PLEASURES OF THE BRAIN

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Treball de Fi de Grau - 2014

Universitat Autònoma de Barcelona

Key concepts

We define **pleasure** as a **positive affective reaction that is added to a sensory stimulus**. The brain generates pleasure as reward's *liking* fraction. *Liking* differs from *wanting* the rewards or the learning associated with this process.

Furthermore, it's important to understand that pleasure has two prior components: The **conscious pleasure** or liking and the **unconscious pleasure** or *"liking"*. There are several methods for studying the neural bases of pleasure, nevertheless none of them is able to explain both components of pleasure.

Currently, some studies suggest that unconscious pleasure can occur in the brain independently from conscious feelings of pleasure and elicit observable affective reactions. The ***core process* hypothesis** posits that **conscious pleasure appears as a result of some unconscious pleasure** that can **activate**, in some occasions, further **psychological processes of conscious awareness**.

Brain structures that mediate pleasure

There are different meanings implicit in the word *mediate*. Areas that *mediate* pleasure, can act as a **neural marker** of the physiological process when there is a correlation between pleasure and the activation of these areas. This correlation can indicate they act as cause of pleasure or that they are activated as a consequence of the pleasurable experience.

There are other kinds of *mediation* when the areas act as sufficient cause or as necessary cause.

An area is **sufficient cause** if when it is activated by microinjections or electrically stimulated, it enhances positive affective reactions. Whereas an area is **necessary cause** when the integrity of that brain area is necessary in order to have normal positive affective reactions.

Nucleus accumbens

The **nucleus accumbens is a forebrain structure** and constitutes the main part of the ventral striatum. This nucleus has two distinguishable portions: core and shell. The **shell** has important **limbic implications** and it is where we can localize concrete areas that increase sensory pleasure, which receive the name of **hedonic hotspots**. Thus the **NAcc is considered sufficient cause of pleasure.**

In the **NAcc shell** it is possible to **increase the *liking* with different substances**, because there are **different hedonic hotspots**, however, **NAcc activation** it's also important for ***wanting* affective reactions**. NAcc shell plays an important **role in motivational behaviors**.

The best known hedonic hotspot within the NAcc is the **opioid hedonic hotspot** which in rat is 1mm³ in the anterior portion of medial shell of the NAcc. This hotspot has been studied with **microinjection experiments of DAMGO** (μ opioid agonist) **and with other opioid agonist**, demonstrating an fourfold increase of elicited *liking* reactions.

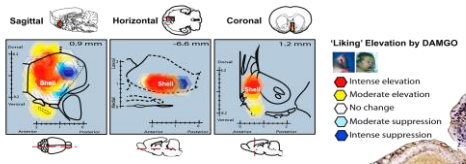


Fig. 1. Opioid hedonic hot spot in nucleus accumbens. The nucleus accumbens hedonic hot spot is localized to the rostrocaudal quarter of medial shell, represented in orange and red in sagittal, horizontal, and coronal views. The colors denote the intensity of μ-opioid amplification of 'liking' reactions elicited by sucrose taste, compared to control vehicle levels in the same rats, and the symbol size shows the diameter of Fos plumes surrounding DAMGO microinjections. A nucleus accumbens affective cold spot is represented in blue and purple in the audal half of the nucleus accumbens, where DAMGO suppressed 'liking' reactions to sweetness. **Modified from Peciña and Berridge (2005).**

A map of the hotspot has been generated by S. Peziña *et al.* (figure 1) and it has been shown that there is **also an opioid coldspot** in the posterior portion of the medial shell. The activation of the coldspot cause the suppression of positive and negative affective reactions.

Other studies with **opioid antagonists** show a **reduced intake of preferred sucrose solutions**, which implies that **opioid neurotransmission is important for normal *liking***. NAcc shell there is also another hotspot; a **cannabinoid hotspot**. The **cannabinoid receptors** are located in neurons of the **NAcc shell**, and **sometimes coexist with opioid receptors**. This coexistence causes a **positive interaction** between these substances, even thought the **activation of cannabinoid receptors** generates an **enhancement of *liking*** and an increase of palatable **food intake by itself**.

GABAergic neurotransmission could also be important in the NAcc for generating affective reactions. It has been observed that a **rostrocaudal gradient exists** in which the microinjections of a GABA agonist produce **different affective reactions (positive or negative** depending on the area). It seems likely that the ***liking* enhancement is related with *allisthesia***.

Allisthesia means an enhancement of sensory pleasure that is produced by the reward, because at that moment the reward is a homeostatic need.

Orbitofrontal cortex

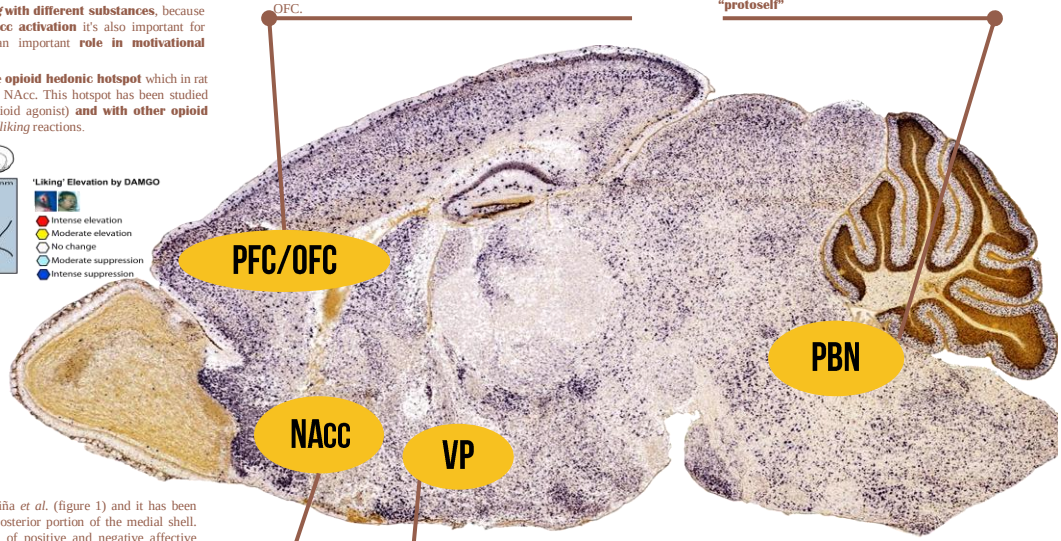
The orbitofrontal cortex is an area of the prefrontal cortex situated in its ventral surface. In **humans** it is clear that the OFC is implicated in value-based decision-making, but there are discrepancies comparing this area with animal models (such as non-human primates and rats), because it has anatomical and histological differences.

Nonetheless in humans some studies show the OFC is implicated in pleasure. It is certain that the OFC acts as **neural marker** for positive and negative affective reactions, however, it is not clear but it seems to be **important for human conscious liking**. In the OFC it is possible to notice that there are **anterio-posterior differences in its activation**: some **abstract rewards** (such as monetary rewards) activate more consistently the **anterio-lateral portion** of the human OFC, **whereas primary rewards** (such as erotic rewards) recruit more **posterior areas** within the human OFC.

Parabranchial nucleus

The parabrachial nucleus (PBN) is a **hindbrain structure**. It mediates pleasure as a **sufficient cause**. It has been demonstrated that **microinjeccions of benzodiazepine drugs** in certain locations in this nucleus **enhance sucrose elicited affective reactions**. Benzodiazepine drugs are known for having an anxiolytic effect because they act promoting the effect of GABAergic neurotransmission. In this nucleus **GABA acts increasing the *"liking"* and food intake**.

This nucleus receives afferent projections from the nucleus of the solitary tract, as well as from the spinal cord; it has been proposed that PBN could elaborate the **first integration of propioceptive information, generating a "protoself"**



Ventral pallidum

The **ventral pallidum is a forebrain structure** that has recently been described as a neuroanatomical nucleus, whereas previously it was just considered as the ventral region of the globus pallidus.

Currently there is evidence that concludes that this nucleus has **special implications in pleasure causation, not just as sufficient cause (like NAcc and PBN) but also as necessary cause for normal sensory pleasure.**

Neural damage experiments in the VP as well as temporal inhibition of the nucleus in animals show **impairments in the generation of positive affective reactions**. In **humans some similar observations** have been reported. There is a clinical case of a bilateral pallidal lesion which experienced **anhedonia** as a symptom.

Furthermore, the VP is also sufficient cause of pleasure and similar to the Nacc, the **VP contains an opioid hotspot,** which **increases sensory pleasure**, and an **opioid coldspot,** which **suppresses affective reactions.**

It is also evident that **the VP is important in *allisthesia***. The **firing rates** within the VP have a **consistent correlation with the hedonic value** of the stimulus. High concentrations of salt would normally generate low firing rates; however in sodium depletion the same salty solutions generate high firing rates as well as hedonic affective reactions. This effect is **probably mediated by an orexin hotspot within the VP**, which increases hedonic impact. Orexin projections that activate this hotspot come from the lateral hypothalamus, and this hypothalamic nucleus has important functions related to detecting homeostatic food levels.

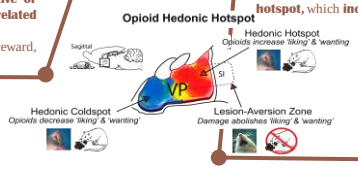


Fig. 2. Neurochemical map of hedonic 'liking' in the ventral pallidum. Microinjections of DAMGO to stimulate opioid transmission in the posterior ventral pallidum hotspot enhance reward 'liking' (increased hedonic orofacial reactions to sweet taste such as tongue protrusion shown in image insert). The same DAMGO microinjections in an anterior coldspot decrease 'liking' below normal (blue). The posterior hedonic hotspot overlaps with the crucial zone where ventral forebrain lesions produce aversion to palatable tastes and aphagia (purple outline). *VP, ventral pallidum; SI, substantia innominata*. **Modified from K.S. Smith *et al.* (2009)**

Conclusions

The study of pleasure was not important a few years ago, however nowadays it is an important subject of study because it helps to explain some eating disorders such as binge-eating and obesity.

These new studies permit to study areas implicated in reward and to dissect components of these rewards, which would be important for posterior investigations.

References

- Berridge KC. **Pleasures of the brain.** *Brain Cognition* 2003; 52:106-128.
- Peciña S, Berridge KC. **Hedonic hot spot in nucleus accumbens shell: where do mu-opioids cause increased hedonic impact of sweetness?** *J Neurosci* 2005; 25:11777–86
- Smith KS., Tindell AJ., Aldridge JW., Berridge KC.. **Ventral pallidum roles in reward and motivation.** *Behav Brain Res* 2009; 196: 155-167.

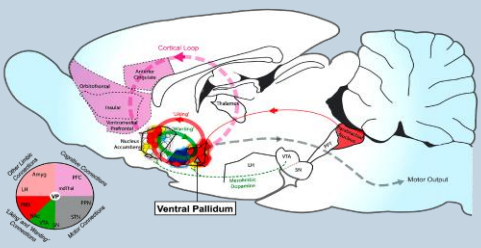


Fig. 3. Sagittal rodent brain diagram highlighting the ventral pallidum as a final pathway for limbic 'liking' and 'wanting' signals. 'Liking' systems (shown in red) link together opioid hedonic hotspots in the posterior ventral pallidum and dorsal-rostral accumbens shell, and potential link with a GABAergic hedonic signal in the parabrachial nucleus. 'Wanting' systems (green) link together mesolimbic dopamine, and opioid motivational signals in the accumbens and ventral pallidum, and larger circuits. The ventral pallidum is also connected with mesolimbic-thalamocortical loops (pink) and basal ganglia or brainstem motor output (gray) to influence cognition and action. Pie chart schematic shows ventral pallidum at an intersection of limbic connections with cognitive, motor, and reward structures. *PPT, pedunculopontine tegmentum; LH, lateral hypothalamus; PFC, prefrontal cortex; STN, subthalamic nucleus; NAc, nucleus accumbens; VTA, ventral tegmental area; SN, substantia nigra; mdThal, mediodorsal thalamus; PBN, parabrachial nucleus; Amyg, amygdala.* **Modified from K.S. Smith *et al.* (2009)**

Interactions between areas and brain circuit for pleasure

The **brain areas implicated in pleasure** generation are included in a **larger circuit of pleasure** and they **work together in order to produce hedonic affective reactions and add them to sensorial stimuli**.

It seems clear that there are **reciprocal projections between the OFC and the Nacc; and also between the OFC and the VP. Information** from the basal ganglia **would be integrated in the OFC** where probably the **cognitive awareness of pleasure will appear.**

However **OFC projections back to basal ganglia** (**NAcc** and **VP**) **act as a top-down control of these areas**.

In the **subcortical level** there are evidences that indicate that **PBN benzodiazepine/GABA hotspot do not increase *liking* reactions** if there is a **microinjeccion of an opioid antagonist** in the **NAcc** nor the **VP**. It seems likely that the **PBN** would **have projections to the NAcc and the VP** and that is why this **hotspot increase *liking***.

The **NAcc and the VP** have an **intense information flow** network between them, It has been demonstrated that **pleasure arises from the interconnection** of these two structures; it's required an **unanimous activation** of both areas **to enhance hedonic impact of an stimulus. VP however seem to be the only necessary cause** of pleasure, and that's why many studies about positive affective neuroscience are focused on this nucleus.