The anterior medial temporal lobes:

Their role in food intake and body weight regulation

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Abstract

The anterior medial temporal lobes are one of the most studied parts of the brain. Classically, their two main structures – the amygdalae and the hippocampi – have been linked to key cognitive and affective functions, related in particular to learning and memory. Based on abundant evidence, we will argue for an alternative but complementary point of view: they may also play a major role in food intake and body weight regulation. First, an overview is given of early clinical evidence in this line of thought. Subsequently, empirical evidence is presented on how food intake, including in the extreme case of obesity, may relate to amygdala and hippocampal functioning. The focus is on the amygdala's role in processing the relevance of food stimuli, cue-induced feeding, and stress-induced eating and on the hippocampus' involvement in the use of interoceptive signals of hunger and satiety, as well as memory and inhibitory processes related to food intake. Additionally, an elaboration takes place on possible reciprocal links between food intake, body weight, and amygdala and hippocampus functioning. Finally, issues that seemed particularly critical for future research in the field are discussed.

Keywords: Amygdala; Hippocampus; Food intake; Body weight; Learning; Memory

The anterior medial temporal lobes – classical role

The anterior medial temporal lobes are composed of two major structures – the amygdalae and the hippocampi. Both of them belong to the most widely studied areas of the brain, notably because of their involvement in key cognitive and affective functions.

It is classical neuroscience textbook knowledge that the amygdala is involved in emotion processing (e.g., Janak & Tye, 2015; Whalen & Phelps, 2009). In particular, its role in fear conditioning paradigms has often been underlined (Ledoux, 1996; Öhman & Mineka, 2001). Recently, the idea that the amygdala acts as a “relevance detector”, rather than only being involved in the processing of fear-related stimuli, appears to have gained traction in the cognitive and affective sciences literature (see Pessoa, 2010; Phelps, 2009, p. 216; Sander, Grafman, & Zalla, 2003). According to this idea, the amygdala is involved in the detection of any stimulus or event that can “significantly influence (positively or negatively) the attainment of [one’s] goals, the satisfaction of [one’s] needs, the maintenance of [one’s] own well-being, and the well-being of [one’s] species” (Sander et al., 2003, p.311). This notion has become central in the study of emotion (see e.g., Armony & Vuilleumier, 2013).

As for the hippocampus, it has been related to various cognitive functions (see Morris, 2006 for a review). It is mainly well-known for its contribution to spatial learning and memory (both in rats, e.g., Kaada, Rasmussen, & Kveim, 1961, and in humans, e.g., Milner, 1965), in particular, explicit memory (e.g., Squire, Stark, & Clark, 2004). Its role in inhibitory processes has also been emphasized (e.g., Davidson, Kanoski, Walls, & Jarrad, 2005).

However, based on abundant evidence, the anterior medial temporal lobes play a major role in functions that have not received sufficient attention in the literature and are far less known

to cognitive and affective scientists: food intake and body weight regulation. In that light, an assumption of the selfish brain theory (according to this theory, the brain gives priority to its own energy needs; see Peters et al., 2004) will be shared in the present review, namely that the limbic system plays “a central role in the pathogenesis of diseases such as anorexia nervosa and obesity” (p. 143). In this framework, the limbic system’s two core regions are defined as the amygdala and hippocampus. In the course of this review, we will endeavor to show that the limbic system’s involvement in these functions is not incompatible with the aforementioned ideas and that it is rather complementary to these ideas.

It is worth noting that similar topics have been the object of several recent reviews (e.g., Areias & Prada, 2015; Higgs, 2016; Kanoski & Grill, 2015; Martin & Davidson, 2014; Morris et al., 2015; Parent et al., 2014; Sample et al., 2015). They include descriptions of studies linking food intake regulation to the amygdala (Areias & Prada, 2015) and the hippocampus (Kanoski & Grill, 2015; Parent et al., 2014) as well as studies showing the influence of memory on food reward processing (Higgs, 2016) and obesity (Martin & Davidson, 2014), and the impact of other factors such as environment and stress on obesity (Morris et al., 2015; Sample et al., 2015). However, rather than reiterating the material covered by these scholarly works, the present review aims to integrate the literature on the functions of both the amygdala and the hippocampus in food intake and body weight regulation in two unique ways. First, this review thoroughly expands on the interactions between these two brain structures and on how important they are for food intake and body weight regulation, thereby filling a gap in the literature. Second, through the presentation of lesion studies in humans, the present work is uniquely ingrained in a neuropsychological and affective sciences perspective. Consequently, this review

may benefit researchers in physiology, but also in psychology, cognitive and affective sciences, who may not be as familiar with this literature.

First, early clinical evidence pertaining to the involvement of the anterior medial temporal lobes in food intake will be presented, focusing on Klüver-Bucy syndrome, epileptic human patients, and amnesic patients who have a bilateral lesion of the medial temporal lobes. In a second part, experimental evidence will be discussed regarding the role of the amygdala in food intake, both in healthy-weight individuals as well as overweight and obese individuals. The third part of this review will be dedicated to the same purpose, but for the hippocampus. Subsequently, the reciprocal and dynamic links between food intake, affective and cognitive functioning, as well as amygdala and hippocampus functioning will be discussed. Finally, some of the current outstanding questions in this literature will be presented.

The involvement of the anterior temporal lobes in food intake regulation: Early evidence

Klüver-Bucy syndrome

In 1939, Klüver and Bucy reported a syndrome that follows bitemporal dysfunction. Among other things, this syndrome is characterized by a hyperorality, bulimia, and the ingestion of non-food items (such as tea bags, feces or even shoe polish). These symptoms were reported both in rhesus monkeys and in humans (see for instance Lilly, Cummings, Benson, & Frankel, 1983). Thus, it appears that the dysfunction of both temporal lobes can lead to excessive intake of food as well as non-food items.

Psychomotor epileptic patients

Gastaut (1955) has reported two types of hunger in patients with psychomotor epilepsy (i.e., epilepsy originating in the temporal lobe). The first of these is called “faim-valle”, which translates to “very intense hunger”. In patients with faim-valle, epileptic crises are often preceded by a violent hunger, and this rare but reliable sign of an impending epileptic crisis cannot be reduced by food intake. This often co-occurs with other symptoms such as olfactory and gustatory sensations, as well as chewing. The second type of hunger, called “faim postcritique”, or post-critical hunger, appears after the crisis and is much more common. It is even present in patients who have had a substantial meal one hour before the crisis, however, this form of hunger can be reduced by food intake. In both cases, patients do not remember these episodes. Importantly, between epileptic crises, these patients do not display pathologic hunger. Thus, the dysfunction of the temporal lobes can also be associated with hunger dysregulation.

Amnesic patients with bilateral lesion of the medial temporal lobes

Patient H.M. had a bilateral resection of the medial temporal lobes (including the hippocampus, parahippocampal gyrus and amygdala). He is famously known for his memory deficit. This deficit was, however, not his only impairment – patient H.M. was also unable to access his internal states. Almost never mentioning hunger unprompted, patient H.M. had a unique pattern of response when asked to rate his internal state, both before and after consuming a meal, using a 100-point scale anchored at extreme hunger on one end and at extreme fullness on the other. H.M. initially rated his internal state at 50. However, his rating did not move toward the fullness end of the continuum after a meal. Moreover, when experimenters offered him a second meal 15 minutes after he was done with the first one, he would eat it. However, he never

rated his internal state as extremely full after the second meal. Finally, Hebben et al. noted that when H.M. stopped eating, he never reported that he was "full", only that he was "finished" eating. Interestingly, "his impairment is not attributable to his well-documented memory deficit. Instead, it is believed that the bilateral resection of the amygdala accounts for H.M.'s poor appreciation of his internal states" (Hebben, Corkin, Eichenbaum & Shedlack, 1985, p. 1031). It should be noted that the misinterpretation of internal states is a mechanism that has been suggested to play a key role in obesity (Schachter, 1968). More specifically, one could argue that because H.M.'s rating of fullness only changed a little after eating, compared to before eating, he may have had difficulty detecting or utilizing inhibitory signals of satiety rather than excitatory hunger cues. A more recent report, which included two amnesic patients presenting extensive damage to both the amygdala and the hippocampus (Rozin, Dow, Moscovitch, & Rajaram, 1998), replicated the results. Additionally, they extended these results by offering the patients a third meal (although for obvious ethical reasons, this could not be tested with a fourth, fifth, or even sixth meal), though the authors attributed this to a lack of conscious memory of previously eaten foods, rather than an impaired perception of internal states. Rozin et al. (1998) suggested that this deficit was due to hippocampal damage rather than amygdala damage. In line with the idea that these deficits could be observed with an undamaged amygdala, Davidson & Jarrad (1993) showed that rats with selective neurotoxic lesions of the hippocampus (the histology revealed no amygdala damage) were impaired relative to controls in their ability to solve a discrimination problem based on using cues related to their internal states (i.e., cues associated with food deprivation). However, the same neurologically damaged rats were *not* impaired at solving a similar discrimination problem based on external cues (i.e., auditory stimuli).

Summary of early clinical evidence

In a variety of conditions (Klüver-Bucy syndrome, psychomotor epilepsy, or bilateral damage or resection of the medial temporal lobes in amnesic patients), malfunctioning of the anterior medial temporal lobes has been reported to go hand in hand with dysregulated feeding behaviors and hunger states. The exact mechanism underlying these conditions is, however, unclear.

Moving forward from these early indications of the anterior medial temporal lobes's involvement in food intake, we will now present experimental evidence that has directly implicated the amygdala as one of the major centers involved in food intake and body weight regulation.

Amygdala: Empirical evidence of its role in food intake and body weight regulation

Rationale for the interest in the amygdala in relation to food intake

If the amygdala is involved in relevance processing in general, it follows that it should also be involved in assessing the (more specific) meaningfulness of food-related stimuli (e.g., Coppin & Sander, 2014), because of their high relevance for homeostasis. Furthermore, the same argument can be applied to cues predicting food intake. In this article, we will consequently develop the hypothesis that the amygdala is involved (1) in the relevance processing of food stimuli, including (2) in the detection of cues linked to food intake. Additionally, we will present its role in (3) stress-induced eating, and briefly mention (4) its uncertain role in satiety signals.

Amygdala and relevance of food stimuli

Several pieces of empirical evidence suggest that the amygdala is involved in the relevance processing of food stimuli. For instance, LaBar et al. (2001) have shown that amygdala activation was higher when participants were watching food pictures while hungry (i.e. when they were relevant) rather than while sated. No such increase was observed for control pictures of tools. Hinton and colleagues (2004) showed that when participants were hungry, amygdala activity was also increased when participants imagined themselves in a restaurant, selecting their favorite item on a menu. Besides hunger-induced relevance, Arana et al. (2003) has shown that amygdala activity was higher when sated participants were reading high-incentive restaurant menus (i.e. displaying the participants' most preferred foods), in comparison to less high-incentive menus (i.e., displaying foods that participants were happy to eat but were not their favorite ones). Moreover, in a task in which participants made purchase decisions about food, amygdala activation was related linearly to the value assigned to a given food (Jenison, Rangel, Oya, Kawasaki, & Howard, 2011). Rudenga & Small (2012) provide evidence that the amygdala's response to sucrose ingestion is negatively correlated with the use of artificial sweetener. Thus, it seems that the extensive use of artificial sweetener, by blurring the relationship between sweet taste and its post-ingestive consequences, rendered sucrose ingestion less relevant. Finally, Blechert, Klackl, Miedl, & Wilhelm (2016) showed that amygdala response is increased when food is available, in comparison to when it is not.

Amygdala and cue-induced feeding

We have described that in patients suffering from Klüver-Bucy syndrome, a dysfunction of the anterior temporal lobes can lead to disrupted food intake behaviors in the presence of a

cue, even if it is loosely related to food (such as a teabag). More recent empirical data have indicated that the amygdala plays a key role in the detection of *cues* associated with food. Using Pavlovian conditioning, Petrovich (2011a, 2011b) has extensively studied the role of the amygdala in *cue-induced feeding* and *cue-induced inhibition of feeding*. Through Pavlovian conditioning, an initially neutral stimulus acquires an affective value by being associated with a punishing vs. a rewarding experience. Applied to the particular case of food intake, such a neutral stimulus, labeled the *cue*, may signal either a favorable or an unfavorable context regarding food intake. Petrovich (e.g., 2011a, 2011b) has called the effects of the first type of cue cue-induced feeding, and the second type cue-induced inhibition of feeding.

In the case of the second type of conditioning, a cue previously associated with danger can prevent feeding, even in a food-deprived state. To the contrary, sensitivity to cue-induced feeding has been proposed to be a mechanism at play in obesity (Schachter, 1968). Although contradictory findings exist (Meyers, Stunkard, & Coll, 1980; Rodin, 1981), it was suggested that while lean individuals mainly eat when their internal physiological state is off balance, food intake in obese individuals is mostly related to their environmental situation. In most current Western countries, many food cues are present in the environment¹. Taken together, in obese individuals, cues previously associated with food intake may consequently easily and frequently stimulate feeding, even when sated (e.g., Reppucci & Petrovich, 2012). This does not mean that cue-induced feeding necessarily promotes an excessive weight gain. Reppucci and Petrovich (2012) did not find significant differences in weight between rats trained to feed upon the perception of certain cues (i.e., rats in a cue-induced feeding condition) and control rats. Moreover, Berthoud (2012), who has reviewed the literature on this topic, failed to identify an

¹ “Easy and inexpensive access to energy dense foods and lack of safe spaces for physical activity” defines an obesogenic environment (Speirs et al., 2016, p. 274).

animal or human study establishing a direct link between exposure to conditioned food cues (even in the long-term) and obesity. Lesion studies in rats have shown that food intake elicited by the presence of cue-induced feeding is mediated by the amygdala (more precisely, according to Petrovich, 2011a, the basolateral area, i.e. the basolateral, basomedial and lateral nuclei, see Figure 1).

Moreover, empirical evidence using functional Magnetic Resonance Imaging (fMRI) in humans has shown that the activity of the amygdala is more pronounced when a food odor predicts the arrival of its associated food, compared to when it does not (Small et al., 2008). Thus, the amygdala responds to food cues (e.g., Tang, Fellows, Small, Dagher, 2012; Dietrich, Hollmann, Mathar, Villringer, & Horstmann, 2016). Additionally, it has been shown that the amygdala's response to food cues are modulated by hunger (Gottfried, O'Doherty, & Dolan, 2003; LaBar et al., 2001; van der Laan, de Ridder, Viergever, & Smeets, 2011) and its response in the absence of hunger could predict weight gain susceptibility (Sun et al., 2015).

Interestingly, it appears that the amygdala's sensitivity to food cues is related to overeating and Body Mass Index (BMI²). Increased amygdala responses to food cues in obese compared to healthy-weight individuals is one of the most replicated findings in the neuroimaging of obesity (e.g., Ng, Stice, Yokum, & Bohon, 2011; Nummenmaa et al., 2012; see Burger, Shearrer, & Sanders, 2015 for a review), including in children (e.g., Boutelle et al.,

² Body Mass Index (BMI) is a measure used to estimate an individual's body fat content. It is computed by dividing an individual's weight by the square of his/her height. BMI is used to classify individuals into underweight (BMI<18.5), healthy-weight (18.5<BMI<25), overweight (25<BMI<30), or obese (BMI>30) categories. Although not without issues (see e.g., Garn, Leonard, & Hawthorne, 1986), BMI is currently the most commonly used measure in obesity research.

2015). External food sensitivity, i.e. a personality trait associated with overeating and obesity³, predicts how the amygdala responds to appetizing food pictures (Passamonti et al., 2009). Additionally, self-directedness (i.e., the ability to set and pursue meaningful goals, which is typically reported as altered in eating disorders, e.g., Sullivan, Cloninger, Przybeck, & Klein, 2007) is negatively correlated with the amygdala response to appetizing food pictures (Grimm et al., 2012). Moreover, in healthy-weight patients, the orbitofrontal cortex and nucleus accumbens, which are both involved in feeding, modulate the amygdala response to food cues. In fact, this modulation is impaired in obese individuals, regardless of the calorie content (low vs. high) suggested by the cues (Stoeckel et al., 2008). Such abnormal amygdala responses to food cues might trigger “non-homeostatic feeding” (also called “hedonic feeding”), i.e. food intake behaviors in states of positive energy, which have the potential to contribute to the development of obesity. Interestingly, the opposite pattern is observed in anorexia nervosa patients. In these patients, the amygdala is hypoactive when patients are presented with high-calorie foods, independently of whether these patients were currently underweight or weight-restored (Holsen et al., 2012).

However, the picture has become slightly complicated, given recent results showing that obese participants have an impaired performance in an implicit conditioned food preference test, which relies on amygdala functioning (Johnsrude, Owen, White, Zhao, & Bohbot, 2000). In this task, three cues were respectively associated with a 10%, 50% or 90% possibility of receiving food. Obese individuals preferred the cue associated with a 10% possibility of receiving food (Coppin, Nolan-Poulart, Jones-Gotman, & Small, 2014, Experiment 1). This result might be explained by a difficulty of learning to avoid negative outcomes in obese individuals (Frank &

³ This personality trait can be assessed by the Dutch Eating Behavior Questionnaire (van Strien, Frijters, Bergers, & Defares, 1986).

O'Reilly, 2006), as this result was not specific to food reward but also replicated with monetary reward (Coppin et al., 2014; Experiment 2).

Amygdala and unhealthy food intake in acute and chronic stress

The amygdala plays a key role in stress-evoked responses (e.g., Gianaros et al., 2004). In the case of food intake, the amygdala may be the brain structure mediating the excessive pursuit of highly palatable food during stress. Thus, acute stress (Rudenga, Sinha, & Small, 2013) as well as chronic stress (Tryon, Carter, DeCant, & Laugero, 2013) potentiates the amygdala response to food. Tryon et al. (2013) also showed that in participants under high chronic stress, in response to high calorie food pictures relative to low calorie ones, the connectivity between the amygdala and regions involved in habit formation, reward, and decision making (bilateral thalamus, left inferior parietal lobe, and left putamen) was increased compared to participants under low chronic stress. By enhancing these connections, high chronic stress may lead to a shift from goal-directed to habitual behaviors. In contrast, in participants under low chronic stress, in response to high calorie food pictures relative to low calorie ones, the connectivity between the amygdala and regions involved in executive functions (e.g., anterior cingulate cortex, dorsolateral prefrontal cortex) was increased compared to participants under high chronic stress. Taken together, these results could explain why stress is associated with unhealthy food intake and poor eating habits (e.g., Pool, Delplanque, Coppin, & Sander, 2015), which could eventually lead to obesity.

Interestingly, this research topic is right at the intersection between affective sciences and food intake research. For instance, Pool, Brosch, Delplanque and Sander (2015) have recently

shown that stress affects one of the components of reward but not others. More specifically, stress increases “wanting” (i.e., the motivation to obtain a reward), but not “liking” (i.e., the hedonic pleasure during the reward consumption) for a sweet reward.

Additional results

One might wonder which aspects of food intake the amygdala might further be involved in. Wang et al. (2008) have demonstrated the involvement of the amygdala in the processing of internal signals of fullness using dynamic gastric balloon distension. In healthy-weight and overweight participants, the activity of the left amygdala was negatively correlated with self-reported fullness. The activity of the right amygdala was negatively correlated with the participants' BMI (see also Geliebter, 2013). The integrity of the amygdala has however been reported as irrelevant in using internal signals of hunger and thirst (Rhodes, Charles, Howland, & Murray, 2012). More specifically, Rhodes et al. (2012) used a task in which rhesus monkeys had to utilize internal contexts (i.e., hunger, thirst) to guide their choices of objects (i.e., objects associated with food, objects associated with water). They showed that learning as well as performance in this task were not disrupted by amygdala lesions. However, there was a slight damage of the hippocampus in three quarters of the monkeys tested in Rhodes et al.' study. As the hippocampus is known to be important in this type of learning based on internal context (see e.g., Kennedy & Shapiro, 2004), it is unclear whether the results reported by Rhodes et al. were caused by lesions of the amygdala, the hippocampus, or both (especially given the important interactions between both structures, see section “Interactions between the amygdala and the hippocampus”). Thus, although, the amygdala seems to be associated with gastric distension, the exact role of the amygdala in fullness signals is still poorly understood (Geliebter, 2013).

Summary and conclusion

The amygdala is involved in food intake and body weight regulation, in particular in the relevance processing of food stimuli and the detection of cues linked to food intake. Heightened amygdala responses to food cues, for instance in stressful contexts, may account for excessive levels of caloric intake in overweight and obese individuals.

In a recent review on how deep brain stimulation might be beneficial to obesity treatment, Taghva, Corrigan, & Rezai (2012) have emphasized the amygdala as one of the key targets in the neuromodulation of obesity. The results of such clinical trials will probably bring new insights into the involvement of the amygdala in food intake and body weight regulation.

We will now present how the second key area of the anterior medial temporal lobes – the hippocampus – might relate to food intake and body weight regulation.

Hippocampus: Empirical evidence of its role in food intake and body weight regulation

Rationale for the interest in hippocampus in relation to food intake

To suggest a potential role of the hippocampus in food intake and body weight regulation may at first strike cognitive and affective researchers in human neuroscience as a somewhat unconventional idea. Although highly connected to the amygdala (Pitkänen, Pikkarainen, Nurminen, Ylinen, 2000), it has been claimed that the “removal of the hippocampus does not affect olfaction or taste” (Bogolepova, 1970, p. 857). However, “evidence exists for input to the hippocampus from the amygdaloid complex, implicating it in the processing of emotional

information and thus indirectly in interoceptive processes” (Cameron, 2002, p. 120). Moreover, there is accumulating evidence that “dietary factors are associated with the emergence of hippocampal pathology and that hippocampal pathology is associated with the emergence of increased food intake and body weight gain” (Kanoski & Davidson, 2011, p. 60; see also Kanoski & Grill, 2015; Parent, Darling, & Henderson, 2014). Three reviews (Davidson et al., 2005; Kanoski & Grill, 2015; Parent et al., 2014) on the hippocampus’ role in food intake have also highlighted the fact that its function in this context is more well-known than the amygdala’s (see also the last outstanding question).

We will argue that the integrity of the hippocampus is necessary for at least three functions related to food intake, namely (1) the use of interoceptive signals of hunger and satiety, (2) memory of prior food intake, and (3) inhibitory processes in the particular case of feeding.

Hippocampus and the use of interoceptive signals of hunger and satiety

The hippocampus expresses receptors for many peptide hormones related to appetite regulation. For instance, Hsu et al. (2015) have shown that ghrelin signaling in the hippocampus can stimulate conditioned appetite. Additionally, glucagon-like peptide-I (GLP-I) receptors in the ventral hippocampus also influence food intake and willingness to work to obtain food (i.e., “wanting”; Hsu, Hahn, Konanur, Lam, & Kanoski, 2015; Kanoski, Fortin, Ricks, & Grill, 2013). Furthermore, there is solid evidence showing that hippocampal neurons form a memory of a meal and inhibit meal onset after a meal has been consumed (Henderson, Smith, & Parent, 2013; Parent et al., 2014; Parent, 2016). These findings show that the hippocampus is a very likely target of the modulation exerted by interoceptive signal of hunger and satiety. Indeed, this

hypothesis has found empirical support, the hippocampus' response to taste stimuli is modulated by internal states of hunger (Haase, Cerf-Ducastel, & Murphy, 2011). It has been shown that after hippocampal lesions, rats were unable to use hunger and satiety cues to perform an internal state-conditional task (i.e., a task where a food-deprived state needs to be used as a contextual cue) (Davidson & Jarrad, 1993; Hock & Bunsey, 1998). These rats were unable to use their food-deprived state as a signal to consume food. However, this deficit did not extend to exteroceptive cues. Similarly, Hirsh, Leber, & Gillman (1978) and Kennedy & Shapiro (2004) have shown that hippocampal lesions impair the ability to use internal signals of hunger or thirst in rats. In a later experiment, Kennedy and Shapiro demonstrated that the hippocampus codes the relationship between an internal deprivation state of food/thirst, the memory of the external environment and the selection of a behavior leading to a decrease of the deprivation state (Kennedy & Shapiro, 2009). Just like H.M. consistently rated his internal states as 50, the Western diet⁴ reduces the sensitivity to internal signals of hunger, and especially of fullness ratings in humans (Francis & Stevenson, 2011). In accordance with an early suggestion from Jean Anthelme Brillat-Savarin (1825), maintaining that “gobbing without appetite is one of the most important causes of obesity” (p. 256), the inhibition of food intake by internal signals may be particularly problematic in the development/maintenance of obesity (Davidson et al., 2010). We will further discuss the importance of inhibitory processes in the third sub-part of this review dedicated to the hippocampus.

⁴ Western diet refers to a diet rich in saturated fatty acids and refined carbohydrates (e.g., Cordain et al., 2005). Its consumption has been linked with the current epidemics of obesity (e.g., Hu et al., 2001), as well as cognitive impairments (e.g., Kanoski & Davidson, 2011; Nilsson & Nilsson, 2009).

Hippocampus and memory for food intake

As alluded in the introduction, the hippocampus is well known for its role in declarative memory. This type of memory has been shown to influence food intake (e.g., Kanoski & Grill, 2015). Thus, the recall of previously eaten food leads to a decrease in subsequent food intake (Higgs, 2005). In contrast, the disruption of the encoding of the last meal leads to an increase in subsequent food intake (Higgs, 2008).

But it is not just our memory that influences food intake – both the quantity and the quality of what we eat influence our memory. Evidence of a link between food intake and impaired memory performance is accumulating (for a review, see Cordner & Tamashiro, 2015). First, for the case of an overly rich diet, such as the Western diet, it has been shown that feeding rats a high-fat diet alters working memory, even after only 3 (Kanoski & Davidson, 2010) or 9 days (Murray et al., 2009). This type of memory is impaired both in the short and long-term (Kanoski & Davidson, 2010). Furthermore, a Western diet leads to an impaired spatial memory in mice and rats (Darling, Ross, Bartness, & Parent, 2013; Magnusson et al., 2015; Underwood & Thompson, 2016). In human participants with a healthy BMI, the Western diet affects the ability to recall previously eaten food (Francis & Stevenson, 2011). More specifically, the quality rather than the quantity of fat ingested matters: a saturated fatty acids diet leads to an impairment of hippocampal activity (Sartorius et al., 2012), whereas this does not occur with an isocaloric monounsaturated fatty acids diet. This does not mean that quantity does not matter. For instance, impairments in declarative memory have been associated with a higher BMI (e.g., Cheke, Simons, & Clayton, 2016), where one might expect a higher consumption of saturated fatty acids. Second, for an overly poor diet, impaired learning and memory skills have been reported in prisoners of war with a history of malnutrition (Sutker, Allain, Johnson, & Butters, 1992;

Sutker, Vasterling, Brailey, & Allain, 1995). It should be noted that a very similar result has been reported in patients suffering from anorexia nervosa, which can be considered another form of malnutrition: visuo-spatial performance – typically considered to rely on the hippocampus – was impaired (Mathias & Kent, 1998). Third, the Western diet has been associated with smaller hippocampal volume (Jacka, Cherbuin, Anstey, Sachdev, & Butterworth, 2015). Finally, memory deficits associated with the consumption of a Western diet may also impact the timing of meals (i.e., the postprandial intermeal interval, see Parent et al., 2014), leading to increased meal frequency and size.

The relationship between food intake and memory performance is thought to be mediated by a dysregulation of hippocampal functioning (e.g., Higgs, Robinson, & Lee, 2012). Based on Francis & Stevenson's (2011) work, it appears that the impairment of the hippocampus functioning could occur without correlating with weight gain, at least in the early stages of obesity. One potential mechanism underlying this result may be the disruption of the hippocampal neurogenesis (see Lindqvist et al., 2006). As indicated above, the hippocampus expresses receptors for many peptide hormones related to appetite regulation, such as insulin. Interestingly, insulin could improve hippocampal-dependent memory function (McNay, 2007).

Similarly, the explicit memory of recently eaten food's impact on food intake amount is thought to be mediated by the hippocampus. Congruent with this argument, other types of food memories, such as sensory-specific satiety, are not impaired in amnesic patients (Higgs, Williamson, Rotshein, & Humphreys, 2008). Sensory-specific satiety can be defined as the implicit memory for consumed food items, characterized by a decrease in pleasure derived from recently consumed food items while other unconsumed food items are still pleasurable. Sensory-

specific satiety is mediated by the orbitofrontal cortex (Critchley & Rolls, 1996) and not by the hippocampus.

Hippocampus and inhibitory processes related to food intake

The reciprocal links between hippocampal functioning, food intake, and body weight regulation have notably been investigated by Davidson and colleagues (e.g., Davidson, Kanoski, Walls, & Jarrad, 2005; Davidson, Kanoski, Schier, Clegg, & Benoit, 2007; Kanoski & Davidson, 2011; Martin & Davidson, 2014; Sample, Martin, Jones, Hargrave, & Davidson, 2015), who focused on the role of the hippocampus in inhibitory learning and memory. Kanoski & Davidson (2011) highlighted how body weight regulation depends on the ability to solve a so-called “serial feature negative discrimination problem”, in which “interoceptive satiety cues (X) signal that environmental food-related target cues (A) will not be followed by an appetitive post-ingestive outcome” (p. 66). In other words, to maintain a constant body weight, it is necessary to suppress associations that are irrelevant in a given context, such as inhibiting the response evoked by cues previously associated with food in the absence of hunger signals. For instance, after a rich meal (i.e., in the absence of hunger signals), and in the presence of an appetizing food item, it is necessary to suppress the association between the consumption of this food item and positive post-ingestive consequences (in this instance, food consumption would likely cause the feeling of being uncomfortably full).

This ability is assumed to rely on the hippocampus. First, following hippocampal lesions, this ability is impaired (e.g., Holland, Lamoureux, Han, & Gallagher, 1999). Second, Sweeney & Yang (2015) have identified a likely brain substrate (i.e., glutamatergic projections from the ventral hippocampus to the lateral septum) for this type of inhibitory control. Coincidentally, the

ventral hippocampus is a key substrate for inhibitory control of approach tendencies within approach-avoidance paradigms (Schumacher, Vlassov, & Ito, 2016). One may conjecture that similar mechanisms are involved in the inhibition of approach tendencies under satiation. Third, the consumption of a Western diet leads to a decrease in GABA levels in the hippocampus, which may disturb inhibitory processes involved in food intake (Sandoval-Salazar, Ramírez-Emiliano, Trejo-Bahena, Ovideo-Solis, & Solís-Ortiz, 2016).

Kanoski & Davidson (2011) took this argument further in suggesting a “vicious circle” where the more the Western diet is consumed, the more impaired the hippocampus functioning is, and consequently, the more inhibition deficits occur, leading to even more consumption of Western-diet food (see also Hargrave, Jones, & Davidson, 2016). Impaired inhibition in overweight and obese individuals is hypothesized to affect food intake (e.g., Guerrieri, Nederkoorn, & Jansen, 2008). In line with this point of view, gastric stimulation in obese individuals activates primarily the right hippocampus, which correlates with a decrease in emotional and uncontrolled eating (Wang et al., 2006). In other words, activation of the hippocampus in obese individuals is linked to inhibitory processes related to food intake.

Summary and conclusion

We have presented evidence that the hippocampus is involved in the use of interoceptive signals of hunger and thirst, memory for previously eaten food and inhibition processes. Because of both its role in the use of interoceptive signals of hunger and thirst as well as in inhibition, an impairment of hippocampal activity may lead to a self-reinforcing vicious circle of unhealthy eating. And because of its role in memory and inhibition, the hippocampus may also be an

important structure for other food intake behaviors, such as guiding food decisions (see notably Wimmer & Shohamy, 2012).

We will now discuss the potential reciprocal links between food intake, body weight regulation and the interactions between amygdala and hippocampus functioning, and other parts of the brain that are involved in food intake.

Reciprocal links between food intake, body weight regulation, and amygdala and hippocampus functioning

Interactions between the amygdala and the hippocampus

As previously mentioned, the selfish brain theory (e.g., Peters, Kubera, Hubold, & Langemann, 2011) assumes that the brain (approximately 2% of the body's mass) gives priority to its energy needs (approximately 50% of the total body glucose utilization is related to its metabolism). The hippocampus/amygdala system is key in this process – it is assumed to be involved in energy homeostasis and metabolic processes (i.e., glucose fluxes; Swanson, 2000). Accordingly, the selfish brain theory assumes that obesity is “the sequelae of a dysfunction in the hippocampus/amygdala system” (Fehm, Kern & Peters, 2006, p.138). More specifically, obesity is purportedly associated with a change in the hippocampal set-point (i.e., the point where the energy needs of the brain are fulfilled and the energy stored in the rest of the body is stable).

But more specifically, how do the amygdala and hippocampus interact? Neuroanatomical and tract tracing studies from rodents have shown direct connectivity between these two brain regions. For instance, anterograde and retrograde studies have given a detailed map of the

interconnections between the amygdala and the hippocampus (see Pitkänen et al., 2000, in particular Figure 7). Different regions of the hippocampus (in particular the temporal end of the hippocampus) project to the amygdala in parallel in several of its different nuclei. Similarly, the amygdala's different nuclei project to different regions of the hippocampus in parallel (Bazelot et al., 2015; Lübke et al., 2015).

As parallel information flowing between the amygdala and the hippocampus is high, the deficits caused by a circumscribed lesion could be partially circumvented (Pitkänen et al., 2000). Several studies have however examined the limits of this parallel information flow – namely, how selective amygdala or hippocampus damage/lesions in rodents can affect food intake and body weight. As previously described, rats with selective neurotoxic lesions of the hippocampus (with no amygdala damage) were impaired at using food deprivation cues as signals for shock, while their use of external cues to solve this discrimination was unimpaired (Davidson & Jarrad, 1993). Additionally, Kesner & Williams (1995) gave amygdala, hippocampal, or control lesions to rats after performing a discrimination task between two objects; one associated with a food reward and the other associated with no food reward. Only amygdala-lesioned rats displayed deficits in this task. While hippocampal-lesioned rats were able to transfer this initial learning to other food rewards containing different amounts of sugar, the amygdala-lesioned rats were not able to perform this transfer. In contrast, Wheeler, Chang, & Holland (2013) have investigated the impact of amygdala and hippocampal lesions on mediated learning, namely, learning about a stimulus while it is not present, based on mental representations. They showed that amygdala lesions did not alter this type of learning, while hippocampal lesions did.

The amygdala and hippocampus interact at several levels, the following examples illustrate some of these significant interactions. First, the amygdala and the hippocampus are

associated with two different memory systems, which interact in significant ways, particularly in emotional situations (e.g., Phelps, 2004). For instance, the connectivity between the amygdala and the hippocampus is increased while individuals encode (e.g., Fastenrath et al., 2014) and retrieve (e.g., Smith, Stephan, Rugg, & Dolan, 2006) emotional material in comparison to neutral material. Second, glucose is known to have memory-enhancing effects, which are mediated via changes in hippocampal (e.g., Messier, 2004) and amygdala (e.g., Schroeder & Packard, 2003) activities. Interestingly, glucose also increases the functional connectivity between the amygdala and the hippocampus (Parent et al., 2011). Third, cued conditioning relies on the amygdala, but in the case of a conditioning relying on context, the hippocampus would additionally be recruited (Marschner, Kalisch, Vervliet, Vansteenwegen, & Büchel, 2008). Fourth, a lot of studies have shown that a stimulation of the amygdala enhances hippocampal-dependent memory and modulates the synaptic plasticity in the hippocampus (e.g., Abe, Fujimoto, Akaishi, & Misawa, 2009; Akirav & Richter-Levin, 2006; Frey, Bergado-Rosado, Seidenbecher, Pape, & Frey, 2001; Ikegaya, Saito, & Abe, 1995; Lovitz & Thompson, 2015; McGaugh, Cahill, & Roozendaal, 1996; McIntyre, McGaugh, & Williams, 2012; McReynolds, Anderson, Donowho, & McIntyre, 2014). Fifth, learning to suppress conditioned responses requires interactions between the hippocampus and the (basolateral) amygdala. More specifically, these interactions underlie latent inhibition, i.e. a slower acquisition of a conditioned response caused by repeated non-reinforced presentations of a conditioned stimulus, before the conditioning procedure actually starts (e.g., Coutureau, Blundell, & Killcross, 2001). Sixth, interactions between the hippocampus and the amygdala are purportedly important for contextual conditioning driven by food reward, although both structures could be complementarily and competitively involved in learning and memory tasks (Ito, Robbins, McNaughton, & Everitt, 2006).

It should be noted that we considered here the amygdala as an entity, although due to the existence of different sub-nuclei of the amygdala, it has been assessed as “*neither a structural nor a functional unit*” (Swanson & Petrovich, 1998, p. 323), and the label of “amygdaloid complex” has been suggested. This more fine-grained view (e.g., Wassum & Izquierdo, 2015) makes sense in terms of the functions we discussed here (e.g., Calandreau, Desmedt, Decorte, & Jaffard, 2005), but also in terms of architecture and connectivity (e.g., Pikkarainen & Pitkänen, 2001). For instance, different sub-nuclei of the amygdala underlie cue-induced feeding behavior and cue-induced inhibition of feeding behavior (Petrovich, 2011a). Current evidence points to the posterodorsal part of the amygdala as the most crucial for food intake regulation and weight gain in rats (Rollins & King, 2000). The nature of the interactions between the amygdala and hippocampus may consequently vary in different sub-parts of these structures and underlie different functions. In line with this notion, Huff, Emmons, Narayanan, & LaLumiere (2016) have shown that the basolateral amygdala interacts with the ventral hippocampus to modulate specific types of learning (e.g., footshock learning) but not others (here context learning).

This also suggests that similarly, the hippocampus may not be one entity (e.g., Ferbinteanu & McDonald, 2000; Henderson, Smith, & Parent, 2013; Kjelstrup et al., 2002; McHugh, Deacon, Rawlins, & David, 2004). For instance, while the ventral hippocampus has bi-directional connections to the amygdala, the dorsal hippocampus does not have any (Fanselow & Dong, 2010). Moreover, as mentioned before, GLP-I receptors in the ventral hippocampus, but not in the dorsal hippocampus, influence food intake and willingness to work to obtain food (Hsu, Hahn, Konanur, Lam, & Kanoski, 2015; Kanoski, Fortin, Ricks, & Grill, 2013). However, the respective roles of the ventral and dorsal hippocampus in meal onset are not currently known (Parent et al., 2014). This functional dissociation between the ventral and dorsal hippocampus

goes beyond food intake and body weight regulation contexts. For instance, in anxiety-inducing contexts, the ventral hippocampus fires more synchronously with the amygdala than the dorsal hippocampus (Likhtik, Stujenske, Topiwala, Harris, & Gordon, 2014).

Given the findings presented in this chapter, a better understanding of the interactions between the amygdala and the hippocampus may bring important insights into the mechanisms underlying food intake and body weight regulation. Moreover, interactions with other brain structures are also important to consider.

Connectivity between the amygdala and the hippocampus and other areas of the brain

Investigating how the anterior medial temporal lobes functionally relate to other parts of the brain is crucial to better understand the dynamics of cerebral dysfunctions and cognitive deficits which accompany food intake disorders such as obesity. In obese individuals, the connectivity between the amygdala and other key structures involved in food intake regulation deviates from the connectivity in lean individuals (Stoeckel et al., 2009). The differential direct and indirect connectivity between the amygdala and other important structures in food intake (e.g., caudate nucleus, hypothalamus, nucleus accumbens, ventromedial prefrontal cortex) may consequently contribute to excessive food intake and weight gain.

Regarding the hippocampus, it is known that its connection with the ventral tegmental area, a key component of the reward circuit, may be crucial for context-reward associations (Luo, Tahsili-Fahadan, Wise, Lupica, & Aston-Jones, 2011). The connectivity of the hippocampus may also change according to an individual's BMI. Recent work has shown that the hippocampal connectivity is decreased in obese individuals in comparison to healthy-weight individuals (Geha, Cecchi, Constable, Abdallah, & Small, 2016).

Conclusion

In this review, we have argued that the anterior medial temporal lobes – composed of the amygdala and the hippocampus - may play an important role in food intake and body weight regulation. The amygdala is essential to assess the relevance of food stimuli, and to cue-elicited feeding and cue-induced inhibition of feeding. In modern environments, where cues associated with feeding are much more present than cues associated with inhibition of feeding, the abundance of these cues may lead to overfeeding. The hippocampus is involved in tracking internal signals of hunger, memory, and inhibitory processes related to food intake. These functions (i.e., relevance of food stimuli, and to cue-elicited feeding and cue-induced inhibition of feeding for the amygdala and internal signals of hunger, memory, and inhibitory processes related to food intake for the hippocampus) complement the functions of the amygdala as a relevance detector and of the hippocampus as involved in memory and inhibition. A better understanding of the role of these two structures in food intake and body weight regulation may bring insights into the dynamics of cerebral dysfunctions and cognitive deficits that accompany food intake disorders such as obesity. Listed below are some of the issues that appear to be particularly critical for the future of the research in this field.

Outstanding questions

Are the anterior medial temporal lobes also crucial for representing *future food intake*? Information related to recent eating is encoded in memory and influences future food intake (e.g., Higgs, 2005, 2008; Higgs, Robinson, & Lee, 2012). The hippocampus encodes

information relative not only to past events but also to future ones (Squire et al., 2010). The amygdala is involved in representing future positive events (Sharot, Riccardi, Raio, & Phelps, 2007). From this evidence the following question follows: Can hippocampus and amygdala dysfunctions relate in difficulties representing future food intake and steady decision-making related to future food intake? This question seems all the more relevant since the links between obesity and decision-making processes are still relatively poorly understood (e.g., Rangel, 2013; Wu et al., 2016) and may lead to fruitful therapeutic interventions. Moreover, Vartanian, Chen, Reily, & Castel (2016) have recently shown that thinking about *future* food intake suppresses eating, similar to *past* food intake, and that the mechanisms underlying this effect need further investigation.

Is it possible to reverse the effects of “vicious circle” between an excessive Western diet consumption, increased body weight, and cognitive impairment? According to Kanoski and Davidson (2011), “if the degree of interference with hippocampal function increases with the duration of exposure or the amount of Western diet consumed, this could lead to a “vicious circle” [...] in which continued eating leads to greater impairment of hippocampal-dependent memory function which further weakens the ability to inhibit intake of the Western diet that promoted hippocampal dysfunction in the first place” (p.66). To what extent can this “vicious circle” be reversed? In other words, can weight gain in individuals suffering from anorexia nervosa and weight loss in obese individuals restore (i) hippocampus functioning? and (ii) cognitive functioning? Inverting the question also seems relevant: Can memory skills training in individuals suffering from anorexia nervosa and in obese individuals restore (i) hippocampus functioning? and (ii) lead to weight gain in individuals suffering from anorexia nervosa and

weight loss in obese individuals? (see Smith, Hay, Campbell, & Trollor, 2011 for a discussion on this topic).

The answer to these questions may open avenues for therapy, which its importance is underscored by the difficulty of long-term weight stabilization in individuals suffering from anorexia nervosa (Steinhausen, 2002) and losing and stabilizing weight in obese individuals and post-obese individuals (Kramer, Jeffery, Forster, & Snell, 1989), respectively.

Does the link between the Western diet and memory impairment depend on the integrity of sleep and hippocampal neurogenesis? Sartorius et al. (2012) have shown that a diet rich in saturated fatty acids (such as the Western diet) impairs sleep behavior in mice. Among the different functions of sleep, its importance for memory has been underlined (Diekelmann & Born, 2010). Hippocampal neurogenesis, on which hippocampus-dependent memory relies (Winocur, Wojtowicz, Sekeres, Snyder, & Wang, 2006), may notably depend on Rapid Eye Movement (REM) sleep (Mueller, Mear, & Mistlberger, 2011). The following question emerges: By consuming an excessive amount of the Western diet, could a perturbation in REM sleep occur, thus leading to altered hippocampal neurogenesis, which in turn impairs memory function? This question seems to be relevant given the bidirectional links between sleep and obesity (Chen, Beydoun, & Wang, 2012).

Are there sub-types of obesity for which memory functions are differently affected? Insulin sensitivity is linked to both obesity and performance in a hippocampus-dependent memory task (Benedict et al., 2011; Gonzales et al., 2010). While we have considered obese individuals as a homogenous group thus far, this classification was purely based on BMI, although both the root causes and the associated symptoms may in fact differ between

individuals. Different sub-types of obesity exist, in particular with regard to insulin resistance – some obese individuals remain insulin sensitive while others develop insulin resistance (Stingl et al., 2012). Do these sub-groups perform differently in a hippocampus-dependent memory task, and more generally, have different cognitive functioning? This question has been raised by Stingl et al., but has not been yet addressed.

Does a Western diet impact amygdala functioning in similar ways as hippocampal functioning? This review has offered an overview of what is currently known on the effects of a Western diet on hippocampal functioning. However, we have not discussed how these effects may also apply to amygdala functioning. For instance, hippocampal and amygdala functioning are similarly affected by the amount of time individuals have been exposed to a Western diet. More specifically, it has been shown that a Western diet impacts hippocampal (Boitard et al., 2012) and amygdala functioning (Boitard et al., 2015) more in the juvenile period than in the adult period. They found similar results for amygdalian functioning. However, while this consumption impairs hippocampal-dependent memory, it may *increase* the amygdala-dependent one (Reichelt et al., 2015). Moreover, the impact of a Western diet is faster on hippocampal functioning than on amygdala functioning, as the hippocampal functioning changes earlier than the amygdalian one (Boitard et al., 2012, 2015). It is however not currently known to what extent the hippocampal functioning's change may drive the amygdalian one. Thus, further research investigating similarities and differences caused by a Western diet on hippocampal and amygdalian functioning may lead to important discoveries about the anterior medial temporal lobes.

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Fig. 3 Probabilistic maps of the amygdala, hippocampus and entorhinal cortex in anatomical MNI space (x , y and z coordinates indicate distances from the anterior commissure (AC) in mm in the medio-lateral, rostro-caudal and dorso-ventral directions, respectively). The left hemisphere is indicated by negative coordinates. Left hemisphere is at the left in the image. The frequency with which an actual anatomical structure was present in the sample of ten brains is colour coded. The scale at the bottom of this figure indicates the degree of overlap in each voxel. *Blue colour* (1) shows that only one brain is represented with its actual structure, *red colour* (10) shows that all ten brains are overlapping

Fig. 1 Cytoarchitecture of the amygdala and neighboring cortical and subcortical structures in a coronal section of a human postmortem brain. The centromedial nucleus is labelled by an *orange line* and the basolateral complex by a *red line*. The *VCo* belongs to the superficially located part of the amygdala. *BL* basolateral nucleus,

BM basomedial nucleus, *BV* basoventral nucleus, *Ce* central nucleus, *La* lateral nucleus, *Me* medial nucleus, *VCo* (ventral) cortical nucleus. Neighbouring structures: *Ci* Claustrum, *Ent* entorhinal cortex, *F* endorhinal sulcus, *Hi* hippocampus, *NbM* Nucleus basalis of Meynert, *TrO* Tractus opticus, *V* lateral ventricle

Figure 1. Representations of the different amygdala nuclei. Figures from Amunts et al. (2005).

*** To the editor: These are 2 suggestions for a figure. Copyright needs to be asked.***