Aim: The overall aim of this thesis was to lay the groundwork to implement causal inference in understanding anhedonia by verifying in a first step whether stimulation of a subcortical region with LIFU can modulate the interaction of an entire network system in which the stimulated region is embedded, using data from a previous study in which this stimulation technique was applied to healthy participants. In a second step further implications and future directions were discussed.

Methods: In the pilot study conducted, the left globus pallidus was stimulated with LIFU in 16 healthy participants while simultaneously recording fMRI data. This subcortical structure is part of a larger higher-level circuit called the cortico-basal ganglia circuitry. In line with the aim of the thesis, a psychophysiological interaction (PPI) analysis was performed.

Results: Stimulation of the left globus pallidus resulted in changes in functional connectivity in the dorsolateral prefrontal cortex, the medial prefrontal cortex, the anterior cingulate cortex as well as in the left striatum, the left hippocampus, the left amygdala, the left thalamus, the left globus pallidus and in the cerebellum.

Discussion: All structures that showed changes in functional connectivity are part of the superordinated cortico-basal ganglia circuitry. Therefore, the results of the pilot study provide a first valuable insight into the potential of LIFU to induce changes in functional connectivity within a specific brain circuit by stimulating a brain region that is also part of that circuit. This offers a promising perspective for further research to gain deeper insights into the underlying mechanisms of reward processing, which appears to be closely associated with the mesocorticolimbic circuit in which subcortical brain structures are thought to play an important role. The gain is to then stimulate relevant areas within this circuit since the data shows that stimulation of small subcortical areas is sufficient to activate a whole circuit.

B. Zusammenfassung

Hintergrund: Im Rahmen der Diagnostik einer Depression wird die Anhedonie als eines der beiden Hauptsymptome beschrieben, welche für eine Diagnosestellung dieser Erkrankung erforderlich sind. Aus verschiedenen Studien geht hervor, dass dieses Symptom für den Gesamtverlauf der Depression eine besondere Rolle einzunehmen scheint. Zudem wurde gezeigt, dass die Anhedonie eng mit einer Störung des Belohnungskreislaufs im Gehirn, auch mesokortikolimbischer Kreislauf genannt, verbunden zu sein scheint. Da die zugrundeliegenden Mechanismen der Belohnungsverarbeitung im Allgemeinen nur unzureichend verstanden sind, besteht ein großer Bedarf an einem tieferen Verständnis, um in weiterer Folge dieses Wissen auf die Anhedonie ausweiten zu können. Eine kürzlich etablierte Gehirnstimulationsmethode, namens fokussierte Ultraschallstimulation niedriger Intensität (LIFU) gewinnt zunehmend an Aufmerksamkeit im Hinblick auf kasuale Schlussfolgerungen im Allgemeinen, wenn sie auf tiefe Gehirnstrukturen ausgerichtet wird.

Ziel: Das übergeordnete Ziel dieser Arbeit war es, die Grundlage für die Anwendung von Kausalschlüssen zum Verständnis von Anhedonie zu schaffen, indem in einem ersten Schritt überprüft wurde, ob die Stimulation einer subkortikalen Region mit LIFU die Interaktion eines gesamten Netzwerksystems modulieren kann, in das die stimulierte Region eingebettet ist. Dabei wurden Daten aus einer früheren Studie verwendet, in der diese Stimulationstechnik bei gesunden Studienteilnehmer*innen angewendet wurde. In einem zweiten Schritt wurden weitere Implikationen und zukünftige Richtungen diskutiert.

Methoden: In der durchgeführten Pilotstudie wurden bei 16 gesunden Studienteilnehmer*innen der linke Globus pallidus mit LIFU stimuliert während simultan fMRT-Daten aufgenommen worden sind. Die stimulierte subkortikale Struktur ist Teil eines größeren übergeordneten Schaltkreises, der kortikalen Basalganglienschleife. In Übereinstimmung mit dem Ziel der Arbeit wurde eine psychophysiologische Interaktionsanalyse (PPI) durchgeführt.

Ergebnisse: Die Stimulation des linken Globus pallidus führte zu Veränderungen der funktionellen Konnektivität im dorsolateralen präfrontalen Kortex, im medialen präfrontalen Kortex, im anterioren cingulären Kortex sowie im linken Striatum, im linken Hippocampus, in der linken Amygdala, im linken Thalamus, im linken Globus pallidus und im Kleinhirn.

Diskussion: Alle Strukturen, die bei der Stimulation des linken Globus pallidus mit LIFU Veränderungen in der funktionellen Konnektivität zeigten, sind Teil der kortikalen Basalganglienschleife. Daher liefern die Ergebnisse der Pilotstudie einen ersten wertvollen Einblick in das Potenzial von LIFU, Veränderungen der funktionellen Konnektivität innerhalb eines bestimmten Hirnkreislaufs zu bewirken, durch die Stimulation einer Hirnregion, die

ebenfalls Teil dieses Kreislaufs ist. Dies bietet eine vielversprechende Perspektive für weitere Forschungen, um tiefere Einblicke in die zugrundeliegenden Mechanismen der Belohnungsverarbeitung zu gewinnen, welche in enger Verbindung mit dem mesokortikolimbischen Schaltkreis zu stehen scheint, in dem subkortikalen Hirnstrukturen eine wichtige Rolle zugeschrieben wird. Der Gewinn besteht darin, in zukünftigen Studien relevante Bereiche innerhalb dieses Kreislaufs zu stimulieren, da die Daten zeigen, dass die Stimulation kleiner subkortikaler Bereiche ausreicht, um einen ganzen Kreislauf zu aktivieren.

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