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NEURAL CORRELATES OF PLEASURE

A review of the neuroscientific litterature of pleasure

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Johan Svensson

Supervisor: Judith Annett
Examiner: Paavo Pylkkänen

Neural Correlates of Pleasure: A Review of the Neuroscientific Literature of Pleasure

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I hereby certify that all material in this final year project which is not my own work has been identified and that no work is included for which a degree has already been conferred on me.

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Abstract

Pleasure is part of hedonic well-being, with roots back to Epicurus 2000 years ago. With the new evolving neuroscientific methods of the late 20th and beginning of the 21st century, we are now able to study the biological components of pleasure. This thesis aims to review empirical studies on the neural correlates of pleasure, which can have important implications for well-being, and treatment of addiction and affective disorders. Recent studies have suggested that pleasure can be separated into coding and causing. Discoveries show that causing of pleasure is created in so called hedonic hot spots, areas of the brain that intensely creates pleasure in the shell of nucleus accumbens and in the ventral pallidum. Areas that codes pleasure on the other hand is represented into more cortical areas of the brain, including orbitofrontal cortex, anterior cingulate cortex and anterior insular cortex. There has been a growing understanding about how pleasure is represented in the brain, and a discussion on interpretations and limitations are provided followed by future research suggestions in the final section.

Keywords: pleasure, reward, hedonic hot spot, nucleus accumbens, ventral pallidum, orbitofrontal cortex

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Introduction

The topic of happiness or well-being goes all the way back to philosophers as Aristotle and Epicurus. Aristotle (384 - 322 BC) argued for the eudaimonic view of well-being, where virtue is central, and that people should strive to actualize one's own full potential, a process on becoming the best possible self (Schwartz & Sharpe, 2006; Deci & Ryan, 2008). Epicurus (341 – 270 BC) was rooted in the hedonic philosophy of well-being, and saw pleasure as the human goal (De Witt, 1954). The hedonic view on well-being in general refers to the experience of positive affect and the absence of negative affect (Deci & Ryan, 2008). Another milestone in the history of hedonia was the famous work of Darwin (1998) and his revolutionary work on emotions in 1872. He found that all mammals could experience core liking (could also be seen as pleasure), meaning that pleasure could serve important evolutionary functions. The processing of pleasure includes several brain structures that include e.g. Orbitofrontal Cortex (OFC), Nucleus Accumbens (NAc), Ventral Pallidum (VP) etc. (Berridge & Kringelbach, 2013). This could mean that the experience of pleasure would not have existed if it had no advantage to animals and humans (LeDoux, 2012).

Happiness or well-being has in the recent years called more attention from researchers and especially since Seligman and Csikszentmihalyi (2000) article with the argument on more focus on positive emotions, traits and institutions. It was in that article that positive psychology was born, with the aim to focus studies more on character strengths than of weakness, positive emotions than of negative and fulfillment than of pathology. But well-being (happiness) is a complex phenomenon and there exists different views on what it contains of. Thus, hedonic and eudaimonic well-being seems to be a core part of well-being regardless of the different theories (Deci & Ryan, 2008; Seligman, 2011; Diener, Suh, Lucas & Smith, 1999).

The topic in this thesis is pleasure, a core hedonic quality (fundamentally different from emotion and mood, although they are closely connected), part of hedonic well-being, and the aim is to review the literature of the neuroscience of pleasure. Furthermore, the thesis will provide relevant research and studies on the topic. In addition, this thesis will provide a conclusion of the main points of the research.

The research of pleasure and its biological components is important in understanding and promoting hedonic well-being. Pleasure is an important function in making people feel good (Fredrickson & Joiner, 2002), and is then important in the branch of positive psychology and in the search of what makes us feel good, and how this is registered in the brain. The topic is also important, because an absence of positive affect is associated with depression (Schwartz, Reynolds, Thase, Frank, Fasiczka & Haaga, 2002; Garland, Fredrickson, Kring, Johnson, Meyer & Penn, 2010). Hence, pleasure in that way can be important in the treatment of depression and other affective disorders (Kringelbach, 2010; Garland et al., 2010). An important function of using the neuroimaging tools in studying pleasure is that it provides an additional way to measure well-being, and is therefore a compliment of traditional scientific methods.

The thesis is divided into the following sections, first, pleasure (in this thesis, pleasure is synonymous with liking) will be described as a component of the broader concept of reward. Here the two other types of reward, wanting and learning will also be reviewed briefly. After that, the thesis will be narrowed down to pleasure and common methodologies of studying it. Then, a section on the neuroanatomical components will be covered and the focus here is on the cortical and subcortical parts of the brain related to pleasure. The thesis will end with a discussion and a summary of the main points, and possible future direction of research that needs to be addressed.

Reward

Food and sex are two things necessary for survival and reproduction, and therefore important for the survival of the human and animal species. In order for humans to approach these types of behavior (and other adaptive behaviors as well), evolution has constructed different biological ways that make people engage in activities that contribute to the existence of human life (LeDoux, 2012). Evolution has therefore made activities like eating (Kringelbach, Stein & van Hartevelt, 2012) and sexual (Georgiadis & Kringelbach, 2012) behavior rewarding, and in that way motivate us to engage in those behaviors again and again, in turn increasing the likelihood of humans to survive and reproduce, and thus spreading the genes into new generations.

Reward is a complex concept, and is often confused with only hedonic pleasure (although pleasure is one of the components of reward). However, reward includes more than that. In recent years, there are three common components that are frequently used in reward studies. These are pleasure (often referred as liking) (Kühn & Gallinat, 2012; Kringelbach, O´Doherty, Rolls & Andrews, 2003; Kringelbach, 2005), wanting (Robinson & Berridge, 1993; Berridge, 1996; Ahmed, Avena, Berridge, Gearhardt & Guillem, 2013) and learning (Seymour et al., 2005; Paton, Belova, Morrison & Salzman, 2006) (see figure 1). Different review papers have also divided reward into these three components (Richard, Castro, DiFeliceantonio, Robinson & Berridge, 2013; Leknes & Tracey, 2008; Berridge & Kringelbach, 2013), and therefore, it is reasonable in this essay to divide reward into wanting, learning and pleasure.

Wanting refers to the motivational aspect of a stimulus, such as wanting sweet-candy, pleasure refers to the hedonic quality of a stimulus, and learning refers to the association of a

stimulus and its hedonic quality and is important for future decisions of behavior (Kringelbach et al., 2012).

Reward has both conscious and non-conscious levels (see figure 1 for overview). Conscious reward is often measured with self-ratings. Kringelbach and his colleagues (Kringelbach et al., 2003) for example, used this approach when studying pleasure, and correlated subjective ratings with neural correlates. Wanting (Xu, Aron, Brown, Cao, Feng & Weng, 2011) and learning (Seymour et al., 2005) can also be measured with self-reports. The non-conscious dimensions can often be measured and observed in different kinds of non-verbal reactions to stimuli. Pleasure can for example, be observed in affective facial reactions to certain pleasant stimulus, which strongly correlate to pleasure (Berridge, 2000). Wanting and learning have also non-conscious dimensions. A common way of observing or measuring non-conscious wanting (often referred to as incentive salience) is by studying and observing the kind of behavior a subject has towards a rewarding stimulus, where approach and withdrawal behavior is related to degree of wanting or not wanting something (Robinson & Berridge, 2008). Thus, individuals or animals that engage with the environment in order to obtain something are showing motivational tendencies towards it. Non-conscious learning can be induced by conditioning (such as Pavlovian conditioning), and in that way learn to associate certain expectations to certain stimuli (Seymour et al., 2005; Paton et al., 2006). The components of reward can hence be separated into conscious and non-conscious dimensions that involve different measurement methods.

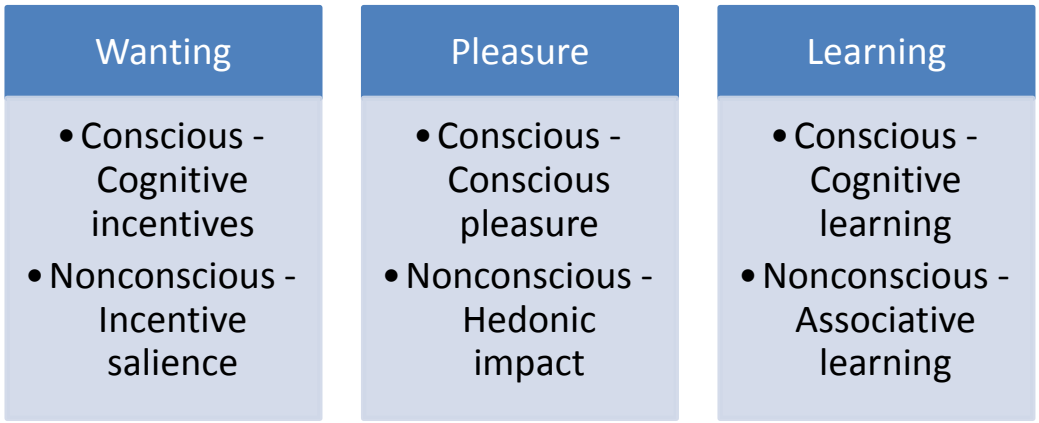

Figure 1 The three components of reward consist of wanting, pleasure and learning. Each of these components exists on a conscious and unconscious level. (Adapted from, Berridge & Kringelbach, 2011).

Here, wanting, learning and pleasure will be briefly conceptualized and summarized, and a brief review of the neurobiological and neurochemical correlations with the reward components wanting and learning will be provided. After that, the focus will be solely on the pleasure component, common methodologies of studying it and the neural correlates of pleasure.

Wanting

Wanting as a component of reward and can be operationalized and characterized by a motivational force of wanting to have something, where an individual in some way engages with the environment to approach a stimulus because of the value it can give the individual (Finlayson, King & Blundell, 2007). Wanting something makes the reward more attractive which alters the desire of obtaining a stimulus, which in turn increases the chances of actually obtaining the stimulus (Berridge, Ho, Richard & DiFeliceantonio, 2010).

Wanting can be both conscious (cognitive incentives) and unconscious (incentive salience) as mentioned above (Berridge & Kringelbach, 2008), meaning that an individual can both consciously desire some stimulus, and also unconsciously want something without consciously be aware of it (see figure 1). Cognitive incentives lead to a self-reported

awareness of a desire to a reward (Berridge & Kringelbach, 2008). This concept is the common sense use of the word wanting, and involves explicit goals (wants) about the future. Incentive salience is distinctive from the common use of the word wanting. This concept relates to more implicit cravings and desires (Berridge & Kringelbach, 2008). This concept does not include cognitive desires, but this motivational force is more autonomous and automatic, and also hard to manage. Drug and food addiction is for example, often related to malfunctions in the brain systems attributed to incentive salience (Robinson & Berridge, 2008). In addiction for example, a person can want something (like a drug) without necessarily liking it, so wanting and pleasure are distinctive components and also feature separate neural substrates (Evans et al., 2006; Berridge et al., 2010). The neural mechanisms of wanting are therefore of special interest in the search for treatment of different kinds of addiction problems.

Mesolimbic dopamine has for a long time been associated with positive affect and pleasure (Ashby, Isen & Turken, 1999). However, more recent studies demonstrate that mesolimbic dopamine and the mesolimbic system is instead associated with incentive salience and not with pleasure (Berridge et al., 2010). In one study showing that mesolimbic dopamine facilitates wanting and not pleasure, Peciña, Cagniard, Berridge, Aldridge and Zhuang (2003) used a genetic mutant approach (knockout procedures) procedure in mice to study this. The knockout procedure manipulates specific genes so that they can no longer be expressed, which allows scientists to study the functional roles of gene consequences. In this study, the gene manipulation caused increases of synaptic dopamine due to a knockdown mutation of dopamine transporter, the results of this being that mice with the genetic manipulation increased behavioral features associated with incentive salience. In addition, the genetic manipulation of the mice failed to enhance pleasure features towards a stimulus. Hence,

synaptic dopamine increased incentive salience without eliciting pleasure. This is consistent with other studies linking mesolimbic dopamine to incentive salience, indicating that mesolimbic dopamine facilitate incentive salience (Berridge, 2007; Berridge et al., 2010).

Another neurochemical substance that can elicit wanting is the μ-opioid (synonymous with mu opioid), that is a neurotransmitter associated with the reward system. In an experimental study using microinjection Fos plume technique (a way of measuring functional consequences of microinjection in different neural substrates, more on this in section "Common Methodologies") in the NAc shell with an mu opioid agonist D-Ala 2-*N*-Me-Phe4-Glycol 5-enkephalin (DAMGO) to map pleasure and wanting behaviors to a sucrose stimulus (Peciña & Berridge, 2005). Researchers were able to localize both pleasure and incentive salience areas of the NAc, they found, that outside of the hedonic hot spot (specific location that generates pleasure, see section "Neuroanatomy of Pleasure") localized in the rostro dorsal quadrant of the medial shell, DAMGO injections increases incentive salience without enhancing pleasure. Hence, mu opioid amplifies both incentive salience and pleasure, depending on the specific location it stimulates.

Wanting processes are also mediated by the mesolimbic brain system, which includes areas such as the amygdala, ventral tegmental area, hypothalamus, NAc and VP (Smith, Berridge & Aldridge, 2011; Saunders & Robinson, 2012; Saunders, Yager & Robinson, 2013; Berridge, 2007; Smith, Tindell, Aldridge & Berridge, 2009). For example, in one study, Mahler and Berridge (2012) wanted to see what parts of the amygdala trigger wanting behavior. By using Fos plume technique, they injected DAMGO in the central nucleus of amygdala, and in the adjacent basolateral amygdala in rats. They found that micro injections of DAMGO in the central nucleus of amygdala triggered incentive salience, while DAMGO injections in the adjacent basolateral amygdala did not.

As described above, incentive salience reactions start in the sub-cortical areas of the brain, and produce it with different neurochemical stimulation such as dopamine or mu opioid in specific locations. However, cognitive incentives, the more conscious experience of wanting use more cortical areas to create that kind of subjective experience, and share these conscious eliciting areas with the learning and pleasure components of reward. For example, the anterior cingulate cortex (ACC) (Beckmann, Johansen-Berg & Rushworth, 2009), OFC (Richard & Berridge, 2013) and the insular cortex (Craig, 2009) is part of the corticolimbic circuit that receives signals from the mesolimbic system that generates incentive salience and translates them in the cortical areas into cognitive incentives. In an fMRI study performed by Rolls and McCabe (2007) they examined both wanting and pleasure aspects of human chocolate cravers and non-cravers. They found that cognitive salience correlated with the medial OFC, thus making the OFC an area that translates basic incentive salience to cognitive salience (Kringelbach, 2005).

Frontal asymmetry

The frontal cortex asymmetry between left and right frontal cortex has originally been thought to be a predictor of hedonic valence (Davidson, 2004; Tomarken, Davidson, Wheeler & Doss, 1992), but later research has shown that it only is indirectly related to affect, and instead predicts wanting (Harmon-Jones, Gable & Peterson, 2010). In lesions studies and studies where one hemisphere is inhibited, they have shown that left and right frontal activity is related to different responses were left hemispheric deactivation is related to depression symptoms because of no approach behavior, and right frontal hemispheric deactivation is related to euphoria and mania because of no withdrawal behavior (Harmon-Jones et al., 2010). This means that stronger activity in the left frontal hemisphere is related to approach motivation and stronger activity in the right frontal hemisphere is related to withdrawal

motivation. Tomarken et al. (1992) found in the 90s that positive affect, what they believed in that time to be, was related to stronger ratio in left frontal activity compared to right, and that stronger right to left activity was related to negative affect. This was later shown to be a miss-confusion with wanting. It is not positive or negative valence per see that hemispheric asymmetry is associated with, but it is the motivational direction that determines it. Stronger left to right frontal hemispheric activation is related to approach motivation, which indirectly generally also mediates positive affect, while stronger right to left frontal hemispheric activation is related to with withdrawal motivation which generally indirectly mediates negative affect (Harmon-Jones et al., 2010). So, frontal hemispheric asymmetry is associated with wanting rather than with pleasure and positive affect as earlier thought.

Learning

Learning as a component of reward is defined as, "the associations, representations and prediction about future rewards based on past experiences" (Berridge & Kringelbach, 2011, p. 4). Furthermore, learning can be both explicit (cognitive learning), meaning that a person can make cognitive learning associations between a stimulus and future events, and it can be implicit, which is related to associative conditioning and Pavlovian associations (associative learning) (see figure 1) (Berridge & Kringelbach, 2008). Cognitive learning means simply that a subject can make cognitive and rational inference about a stimulus in the future, and that the subject can communicate this internally (thinking about it) or externally (in questionnaires or interpersonally). Associative learning on the other hand needs no direct conscious awareness of a stimulus and its implication on future events. This means that a stimulus can be learned unconsciously to have a positive or negative value that in the future will predict motivation directions towards it. A stimulus can therefore be learned as good or

bad, and the next encounter with that stimulus will elicit either desire or dread responses (Berridge, Robinson & Aldridge, 2009).

Learning is important for evaluating and making appropriate decisions on which behaviors will be appropriate in certain situations, based on past experiences (Klein-Flügge, Baron, Brodersen, Dolan & Behrens, 2013). In this sense, learning is important in judging certain events, foods or other types of stimuli to be appropriate or inappropriate. Erroneously learning can be fatal in the future (e.g. not learning that old food can be bad), while good learning can give survival advantages (e.g. learning that a plant that there is plenty of can be eatable) (Klein-Flügge et al., 2013).

The learning component, as with the two other components of reward share the same mesolimbic brain circuit system. Associative learning is represented in the subcortical areas of the brain. One study by Gottfried, O´Doherty & Dolan (2003) found that conditioned stimuli (associative learning) evoked neural responses in the amygdala, OFC, ventral striatum, insula and cingulate cortex, and hypothalamus. Other findings demonstrate that neural activation in part of the hippocampal formation and the associated area of the dentate gyrus were correlated with associative learning (Wolosin, Zeithamova & Preston, 2012). Also, the VP that serves as a major output structure in the limbic system is important in the learning process, and inactivation in the VP heavily reduces associative learning function (Smith et al., 2009).

The role of the neurotransmitter mesolimbic dopamine in learning has been a topic of interest for a time now (Robinson & Berridge, 2000; Everitt, Belin, Economidou, Pelloux, Dalley, Robbins, 2008; Volkow, Wang & Baler, 2011). Mesolimbic dopamine has been found to be important in conditioning responses, enabling different experiences to be stored in the brain as associative learning.

When it comes to cognitive processes of learning, that is more rational and conscious evaluations of a reward in the future, more cortical areas play a role here. For example, the medial OFC is linked to cognitive learning, thus making the learning association conscious (Kringelbach, 2005; Klein-Flügge et al., 2013). Other structures involved in cognitive learning are the ACC (Beckmann et al., 2009) and the insular cortex (Craig, 2009). These cognitive learning processes relies on information from the more basic associative learning process, and then in the cortical areas are being translated into more cognitive learning processes.

Pleasure

Berridge and Kringelbach define pleasure as "the actual pleasure component or hedonic impact of a reward" (Berridge & Kringelbach, 2008, p. 2). Pleasure is therefore a positive dimension of hedonic processing that is distinct from the other types of rewards (wanting and learning) mentioned earlier, and is the hedonic quality followed by a rewarding stimulus. Furthermore, pleasure is divided into two dimensions, conscious pleasure and unconscious pleasure (see figure 1) (Berridge & Kringelbach, 2008). In conscious pleasure, the subject is aware and can report hedonic liking of a stimulus. This means that a person can communicate this internally (thinking about it) or externally (in questionnaires or interpersonally). This conscious pleasure is what is usually meant in describing something pleasant, that we consciously are aware of a rewards hedonic quality. In unconscious pleasure however (hedonic impact), there is a hedonic quality that cannot be self-reported, hence there is an unconscious hedonic reaction to a stimulus. This unconscious hedonic liking can often be observed in affective facial expressions in humans and animals (Berridge, 2000).

Pleasure is commonly induced or stimulated by our sensory systems, but the hedonic liking quality of pleasure is a hedonic reaction created in our brain (Kringelbach et al., 2003;

Kringelbach, 2005; Smith & Berridge, 2007; Kringelbach & Berridge, 2009; Richard et al., 2013). Hence, pleasure and sensation is not the same thing. Sensation can e.g. be a smell, a taste, a touch or a sight, while pleasure is the hedonic reward followed by a sensation. There are underlying neural circuits that generate the pleasure reaction that give a sensation its affective tone, and these circuits are divided into cortical and sub-cortical areas.

Pleasure can further be divided into two categories of hierarchy, a category of fundamental pleasure and a category of higher-order pleasure (Berridge & Kringelbach, 2008). Fundamental pleasure includes the sensory pleasure linked to food and sex. The fundamental pleasures are important, foremost because the hedonic quality followed by fundamental survival and reproducing stimuli like food and sex that is pleasant, and this hedonic reward makes people want to experience the same thing again and therefore increases our likelihood of surviving and reproducing (Kringelbach et al., 2012; Georgiadis & Kringelbach, 2012). The other category of pleasure, higher order pleasures refers to things such as art, music and altruistic pleasures (Berridge & Kringelbach, 2008). In this thesis, most of the studies that will be reviewed are linked to fundamental pleasure, but some studies of higher order pleasures will also be covered.

These three reward components do not work alone, but instead works in collaboration with each other. In each stimulus, these three components normally occur, e.g. if someone sees a chocolate piece, he may want to eat it (wanting), when he eats it, he feels pleasure, and associating chocolate with something pleasant makes him want chocolate again the next time he sees it. Generally, this is how the three components works together in common processes. The following sections will now only focus on pleasure, common methodologies of studying it and neural components of pleasure.

Common Methodologies

Pleasure is a complex phenomenon and can be hard to measure, therefore a clear operational definition must exist to know how to measure it. As mentioned earlier, pleasure is defined as the hedonic quality or liking reaction of a stimuli that can be both conscious and unconscious (Berridge & Kringelbach, 2008). The conscious and the unconscious levels are assessed in different ways (see figure 2).

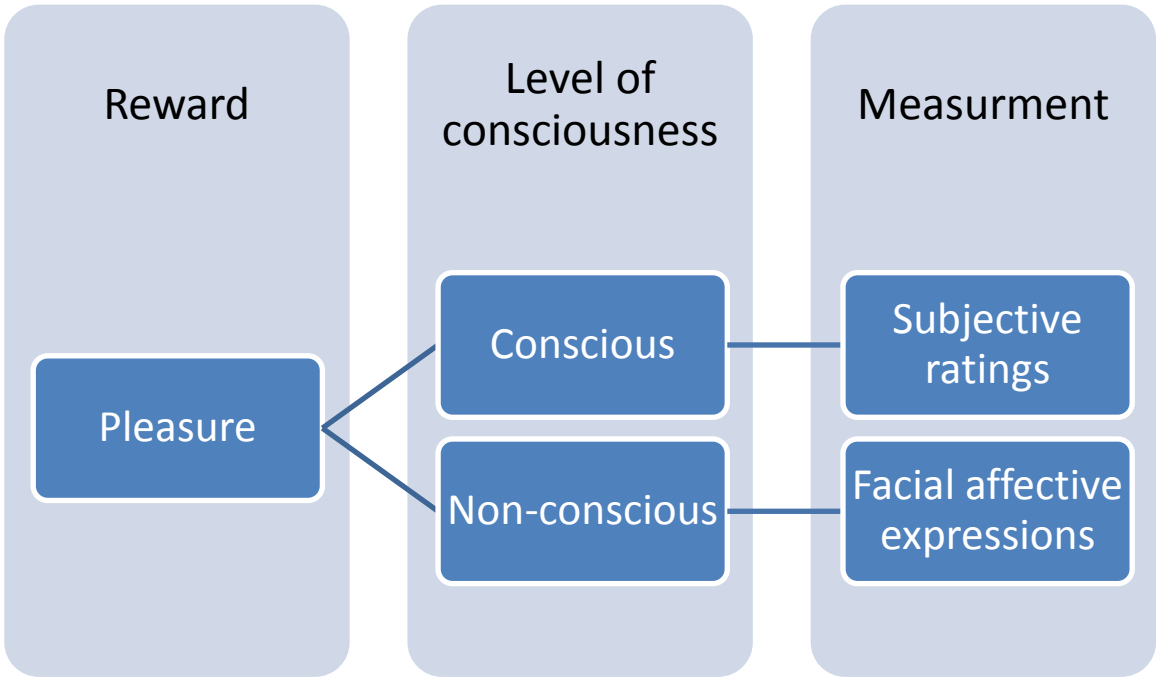

Figure 2 The left column shows the pleasure reward, the middle column shows the level of consciousness, and the right column shows the kinds different measurement methods. (Adapted from, Berridge & Kringelbach, 2011).

Unconscious and Conscious Pleasure

The human mind does not always work in a conscious and logical way. We are frequently exposed to thousands of stimuli, and not all stimuli reach our awareness but instead unconsciously affect our decisions and affective reaction (Laeng et al., 2013; Bornemann, Winkielman & der Meer, 2012; Winkielman, Berridge & Wilbarger, 2005). So, to study the non-conscious hedonic impact, Berridge (2000) developed some guidelines to assess this based on affective facial reaction in humans and other primates on taste injected stimuli (see

figure 2) (to see images of positive hedonic facial reactions vs. aversive facial reactions, see Berridge, 2000). The central point from this is that different tastes elicit different kinds of facial reactions that represent different kinds of affective valence (pleasure or displeasure). Pleasant tastes has some characteristic facial expression reactions such as licking the lips, lip smacking, tongue protrusion, relaxation of the middle face as well as occasional smiles. Displeasure on the other hand is associated with expressions such as wrinkling the nose, headshake and retraction of the head, retraction of the lips, disgust gapes, shrinking of the eyes and brows. By measuring these affective facial reactions, researchers are able to correlate different kinds of stimuli with different kinds of brain circuits (De Luca, Solinas, Bimpisidis, Goldberg & Di Chiara, 2012; Peciña & Berridge, 2005; Smith et al., 2011). Examples of this come in the section "Neuroanatomy of Pleasure". This non-conscious pleasure is the core hedonic impact by a stimulus and is necessary for further processing the hedonic impact into a conscious pleasure. Therefore, hedonic impact measurement methods of affective facial reactions can also be observed and measured when studying conscious pleasure.

Conscious pleasure is the conscious hedonic experience followed by a stimulus and this is often measured through subjective ratings (see figure 2) (Geha, de Araujo, Green, Small, 2013; Grabenhorst, D'Souza, Parris, Rolls & Passingham, 2010; Kringelbach et al., 2003). Through this procedure, researchers are able to correlate subjective ratings of pleasantness with different kinds of brain activity, and in that way identifying neural correlates of conscious pleasure. In one study, subjects were put in a functional magnetic resonance imaging (fMRI) scanner and were asked to rate the pleasantness of two types of liquids (Kringelbach et al., 2003). The participants were also asked to rate their thirst and hunger four times during the experiment, one set of ratings before the experiment started, one at the end of the experiment and two in between. The subjective ratings were then correlated with different

brain regions to determine which regions that is associated with conscious pleasure. More examples of this come in the section “Neuroanatomy of Pleasure”.

Neuroscientific Methods

The neuroscientific method has been a useful tool in helping researchers understand the functionality of the brain. There are different methods of studying pleasure in the brain, and here is a brief review of some of the most common methods in doing so.

A widely common used method to study the underlying brain circuits of pleasure in animals is by using functional mapping procedure (Peciña & Berridge, 2000; Peciña & Berridge, 2005; Mahler, Smith & Berridge, 2007; Faure, Richard & Berridge, 2010; Smith et al., 2011; Richard et al., 2013). Here, scientists inject different kinds of neurotransmitter agonists into different substrates to see if they produce affective facial reactions characterized by pleasure or displeasure, or other types of reward. For example, Peciña and Berridge (2005) used this procedure to localize the hedonic hot spot in the NAc medial shell. By using DAMGO, a mu opioid agonist, and injecting this with Fos plume technique in the NAc shell, they were able to localize a cubic millimeter site that is causing pleasure. The Fos plume technique is a novel way to measure functional consequences followed by neural activation (Peciña & Berridge, 2000). So, by using the Fos plume technique, researchers are able to map behavioral consequences followed by microinjection of drugs. In Peciña and Berridge (2005) study for example, they found that by microinjecting DAMGO into a specialized location in the medial NAc shell, they generated affective facial reactions that represents pleasure.

This method allows scientists to use higher level of constraints in the studying of pleasure, in that they can directly manipulate brain substrates and then see what type of reward behavior it creates. The biggest limitation with this method is that it can only be used in rodents, because of the understandable ethical issues of performing brain surgery in humans.

Other ways of studying the neural components of pleasure are by using correlation studies. For example, by using the sensory system, researchers are able to induce or produce pleasure (Berridge & Kringelbach, 2013). Pleasure can for example be stimulated by touch (Rolls et al., 2003; Morrison, Björnsdotter & Olausson, 2011) or taste (Kringelbach et al., 2003; de Araujo, Rolls, Kringelbach, McGlone & Phillips, 2003; Kringelbach et al., 2012), and is then correlated with brain activities by using brain scanning devices, such as functional magnetic resonance imaging (fMRI), computed tomography (CT) scan, electroencephalography (EEG), positron emission tomography (PET) and magnetoencephalography (MEG).

Another way of studying and understanding pleasure and its neural correlates is through looking at people with brain damage to particular areas (Damasio, Damasio & Tranel, 2012; Hornak et al., 2003). This is not an experimental method per se because we cannot produce lesions in humans, but we can look at people who have naturally damaged their brains, and correlate this with affective impairments.

The neuroscientific method of psychology has been a revolution, allowing us to observe and study the brain in a totally different way, providing new insights that can further improve theories. But, despite this growing interest in neuroscientific technologies, scientists still need to be skeptical about what really is being measured. Shermer (2008) wrote an article about this topic to raise an objective and more skeptical view point of brain scans. Often, the results of brain scans is oversimplified, like that specific neurons of an area in the brain lights up during a specific task, with the conclusion that that specific area represent a specific function (Shermer, 2008). However, these technologies do not always measure the neural correlates of functions. With the fMRI and PET for example, these devices do not measure the neurons per se, but it measures changes in metabolism or regional changes of blood flow (correlated with neural activity) to areas of the brain (Buckner & Logan, 2001). In Shermers (2008) article, he

states other important reasons to be skeptical to brain scans as well. For example, brain scans are performed under unnatural environmental conditions which reduce internal and external validity. He also states that brain scans are the average results of statistical compilations of different subjects and that a specific brain area can serve multiple functions. It is then important to understand the limitations of the neuroscientific method and to be more objective in interpreting these results. But in spite of this, these methods are good compliments to traditional psychological methods and can with carefulness provide new interesting insights in psychology and the science of pleasure.

Neuroanatomy of Pleasure

As mentioned earlier, pleasure is never a sensation (even though pleasure can be manipulated by sensations), but the pleasure followed by a stimulus is created in the brain, hence the pleasant feeling occurs in the brain (Berridge & Kringelbach, 2013). These areas are important to experience affect in life, and for example anhedonia is associated with impairments of the pleasure areas (Der-Avakian & Markou, 2012). This means that people can for example, experience the sensory sweetness of sugar without feeling the hedonic quality usually followed by that, because of the impairment in these affective areas. The study of pleasure has evolved with time, and nowadays, there has been a differentiation between sites that code vs. sites that cause hedonic pleasure (Berridge & Kringelbach, 2011). Coding refers to brain activity correlated with pleasure. Coding does not mean that pleasure and a brain area has a causal relationship, it simply means that a brain area and pleasure has some type of degree of relationship with each other. Coding brain areas is also often associated with other types of cognitive functions, such as decision making, planning, and learning (Liu, Hairston, Schrier & Fan, 2011). These coding areas may therefore have a function in translating pleasure signals into more cognitive functions. A causing brain region on the other

hand means that an area has a function in generating pleasure (Berridge & Kringelbach, 2011). A causal relationship means that a change in a brain area (e.g. by microinjections of drugs) creates a change in pleasure, and that confounding variables can be rejected as a cause of the change. Hence, the only way to find causing areas of pleasure is to manipulate different sites of the brain and try to find a changes in pleasure reactions. Some areas may both code and cause pleasure and can therefore sometimes go together. These two components will be important in categorizing the brain areas in the following text.

The neurobiology of pleasure can be divided into cortical areas, including the OFC, ACC and the anterior insular cortex (AIC) (Grabenhorst & Rolls, 2011; van den Bosch et al., 2014) and sub-cortical areas including NAc medial shell and VP (Richard et al., 2013). Observe that these areas are not the only areas related to pleasure and the reward system, other areas that are not covered here can also be relevant to the reward pleasure, like the left thalamus, amygdala, ventromedial prefrontal cortex etc. (Kühn & Gallinat, 2012; Richard et al., 2013).

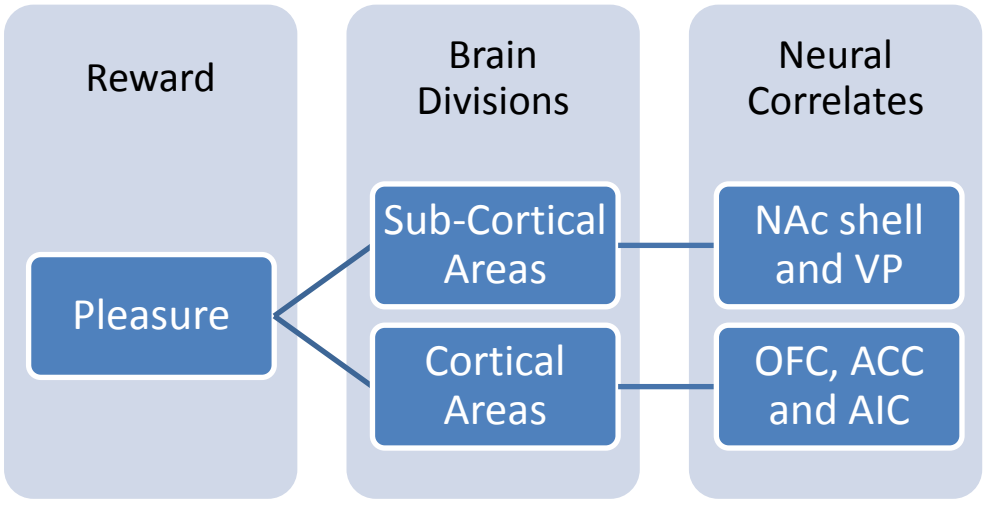

Figure 3 The left column shows the reward pleasure, the middle column shows the brain divisions and the right column shows the neural correlates of each division. (Adapted from, Berridge & Kringelbach, 2011).

Sub-Cortical Areas

In the sub-cortical areas, it is mainly the NAc shell and VP that is associated with pleasure (Richard et al., 2013). These areas of the brain are the so called hedonic hot spots, areas of the brain that intensely increases hedonic pleasure.

It was back in the 70-80s that the study neuroscience of reward had its roots, and Ann Kelley was later to be known as a pioneer in that area (Richard et al., 2013). She used microinjections of drugs in the mesolimbic system, to see reward related behavior alterations (Kelley & Iversen, 1979; Kelley, Stinus & Iversen, 1980). These early studies later inspired researchers to follow up in her footsteps and use same methodologies, in finding hedonic facial taste reactions followed by opioid agonist (morphine) drug injections in rats (Doyle, Berridge & Gosnell, 1993; Rideout & Parker, 1996). Studies continued to investigate the opioid agonist's role of generating hedonic pleasure in neural substrates (Peciña & Berridge, 1995; Peciña & Berridge, 2000), until the first hedonic hot spot could be localized in the NAc shell (Peciña & Berridge, 2000). From that study, several new studies have been done in the field of hedonic impact, which will be reviewed in the following sub-sections.

Nucleus accumbens

The NAc lies in a part of the sub-cortical area of the basal ganglias ventral striatum (Thompson & Swanson, 2010). The NAc is divided into a core region and into a shell region that are anatomically different (Heimer, Zahm, Churchill, Kalivas & Wohltmann, 1991).

As mentioned earlier, the hedonic hot spot in NAc shell was first mentioned in Peciña and Berridge (2000). Fifty-two male rats were used in that study. The authors sought to investigate functional differences in the NAc (both shell and core) by using a Fos plume mapping technique. They were microinjecting opioid agonist morphine into different neural tissues of the NAc to see which sites that is activated by morphine and that produces hedonic

affective facial reactions of sucrose taste. By using this technique, they were able to localize a region that mediates hedonic pleasure to taste of sucrose, a 1 mm^3 region in the medial caudal NAc shell, which would later be redefined to be localized in the rostro dorsal medial shell. Other sites of the shell or the core did not show the same hedonic reactions.

The criteria for NAc shell boundaries has changed today, sites that were defined as caudal before are part of the rostral half of the shell today because of a remap that allows more caudal regions of medial shell (that earlier were not considered as NAc shell) to be considered as part of it (Peciña & Berridge, 2005). The findings by Peciña and Berridge in their 2000 paper, is nowadays considered as part of the rostro dorsal medial shell (Peciña & Berridge, 2005; Richard et al., 2013). Because of this redefinition of the NAc shell, Peciña and Berridge (2005) set out to do a new study with the same methodologies to investigate the new more caudal sites of the NAc medial shell as well. However, instead of using mu opioid agonist morphine this time, they used DAMGO. By using 50 male rats, they injected DAMGO in different sites of the NAc medial shell and elicited pleasure by injection of pleasant sucrose solution in the mouth of the rats. They measured the hedonic impact by observing the rat's affective facial reactions. What they found was an increased hedonic liking above normal after the microinjection in the rostro dorsal medial shell of NAc (for images, see Peciña & Berridge, 2005). This hedonic hot spot is around 1 mm^3 in volume, and represent the same location that Peciña and Berridge reported in 2000. Other sites of the NAc shell reported from Peciña and Berridge (2005) was either linked to increased reward wanting, or suppressed hedonic pleasure (so called cold spot), and notably is also that stimulation to the entire shell increased food intake, even in the cold spot area.

Later studies support this location of hedonic hot spot in the NAc, indicating that the location of this pleasure generating area lies in the rostro dorsal quadrant of the medial shell

(Peciña, 2008; Castro & Berridge, 2014). Also another neurotransmitter, namely endocannabinoid is associated with generating hedonic impact in the NAc hot spot (Mahler et al., 2007; De Luca et al., 2012; Mechoulam & Parker, 2013). For example, when endocannabinoid agonist was microinjected in the hedonic hot spot in the NAc, it generated the doubled pleasure reactions (compared to normal) to sucrose taste (Mahler et al., 2007). This makes endocannabinoid to another neurotransmitter related to generating pleasure in the brain except from opioid.

These studies indicate that the NAc shell hedonic hot spot is a region linked to causing pleasure. Note, however, that this does not mean that lesions or damage to this region will impair hedonic pleasure. There may still be circuits of hedonic pleasure in different sites of the brain necessary to mediate pleasure.

These types of studies have only been carried out on rats. In humans, different brain scanning methods has been used in trying linking pleasure to neural correlates. In a study by Blood and Zatorre (2001), they were investigating higher order pleasure of music, they let 10 (5 male and 5 female) subjects listen to self-selected music and correlated subjective rated "chills" (a pleasant response) and contrasted this with other music pieces as a control. There were activations in several brain structures, including the NAc and VP in the ventral striatum. Although anatomical boundaries of the NAc shell are impossible to see in a PET scan, this study implies that NAc may serve a role in generating pleasant feeling by listening to music. Limitation of the study is that it can be hard to exactly correlate the hedonic impact (pleasure) of music with the other reward components because of the confounding variables. For example, the subjects had chosen their pieces of music that they knew were pleasant, hence, the subject could have to some degree anticipated (wanting) and associated (learning) their self-selected music. So, the results of the study may equally reflect other reward components

as well as other cognitive functions. In order to eliminate the anticipation and associating variables and other cognitive processing of making judgments, Brown, Martinez and Parsons (2004) performed a new study of pleasant music. The music in this study was not self-selected by the subjects, but was carefully chosen by the researchers. The authors choose unfamiliar popular Greek music from the 1930s, which the participants rated on a 1 (strongly disliking) to 10 (strong liking) scale after the first scan. The mean score was 8.4 (± 1.43), which resembles strong positive liking to the Greek songs. The result of the study indicated activation in limbic and paralimbic systems, and also activation in the NAc. Menon and Levitin (2005) also confirmed these findings in a study, for the first time, using fMRI in the study of pleasant music listening. Similarly, a study on pleasant flavors in human subjects activates the NAc (van den Bosch et al., 2014), and a meta-analysis on 40 human studies also found correlates in the NAc with pleasure (Kühn & Gallinat, 2012). However, it is not known if these studies stimulate mu opioid receptors in the NAc medial shell.

Ventral pallidum

The VP is a structure localized near the hypothalamus and lies in the basal ganglia, and is part of the limbic brain circuit (or loop), and receives input and project output signals from and to the NAc (Smith & Berridge, 2005; Churchhill & Kalivas, 1994). The VP has been associated with disgust (Calder, Beaver, Davis, Van Ditzhuijzen, Kean & Lawrence, 2007) and has a central role in reward wanting and pleasure (Richard et al., 2013). For example, a lesions study of the VP in rats diminished the hedonic impact of sucrose injection (Cromwell & Berridge, 1993). In addition, the hedonic impact is replaced by aversive reactions of displeasure and causes aphagia. This make the VP an especially important structure in reward pleasure, because it is the only structure that, when damaged, totally eliminates normal pleasure reactions (Berridge et al., 2010).

The VP is also a structure containing a hedonic hot spot. In one of the first studies in trying to localize hedonic hot spot of the VP done by Smith and Berridge (2005), they used a microinjecting procedure of mu opioid agonist DAMGO. Similarly as Peciña and Berridge (2005), they used a Fos plume mapping technique and tried to relate that drug stimulation with affective facial reactions (pleasure) to localize the hot spot. In this study, they investigated 30 rats, and injected DAMGO in different microinjection sites across the VP to see how the injections affected the hedonic reactions to sucrose. The hedonic reaction was measured by observing the rat's affective facial reaction. The findings of the study were increased hedonic pleasure in a 0.8 mm^3 area in the posterior VP following DAMGO injection, while DAMGO injection in more anterior and central parts of the VP suppressed the hedonic pleasure of sucrose. The mu opioid neurotransmitter therefore, seems to play a bivalent role in pleasure in the VP. Subsequent studies have also found identical location of the VP hot spot (Smith & Berridge, 2007; Smith et al., 2011). The evidence seems to suggest that the VP is linked to actually causing pleasure, because of the increases in pleasure reaction following drug injection.

Nucleus accumbens and ventral pallidum as a hedonic circuit

The NAc and the VP hedonic hotspot do not seem to work as separated units in generating pleasure, but they work together as a hedonic circuit. That is what Smith and Berridge (2007) wanted to investigate, how these two different hedonic hot spots in the NAc and in the VP cooperate. Even though the hedonic hot spots are localized separately from each other, the evidence suggests that they form an integrated network that works together. In addition, these hot spots work collaboratively together to produce a hedonic liking response. Smith and Berridge (2008) also found that the NAc and the VP hot spots can activate or deactivate hedonic liking activity in each other. More exactly, what they did was injecting either mu

opioid agonist DAMGO to generate hedonic pleasure or mu opioid antagonist naloxone to block the hedonic pleasure in either the NAc or VP hot spot. What happened was that when a drug was injected in one hot spot, the reaction happened in the other hot spot as well. So, to produce a pleasure response, these two hot spots work as one circuit to generate it.

In another study, Thompson and Swanson (2010) developed an experimental circuit-tracing strategy, to investigate the connectivity between the two hedonic hot spots. They applied this strategy into the NAc hedonic hot spot as an anchor point to see the pattern of connectivity. The study indicate that the NAc and the VP arrange a series of parallel and segregated loops that create a circuit where information and signals is sent back and forth between the two hot spots. It thus seems that in the NAc – VP circuit, there exists multiple paths of connectivity. Another more recent study also support this finding by using a tracing technique (Zahm, Parsley, Schwartz & Cheng, 2013), making the two hot spots into one cooperating network in generating pleasure. These studies support the view that the VP and the NAc is working together reciprocally to underlie hedonic pleasure reactions. Because of the ethical limitations of studying these hot spots in humans, these hot spots have only been identified in animals so far, but is assumed to be around 1 cm^3 in humans (in contrast to 1mm^3 found in rats) (Berridge & Kringelbach, 2013).

Cortical Areas

In the previous section, the focus was on sub-cortical neural groups in the NAc and VP. Here, the focus will be on the more cortical areas of the brain that is associated with pleasure. This section will be divided into three parts, each with focus on specific brain region that are relevant to pleasure, which are the OFC, ACC and the AIC (see figure 3). These cortical areas are not as strongly related in causing pleasure as the NAc and the VP, but they are more related to coding of pleasure (Damasio et al., 2012). For example, a person with damaged

insular cortex, OFC, temporal regions, ACC, hippocampi, amygdaloidal nuclei among others, could still feel pleasure and other emotions (Damasio et al., 2012). So, this may indicate that cortical areas are not needed in causing pleasure, but only in coding it.

Orbitofrontal cortex

The OFC is located in the frontal lobe in the prefrontal cortex (Kringelbach, 2005). In the cortical areas, the OFC is the area most linked to pleasure (Berridge et al., 2010). The OFC is also known to have inputs from our five senses, the visual (Aharon, Etcoff, Ariely, Chabris, O'Connor & Breiter, 2001), gustatory (Small et al., 1999), auditory (Frey, Kostopoulos, Petrides, 2000), olfactory (Zatorre, Jones-Gotman, Evans, Meyer, 1992) and somatosensory (Rolls, O'Doherty, Kringelbach, Francis, Bowtell & McGlone, 2003). Because the OFC receives these inputs from the different senses, it is a candidate region in generating conscious subjective ratings of pleasantness and also an area that codes pleasure. In a study by Kringelbach and his colleagues (Kringelbach et al., 2003) they investigated exactly this. With 10 male subjects (mean age, 28.5) participating in the experiment, they were all fed to satiety with either tomato juice or chocolate milk. Researchers then scanned the participants in an fMRI brain scan while the participants rated the pleasantness and intensity of the chocolate milk and tomato juice. Kringelbach and his colleagues then correlated the brain scan images and the subjective ratings of the liquids, and found that when people were sated with a liquid, their subjective pleasantness ratings dropped, and also more importantly, this was correlated with mid-anterior OFC. In addition, the subjective ratings to the other liquid that the subjects had not consumed remained high, and the activation of the OFC to this liquid remained the same. The result of this study shows that the OFC may be a region involved in the conscious and subjective experience of pleasure, and also of the coding of pleasure. Similar studies on self-rated pleasant food experience show similar correlation with the OFC (van den Bosch et

al., 2014; Grabenhorst, Rolls, Parris & d'Souza, 2010; Rolls & McCabe, 2007; Veldhuizen, Albrecht, Zelano, Boesveldt, Breslin & Lundström, 2011).

Similarly evidence from Blood and Zatorre (2001) show that subjective reports of pleasant music are correlated with activation in the OFC, amongst other structures, although, reward wanting and learning can be proposed as a causing variable because of methodology limitations. Other results from studies of pleasant music are also showing a correlation to OFC and pleasure, but in contrast to the study from Blood and Zatorre, the researchers here excluded reward wanting and learning as confounding variables (Brown et al., 2004; Menon & Levitin, 2005).

In addition to pleasant taste and music as mentioned above, pleasant touch is also represented in the OFC. It has been found that neutral touch and pleasant touch in humans produce activation in the OFC, where pleasant touch produces greater activation than neutral touch (Francis et al., 1999). They also found that neutral intense touch activated the primary somatosensory cortex, showing for the first time that pleasant touch can be functionally discriminated in the brain compared to neutral and intense touch. Later studies similarly showed that activation in the OFC was correlated with pleasant touch more than neutral touch (Rolls et al., 2003; Rolls, 2010). On the other hand, in one study investigating pleasant human touch in the OFC, the null hypothesis could not excluded because that the OFC did not show any statistical significant activation, meaning that this study found no correlation between pleasant stimuli and the OFC (Lindgren, Westling, Brulin, Lehtipalo, Andersson & Nyberg, 2012). Because of the OFC involvement of coding subjectively experienced pleasant stimuli, it is likely that Lindgren et al. (2012) result could be contributed due to that the subjects in that study were not instructed to subjectively rate the pleasantness while they were in the scan.

Warm and cold stimuli are other factors that can produce affective reactions. In an fMRI study using 12 (6 males and 6 females) human subjects, researchers used either warm (41 °C) or a cold (12 °C) stimulus, or a warm and cold stimulus simultaneously to produce different affective states (Rolls, Grabenhorst & Parris, 2008). All participants were tested under all three conditions. The participants rated the pleasantness of each condition under every trial. The study showed that the subjective pleasantness by the ratings correlated with the mid OFC activity among other regions. A recent meta-analysis on the neural correlates of subjective pleasure of 40 studies, researchers concluded that subjective pleasure is correlated with activation in the OFC, and more precisely in the mOFC (Kühn & Gallinat, 2012).

Other neuroimaging studies of the OFC show that this area plays a pivotal role in converting sensory stimuli into hedonic reward of pleasure and using this hedonic information in decision making (Elliott, Agnew & Deakin, 2010; FitzGerald, Seymour & Dolan, 2009; Grabenhorst & Rolls, 2011; Sescousse, Redouté & Dreher, 2010; Noonan, Walton, Behrens, Sallet, Buckley & Rushworth, 2010; Peters & Büchel, 2010; Plassmann, O'Doherty & Rangel, 2007; Liu et al., 2011). In one study, researchers used 12 male subjects (mean age, 31.7) and used a procedure that involved both hedonic reward and decision making based on choice alternatives (Elliott et al., 2010). The authors sought to investigate what consequences hedonic reward has on decision making, and what they found foremost that positive hedonic reward (can also be viewed as pleasure) correlated with activation in the mid anterior OFC, whereas punishment correlated with bilateral lateral OFC. Furthermore, decision making behavior was also correlated with activation in the right lateral OFC, and in ventral and anterior bilateral OFC.

These studies indicate that the OFC is therefore an important region for experiencing and coding pleasure, and thus has a key role in conscious pleasure and in evaluating reward

outcomes. In addition, the OFC has a role in translating pleasure into more cognitive functions such as decision making.

Anterior cingulate cortex

The ACC is localized in the cortical area of the brain, more exactly in the frontal midline cortex, inferior to the cingulate sulcus (Holroyd & Yeung, 2012) and is interconnected with the OFC and the AIC (Beckmann et al., 2009).

The cingulate cortex is related to many different functions depending on its regional divisions, functions such as action, reinforcement, reward (wanting, learning and pleasure), pain experience, social interactions, emotions etc. are associated with the ACC (Beckmann et al., 2009). More specifically, the ACC is a regional area that has been correlated with subjective pleasant sensory stimulation (Beckmann et al., 2009; de Araujo, Kringelbach, Rolls & McGlone, 2003; Grabenhorst et al., 2010; Rolls et al., 2003; Lindgren et al., 2012). So the ACC is a sort of higher order cortical area that helps to produce the subjective experience of pleasant sensory stimuli. The ACC can thus be thought of not as an area that generates the pleasant hedonic feeling alone, but which is more related to coding of pleasure. Evidence for this view has shown in for example, Grabenhorst et al. (2010) work, where they tested 14 subjects in an fMRI scan and correlated their subjective ratings of the pleasantness of the fat texture and flavor. Activity in the ACC correlated with pleasant fat texture and flavor. In another study on 34 subjects, researchers used an fMRI to correlate brain activation with experience of pleasant and unpleasant flavors (van den Bosch et al., 2014). They found that brain activation in the ACC (among others) correlated with pleasantness of flavors, which resembles the ACC role in coding of pleasure. Other studies indicate the same role of the ACC in pleasant flavors coding (Rolls & McCabe, 2007; Veldhuizen et al., 2011).

The ACC does also play a role in the representation of pleasant touch in the human brain. In a study on nine subjects, researchers used fMRI to correlate pleasant, painful and neutral touch with cortical brain areas (Rolls et al., 2003). To produce different affective states, they used different stimuli like soft velvet, artificial fur and different kinds of sandpapers (smooth, medium and rough). The stimuli were placed on the hands of the subjects and rotated. The subjects then rated the pleasantness of the stimuli on a scale from -2 (very unpleasant) to +2 (very pleasant), were 0 was neutral. They also rated the intensity of each stimulus on a similar scale. The most pleasant stimuli was the soft velvet (+1,2 on the scale), followed by the artificial fur (+0,69 on the scale), and then followed by the smooth (0.0 on the scale), the medium (-0,35 on the scale) and the rough sandpapers (-0,68 on the scale). The general outline of the study was to compare the pleasant stimulus (the soft velvet) with neutral (smooth sandpaper) and unpleasant (rough sandpaper) stimuli and to investigate the correlations of these types of stimuli. The fMRI data showed results that the ACC activity (as well as the OFC) is correlated with pleasant touch. More specific, it was the anterior part that correlated with pleasure, while the more posterior and dorsal part correlated with painful (or unpleasant) stimuli. More recent research also target this anterior part of the cingulate cortex, a location that is called pregenual ACC (pgACC) (Lindgren et al., 2012; Rolls, 2010). In one study, researchers used four conditions and the subjects were to rate the subjective pleasantness of each of the conditions before the fMRI scan (Lindgren et al., 2010). The result showed that pleasant touch correlated with the pgACC activity, and is thus consistent with other studies (Rolls, 2010). Also, in the study by Rolls et al. (2008) on thermal stimuli (explained under the sub-section “Orbitofrontal cortex”), activation of the pgACC was correlated with the subjective pleasantness rating of the thermal stimuli. A recent meta-

analysis on 40 studies also found activation in the pgACC that correlated with subjective pleasantness (Kühn & Gallinat, 2012).

The evidence seems to suggest that the ACC is more related to coding of pleasure, because of the correlation of the area and subjective experience of pleasure. The ACC is also associated with cognitive functions such as decision making and learning (Beckmann et al., 2009), which further indicate that the ACC has a role in coding pleasure, and to further process this information into cognitive functions. This may be likely, because the ACC has connections with both hedonic neural substrates and other cortical areas related to cognitive functions (Beckmann et al., 2009).

Anterior insular cortex

The AIC is localized deep within the lateral sulcus in the cerebral cortex and has interconnections with widespread structures such as the OFC, ACC, basal ganglia and other parts of the limbic and frontal regions (Gu, Hof, Friston & Fan, 2013; Jones, Ward & Critchley, 2010). The insular cortex is roughly divided into three parts, the AIC, the middle and the posterior insular cortex (Gu et al., 2013). The AIC serves many different functions, neuroimaging studies include that except from pleasure, the AIC is associated with functions such as disgust, wanting, learning, decision making, taste etc. (Wicker, Keysers, Plailly, Royet, Gallese & Rizzolatti, 2003; Craig, 2009; Calder et al., 2007). It has also been associated with human introceptive awareness, and can therefore be an important neural structure of human conscious experience (Craig, 2009; Gu et a., 2013).

Moreover, the AIC codes pleasure and thus enable pleasure to be a subjective feeling (Gu et al., 2013; Craig, 2009). The AIC has somewhat similar functions as the ACC, for example, activity in the AIC is correlated with pleasant gustatory and in some cases also somatosensory stimuli (Kringelbach et al., 2003; Brown et al., 2004; Menon & Levitin, 2005; Löken,

Wessberg, Morrison, McGlone & Olausson, 2009). In one study, investigating scratching induced pleasantness because of itching, researchers wanted to see the cerebral correlation of this (Mochizuki, Tanaka, Morita, Wasaka, Sadato & Kakigi, 2013). Itch, is an unpleasant sensation, and urges people to scratch which is pleasant. In the study, 16 subjects (10 men and 6 women) with a mean age of 31.6 experienced electrical stimulation designed to create the sensation of itch. To evoke the pleasant feeling of scratching, the participants got two L-shaped scratching plates to scratch either on the wrist where the itchy electrical stimulus was placed which was the pleasant condition, or on the dorsal forearm as a control condition (were no itchy electrical stimulus was placed). The participants were placed in an fMRI in four sessions, and with the two conditions (the pleasant condition and the control condition) performed at each sessions. The findings from the study showed activation in the insular cortex. The researchers interpreted the correlation with the insular cortex as that this structure enables pleasant stimuli to be brought into a subjective experience (conscious pleasure).

C-tactile nerve fibers (CT fibers), an unmyelinated mechanorecptor that carry somatosensory information is associated with carrying pleasant somatosensory information to the left AIC (Löken et al., 2009; Lindgren et al., 2012). In one study, researchers tested what kind of neural responses different kinds of touches would elicit (Lindgren et al., 2012). There were four conditions, a human touch condition, human touch with movement condition, rubber glove condition and a rubber glove with movement condition. The 18 subjects (8 female and 10 male) rated the pleasant sensation on a scale from -5 (very unpleasant) to +5 (very pleasant). The touch stimuli with both human hands and the rubber gloves condition activated the bilateral insula. This is consistent with the CT fibers and its relation to the insula cortex. Nevertheless, in this study there was no correlation between the insular and pleasant stimuli. The insula only correlated with neutral somatosensory touch. This is consistent with

other studies, that the insula is only related to neutral somatosensory touch and not pleasant touch (Rolls et al., 2003; Rolls et al., 2008; Rolls, 2010). The role the AIC in somatosensory stimuli is in that sense unclear, but at the same time it is clear that the AIC is important in representation of neutral somatosensory stimuli.

As well as the somatosensory sense, the AIC is activated during pleasant music reaction. That is, while listening to pleasant music the AIC is activated (Menon & Levetin, 2005; Brown et al., 2004). In one case study, the participant, as a result of a stroke, had lost the pleasant affective reaction produced by listening to music because of damage to the left insula that extended to more anterior parts of it, and to the left frontal lobe and inferior to the left amygdala followed by a stroke (Griffiths, Warren, Dean & Howard, 2004). The pleasantness produced by music had thus disappeared, while other musical perceptual abilities were intact. Indeed, other studies also demonstrate that the insular cortex is an important region involved in awareness of subjective pleasantness (Craig, 2002; Craig, 2009). This indicates that the AIC is associated with conscious pleasure and coding of pleasure.

In another set of study, researchers aimed to investigate which specific parts of the insula that is engaged during hedonic experience (Zaki, Davis & Ochsner, 2012). By using fMRI scan, participants performed tasks that involved monitoring of ones hedonic experience. Activity in the AIC correlated with participant's subjective report of their affective state. It is worth noting that researchers did not differ between positive and negative affect, instead, they wanted to investigate the affective experience per se and not if the affective tone was positive or negative.

The anterior and dorsal part of the insula is involved in many different functions, and in this area lies also the primary taste cortex, an area with functions that represents the reward components learning, wanting and pleasure, and more specifically with functions such as

taste, temperature and texture of food (Rolls, 2007; Rolls, 2010). Moreover, a study on subjective pleasantness of flavors found a correlation with the AIC and pleasure (van den Bosch et al., 2014).

Another part of the insula that should not be confused with the primary taste cortex (in the AIC) is the agranular insula (Grabenhorst et al., 2010). This area in the far anterior part of the insula is negatively associated with pleasantness of oral texture.

The AIC may also be a brain area associated with higher order pleasures. For example, in a meta-analysis of 93 studies, researchers were interested to see what brain areas are activated during pleasant objective appraisals (Brown, Gao, Tisdelle, Eickhoff & Liotti, 2011). The main finding from the study was an observation in activation of bilateral AIC. Note, however, that this was a study on higher order pleasure and not on fundamental pleasure, which can or cannot share distinct neural representations.

The AIC has been shown in many studies to be correlated with pleasant experience, but pleasant subjective experience does not necessarily need the insula to generate this. In a case study on a human subject, researchers found that pleasure (as well as other affective states) remained intact after bilateral damage of the insula (Damasio et al., 2012). The study suggest that the insula cortex is not necessary to experience pleasure (or other emotions), but only related to coding of it.

All in all, the AIC has been associated with different kinds of functions, and here, the focus has been on its relation to pleasure. In general, the AIC is correlated with subjective experience of pleasure. Although it is correlated with pleasure, it is not necessarily for experiencing pleasure as found by Damasio et al. (2012). This suggests that the AIC is not related to causing pleasure, but is more related to the coding of pleasure, and that the AIC can

translate pleasure into other cognitive processes such as decision making or planning (Damasio et al., 2012).

Discussion

The thesis focused to review empirical studies on pleasure and its biological components. Pleasure can be viewed as part of hedonic well-being, one of the two fundamental parts of well-being (Deci & Ryan, 2008; Seligman, 2011; Diener et al., 1999). Progress have been made in understanding pleasures role for living organisms, and studies on pleasure indicate that it can serve evolutionary advantages (LeDoux, 2012) as well as it contributes to human well-being (Fredrickson & Joiner, 2002). Important insights on how to treat affective disorders such as anhedonia or depression can be made by further studying pleasure and its biological processes (Schwartz et al., 2002; Garland et al., 2010; Kringelbach, 2010). This means that the topic of pleasure is an important subject and deserves more attention from future research.

Pleasure is defined as a hedonic quality or liking reaction to some type of stimulus, and is a component of the larger concept of reward (Beridge & Kringelbach, 2008). Reward is important for a normal everyday functioning, and without a normal reward system, the consequences could be addiction, anhedonia, depression, poor decision making etc. (Berridge & Kringelbach, 2013). Reward is a complex concept, but can simply be divided into three sub-components, which are pleasure, wanting and learning, all of which has conscious and non-conscious levels (Berridge, et al., 2009). These different components are closely related, and also share related neural components. A rewarding stimulus typically activates brain regions like the NAc, VP, OFC and the ACC (Richard et al., 2013; Berridge et al., 2009; Kühn & Gallinat, 2012). But still, the components are conceptually distinguished and can also be distinguished in studies by careful experimental manipulations.

In the later years, the study of the neural components of pleasure has been divided into regions that codes vs. regions that cause pleasure (Berridge & Kringelbach, 2011). An area that codes pleasure is an area that simply correlates with pleasant stimuli. Pleasure coding areas can in that sense activate a large category of regions, and coding areas can also involve other functions. So first of all, coding areas can first code pleasure, and second, it can use this information into further proceeding into higher order functions such as cognition, decision making, memory and more complex forms of emotions. An area that causes pleasure on the other hand is an area that when activated generates pleasure.

There has been successful studies that has identified areas in the brain that causes vs. that codes pleasure. Generally, areas that cause pleasure are sub-cortical regions in the brain such as the NAc and the VP (Thompson & Swanson; Zahm et al., 2013) and areas that codes for pleasure are cortical areas such as the OFC (Kringelbach, 2005), ACC (Rolls, 2010) and the AIC (Gu et al., 2013).

For example, Peciña and Berridge (2005) have identified a hedonic hot spot in the NAc shell that generates pleasure. They used mu opioid agonist DAMGO and injected it in different parts of the NAc in rats. They found a 1 mm^3 area in the rostro dorsal medial shell of the NAc that strongly generates pleasure reactions to sucrose when stimulated with DAMGO. Another hedonic hot spot in the VP has also been found (Smith & Berridge, 2005). By using similar methods in the study of NAc, the researchers used DAMGO and microinjected it in different parts of the VP in rats. They found a 0.8 mm^3 area in the posterior VP that generates greater pleasure reactions to sucrose in the rat's mouth. The hedonic hot spots in the NAc and in the VP do not work alone, but instead they seem to work as a hedonic circuit, where they are cooperating as a unified network in creating pleasure (Smith and Berridge, 2007). For example, when one of the hot spots were microinjected with DAMGO to generate pleasure,

the other hot spot participated by endogenous opioid like activation. And when one hot spot was microinjected with a mu opioid antagonist naloxone to prevent hedonic pleasure of sucrose, it also activated the other hot spot to do the same. The conclusion from this is that these two hedonic hot spots work together in causing pleasure.

The areas that codes for pleasure are on the other hand more cortical areas. These areas are not related to causing of pleasure because damage to them does not prevent normal pleasure to occur (Damasio et al., 2012). In a study showing the coding function of OFC and the ACC, researchers were able to correlate activity in this region with subjective ratings of liquid taste (Kringelbach et al., 2003). They found activity in the mid anterior OFC and the ACC that correlated with pleasantness of the liquids. In a similar study, researchers correlated pleasantness of flavors with brain regions, and observed activation in the OFC, ACC and the AIC associated with pleasure (van den Bosch et al., 2014). Moreover, scratching that can be a pleasant sensation activates the AIC (Mochizuki et al., 2013).

To summarize the main findings in this thesis, neural correlates of pleasure has been identified across several studies. Correlations of sites that codes for pleasure are located in the cortical areas of the brain, while sites that causes pleasure are located in the hedonic hot spots located in the sub-cortical areas of the brain.

It is worth mentioning that the regions related to pleasure (and the other reward components) serve not only a reward function, but can be related to many different kinds of behaviors and functions as well. For example, the NAc produce pleasure when stimulated with DAMGO at the right location, but 1mm more posterior it produces intense motivation (Peciña & Berridge, 2005). This is also true with the OFC, VP, ACC and AIC, they all serve more function than pleasure. So, while it is true that these areas are related to pleasure, they cannot be viewed as specialized areas of pleasure because they are dedicated to other tasks as

well. So for example, if the OFC or the ACC is activated, it does not mean that someone is experiencing pleasure, it is much more complicated than that.

Another thing worth being aware of is that many of the studies reviewed in this essay on pleasure, have mostly focused on sensory stimulation in experimental settings. That makes it inappropriate to draw the conclusion that these results represent pleasure in a general sense. Pleasure is not only experienced by food and touch stimuli as the most studies reviewed here have done, but pleasure can be elicited by social, artistic and altruistic situations, so called higher order pleasures. It could be that these higher order pleasures have distinct neural correlates. At the same time, it is very different to experience pleasure in experimental settings as it is to experience it in naturalistic settings. In addition, a lot of the studies (especially on the hedonic hot spots) have been used non-humans, so also here is a caution in generalizing these findings to humans. Moreover, a lot of the findings of the neural correlates of pleasure are just correlates of pleasure. Neuroimaging tools like fMRI and PET do only provide us with indirect measures of neural activity, and nothing more.

These results have already taken us somewhat closer in understanding hedonic well-being, but still there exists much more research to be done. There still needs more research on higher order pleasure, and especially on social pleasure because of its importance to well-being (Seligman & Csikszentmihalyi, 2000). Because of the vast amount of studies on animals, we need to further explore if human pleasure and animal pleasure is similar or distinctive. Maybe more importantly, we need more human studies to confirm some of the findings that so far only have been found in animals. For doing this, we may need to develop new kinds of tools and methodologies of studying pleasure.

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