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Sensations hédoniques impliquées dans le contrôle de la prise alimentaire chez l'homme :

Alliesthésie alimentaire et Rassasiement sensoriel spécifique

Hedonic sensations implicated in the control of human food intake:

Alimentary alliesthesia and sensory-specific satiety

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„Alle Wahrheit durchläuft drei Stufen. Zuerst wird sie lächerlich gemacht oder verzerrt. Dann wird sie bekämpft. Und schließlich wird sie als selbstverständlich angenommen."
-- unbekannter Author (Arthur Schopenhauer zugeschrieben)

"All truth passes through three stages: First it is ridiculed or distorted. Then it is violently opposed. And finally it is accepted as being self-evident."
-- unknown author (attributed to Arthur Schopenhauer)

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I.1. Summary

The control of food intake is a complex and multifactorial process controlled by the CNS. It is implicated in the regulation of body weight and the supply of energy substrates, as well as the supply of a panoply of nutrients to cover the specific needs of the organism. Among all the factors involved, hedonic sensations play an important role in guiding food selection and limitation of intake.

The theoretical section of this thesis takes into account the physio-anatomical aspects of the control of food intake, in particular sensory pleasure and its evaluation, within the framework of the three principal hedonic phenomena: Conditioned Satiety (CS), Alimentary alliesthesia (AA) and sensory-specific satiety (SSS).

The experimental section evaluated the impact of various manipulations of food (adding non-caloric and caloric condiments to simple or prepared foods, offering condiments successively or simultaneously, alternating foods in a meal) on hedonic sensations and on food intake in the short term. Four studies were performed in normal-weight and overweight human subjects of both genders.

The first study in three experiments in simple foods suggests that specific satiation and energy intake depend on the sensory properties of foods and thus on the sensory stimulation exerted on oropharyngeal receptors. Under the present experimental conditions, the influence of SSS turned out to be more important than that of AA in limiting specific intake. However, this limitation by SSS could be overridden by modification of the sensory properties of the food eaten to specific satiation: in parallel with the re-increase in pleasure for the flavor, food intake was resumed when a second food with distinctive flavor was offered or when non-caloric condiments were added.

The second study re-examined the data of the first one according to anthropometric and demographic characteristics of the population and provided evidence for similar hedonic control of food intake in obese and normal weight persons with simple unseasoned and unprocessed foods. These results suggest that the nature and the presentation of food stimuli impacted food intake more than person-related traits like gender, age or BMI.

The third study induced successive and simultaneous sensory variety by adding condiments to 'fast food' style meal, and increased food pleasantness and intake. Successive variety was more efficient in increasing intake than simultaneous access to condiments. These results seem to show that renewal in sensory stimulation produces disruption of sensory-specific satiety which may explain the increase of food intake and might be playing a role in the actual obesity epidemic.

The fourth study investigated the impact of several levels of alternation of foods. Moderate alternation in a two-course meal increased food intake in the short term, probably by disruption of sensory tuning to a given flavor and may explain the increased intake with sensorily varied meals. Multiple alternations of foods however decreased intake, probably caused by sensory overstimulation.

SSS seems to have two opposite intrinsic teleonomies: on the one hand it specifically limits intake of foods eaten, while on the other hand it promotes variety seeking. In this thesis, both functions could be manipulated through simple modifications of the sensory properties of foods or of the way they were offered. In the long term, these kinds of manipulations might compromise a body-mass index medically considered as healthy.

The modification of the flavor alone was sufficient to increase pleasure and in turn food intake. The prolongation of intake of the same food when offered with two distinct flavors seems to be related to cerebral representation as two distinct foods. The question on whether sensory pleasure is a sign of usefulness of food stimuli or mere sensory stimulation of the chemical senses may ultimately depend on the nature of the food stimulus.

I.1.1. Keywords

I.2. Résumé

Le contrôle de la prise alimentaire est un processus complexe et multifactoriel contrôlé par le système nerveux central. Elle est impliquée dans la régulation du poids corporel, la fourniture de substrats énergétiques ainsi que dans l'apport d'un grand nombre de nutriments nécessaires pour couvrir les besoins spécifiques de l'organisme. Parmi tous les facteurs impliqués dans la prise alimentaire, les sensations hédoniques jouent un rôle important dans les choix alimentaires et la limitation de l'ingestion.

La partie théorique de cette thèse prend en considération les aspects physio-anatomiques du contrôle de la prise alimentaire, notamment le plaisir sensoriel et son évaluation, dans le cadre des trois phénomènes hédoniques principaux : le rassasiement conditionné (RC), l'alliesthésie alimentaire (AA) et le rassasiement sensoriel spécifique (RSS).

La partie expérimentale tente d'évaluer l'impact des diverses manipulations des aliments (ajout de condiments non-caloriques ou caloriques aux aliments simples et aux mets préparés, offrir des condiments de manière successive ou simultanée, alternance des aliments dans un repas) sur les sensations hédoniques et sur la prise alimentaire à court terme. Quatre études ont été réalisées chez des sujets humains des deux genres, de poids normal et en surpoids.

La première étude comprenait trois expériences avec des aliments simples suggérant que le rassasiement spécifique et la prise énergétique dépendent des propriétés sensorielles des aliments et donc de la stimulation sensorielle exercée sur les récepteurs oro-pharyngiens. Dans les conditions expérimentales présentes, l'influence du RSS s'est avérée plus importante que celle de l'AA dans la limitation de l'ingestion spécifique. Toutefois, cette limitation par le RSS a pu être repoussée par la modification des propriétés sensorielles de l'aliment consommé jusqu'au rassasiement spécifique : en parallèle avec la re-augmentation du plaisir pour la saveur, l'ingestion était repris lorsqu'un deuxième aliment de saveur distincte était offert, ou lorsque des condiments non-caloriques étaient ajoutés à l'aliment consommé.

La deuxième étude reprenait les données de la première en fonction des caractéristiques anthropométriques et démographiques des sujets et mettait en évidence un contrôle hédonique de la prise alimentaire similaire chez les personnes obèses et de poids normal avec des aliments simples non assaisonnés et non transformés. Ces résultats suggèrent que l'impact de la nature et de la présentation des stimuli alimentaires sur la prise alimentaire peut être plus important que celui des traits liés aux personnes, comme le sexe, l'âge ou l'IMC.

La troisième étude introduisait une diversité alimentaire soit successive soit simultanée par ajout de condiments à un repas de type « fast food », avec pour effet une augmentation du plaisir alimentaire et des quantités ingérées. La diversité successive a été plus efficace sur l'augmentation de l'ingestion que l'accès simultané aux condiments. Ces résultats laissent penser que le renouvellement de la stimulation sensorielle produirait une perturbation du rassasiement sensoriel spécifique, expliquant l'augmentation de la consommation et pouvant jouer un rôle dans l'actuelle épidémie d'obésité.

La quatrième étude évaluait l'impact de différents niveaux d'alternance des aliments. Une alternance modérée dans un repas comprenant deux plats différents augmentait la prise alimentaire à court terme, probablement par suite d'une perturbation de l'habituation sensorielle à une saveur donnée, apportant une explication à l'augmentation de l'ingestion avec des repas sensoriellement variés. Des alternances multiples des aliments diminuaient en revanche la consommation, probablement par l'effet d'une surstimulation sensorielle.

Le RSS semble avoir des téléonomies intrinsèques opposées : d'une part, il limite spécifiquement l'ingestion d'aliments récemment consommés ; d'autre part, il favorise la diversification de la prise alimentaire. Dans cette thèse, les deux fonctions ont pu être manipulées par des modifications des

qualités sensorielles des aliments ou de leur présentation. A long terme, ce type de modifications pourrait entraîner une dérive de la norme considérée médicalement comme saine de l'indice de masse corporelle.

La modification de saveur s'est avérée suffisante pour augmenter le plaisir et par suite la prise alimentaire. La prolongation de l'ingestion d'un même aliment, lorsque celui-ci est présenté sous deux saveurs différentes, pourrait être liée à la représentation cérébrale de deux aliments différents. La question de savoir si le plaisir sensoriel serait un signe d'utilité des stimuli alimentaires ou se limiterait à une simple stimulation des sens chimiques pourrait finalement dépendre de la nature du stimulus alimentaire.

I.2.1. Mots-clés

Prise alimentaire, régulation, hédonisme, rassasiement sensoriel spécifique, alliesthésie alimentaire, obésité, olfaction, goût

II. PHYSIOLOGIC CONTROL OF FOOD INTAKE BEHAVIOR

II.1. Introduction

Understanding the theoretical foundations of the control of food intake including among others anatomy of the central nervous system, regulatory systems and the role of the hedonic functions is crucial for the understanding of body weight regulation, nutritional issues, and obesity. Food intake-related behavior describes the sum of conducts of an individual concerning food consumption. It has three principal physiological functions [1,2,3]:

1, supply of metabolizable energy substrates for the cells of the organism;

2, supply of biochemical compounds as building blocks for the cells of the organism.

3, supply of biochemical substances capable of antagonizing pathogenic agents

The purpose of this introductory chapter on the control of food intake behavior is to give the reader an insight into the physiology of the organization of food intake, including the anatomical structures, neurotransmitters and derived phenomena or functions implicated in its regulation.

II.2. 'Regulation' or 'Control' of food intake?

In the literature on food intake, both terms, regulation and control, can be found. Therefore, the question arises as to which components of food intake behavior are regulated and which are controlled.

II.2.1. Regulation

Classically, regulation[1] [4] is the property of a system with a negative feedback loop minimizing the variations that participation can produce on a given variable. The domination of outputs by a positive feed-forward can also determine a regulation [4].

The concept of internal regulation in physiology is attributed to Claude Bernard[2] [5, 6] and later Walter Bradford Cannon[3] [7,8,9]. Bernard was the first to understand blood as an internal environment which supplies nutrients to all cells of an organism just as the primordial soup [10] did to monocellular life forms. Regulation, *i.e.* maintenance of the internal environment at a constant level is a major responsibility for all vital functions [11]. This concept led to the concept of homeostasis, *i.e.* the self-regulation of vital processes [12].

Since the 1960s, the term regulation has been used to indicate "the maintenance of a steady state through physiological mechanisms which themselves depend on receptors detecting change in the steady state" [13]. In this way, the notion of 'regulation' comprises the description of the regulated physiological phenomenon as a whole. Thus the regulation of food intake comprises both the central regulation of this behavior, the effects of food intake upon multiple processes (digestion, metabolism, energy homeostasis) and physiological variables (plasma glucose, hormone secretion, plasma hormone levels, energy stores), and the feedback mechanisms involved [2,14,15].

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[1] 'to regulate' is a neologism derived from 'regulation', indicating the action of a regulation. This verb is different from 'to rule' which indicates the action of adjustment. (*lat. regulare* – to rule)

[2] Claude Bernard (*1813 – †1878), French physiologist

[3] Walter Bradford Cannon (*1871 – †1945), American neurologist and physiologist

In 1982, Cabanac et Russek stated that a regulated system is always thermodynamically open and comprises closed loops in which energy and matter in- and output are controlled by information on the regulated variable. The steady state of this variable resists permanent perturbations. Regulated systems have an inherent 'purpose', 'finality' or 'teleonomy' [16,17] which is to maintain the value of the regulated variable in the steady state. In the case of regulated biological systems, this teleonomy is the result of a long evolutionary process. The teleonomy of living organisms is their survival when facing challenges and changes of the environment. In other words, it is to maintain their steady state or 'homeostasis'.

A regulated variable therefore is kept within a certain margin. All physiological constants such as pO_2, blood pressure, glycemia, *etc*. are regulated variables [4].

II.2.2. Control

When only one independent variable x determines the value of a dependent variable y, then x controls[4][22] y [23]. The term 'control' can be used as the influence that information exerts from the regulated variable on the input and/or output of a regulating system [4].

Homeostatic control mechanisms consist of at least three components: a receptor, a control center and an effector. The receptor is tuned to a given variable. Whenever it senses a change, it will send a signal to the control center (the brain in most homeostatic mechanisms), which determines 1, at which range the variable is maintained and 2, a response to the stimulus. It then sends a signal to the effector, which in turn modifies the value of the variable [18].

In 1960, Brobeck put forward the hypothesis that control corresponds to the "management of a rate of functioning" [13]. Cabanac stated in 1982 that a controlled variable varies when the system is perturbed, it can be maintained at a new level in order to preserve the regulated variable constant. For example, pulmonary ventilation is controlled to regulate pO_2 and pCO_2. Cardiac frequency and arteriolar diameter (*i.e*., peripheral cardiovascular resistance) are controlled to regulate arterial blood pressure [4].

In his publications of 2002 and 2004, Daddoun argued that the term 'control' usually refers to "the factors or physiological process that influence a physiological phenomenon". Thus, food intake behavior is under the physiological control of the CNS, and numerous central and peripheral factors intervene in such a control or alter this control [2,14,15].

II.2.3. Regulation versus Control

In 1976, Bell, reviewing the regulation of food intake, appreciated that 'regulation' and 'control' are not alternatives [19]. In the same way, Cabanac *et* Russek stated in 1982 that the terms 'regulation' and 'control' are not synonyms and therefore not interchangeable [4].

However, the difference is mostly a matter of semantics, and when authors refer to the 'control of food intake' or to the 'regulation of food intake', they usually refer to the same physiological process or phenomenon [2,14,20].

In 2000, Cabanac noted that the animal organism can be described as a series of regulatory systems of increasing complexity, from biochemical intracellular regulations to behavioral regulations that affect the entire body. The subsystems of in- and output can be described by mathematical functions or by physiological functions controlled by the regulated variable. In contrast, the systems that regulate through control of behavior can be considered as thermodynamically open only during the duration of the behavioral response and sometimes during the ensuing period [21].

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[4] Etymology: *Lat. contrarotulus* (*contra* – against; *rotulus* – roll); to check, test, or verify by evidence or experiments; to have power over: to rule

According to Finlayson *et al.*, strictly speaking, we should refer to the control of food intake whose expression is modulated in the interests of the regulation of body weight. In other words, behavior, and as such food intake, is controlled, while body weight is regulated [20].

II.3. Energy homeostasis

Food intake, like the majority of vital physiological processes, obeys the principle of homeostasis and is a finely controlled behavior. Its regulation aims to ensure 1, energy balance, and 2, constancy of energy reserves (body-fat mass and liver glycogen).

Energy homeostasis aims to ensure energy balance and thus represents the principal factor in the control of food intake. The control of food intake represents only one of the elements of energy homeostasis, of which the 2nd component, energy expenditure, takes place in a coordinated and schematically opposite way.

The regulation of the level of energy reserves and thus of body-fat mass has been demonstrated through many experiments carried out in animals and humans showing that following a period of energy restriction, the behavioral response is an increase in food intake. On the other hand, if body fat mass is increased after a period of forced overfeeding, a compensatory reduction in food intake occurs until restoration of the prior level of body-fat mass [24,25]. The level of energy reserves is stable in the long-term for a given individual, but this level is variable between individuals, and for a single individual can vary over a lifespan.

II.4. CNS Centers of food intake control

Food intake behavior is controlled by the central nervous system (CNS).

II.4.1. The hypothalamus

The principal regulatory centers have been found within the hypothalamus [26,27,28,29,30,31].

Experiments of the 1940s and 1950s showed that electric stimulation and specific lesions of hypothalamic areas modify food intake. These experiments led to the assumption of the existence of a 'feeding centre' (lateral hypothalamus, LH) and a 'satiety centre' (ventromedial nucleus hypothalami, VMN) [32,33,34,35,36].

However, this traditional view of the hypothalamus as integrating the influences of two opposing centers has lost ground because of several findings:

1, the hypothalamus acts by signaling a body weight set point and hypothalamic damage affects this set point [37],

2, selective experimental bilateral destruction of one of these "feeding control centers" also destroyed passing pathways [37],

3, the progressive discovery of neuronal populations, neuronal circuits, neurotransmitters and receptors which mediate effects on food intake [2,38,39];

These neurons receive and integrate information on energy status of the organism from afferent nerves and humoro-hormonal pathways, ensuring accurate adaptation of intake to needs [2]. Their functional importance, interactions and physiological role, however, still remain far from being entirely understood.

1. Hypothalamic nuclei participating in food intake regulation
According to histoanatomical structure, several hypothalamic nuclei have been described (Figure 1).
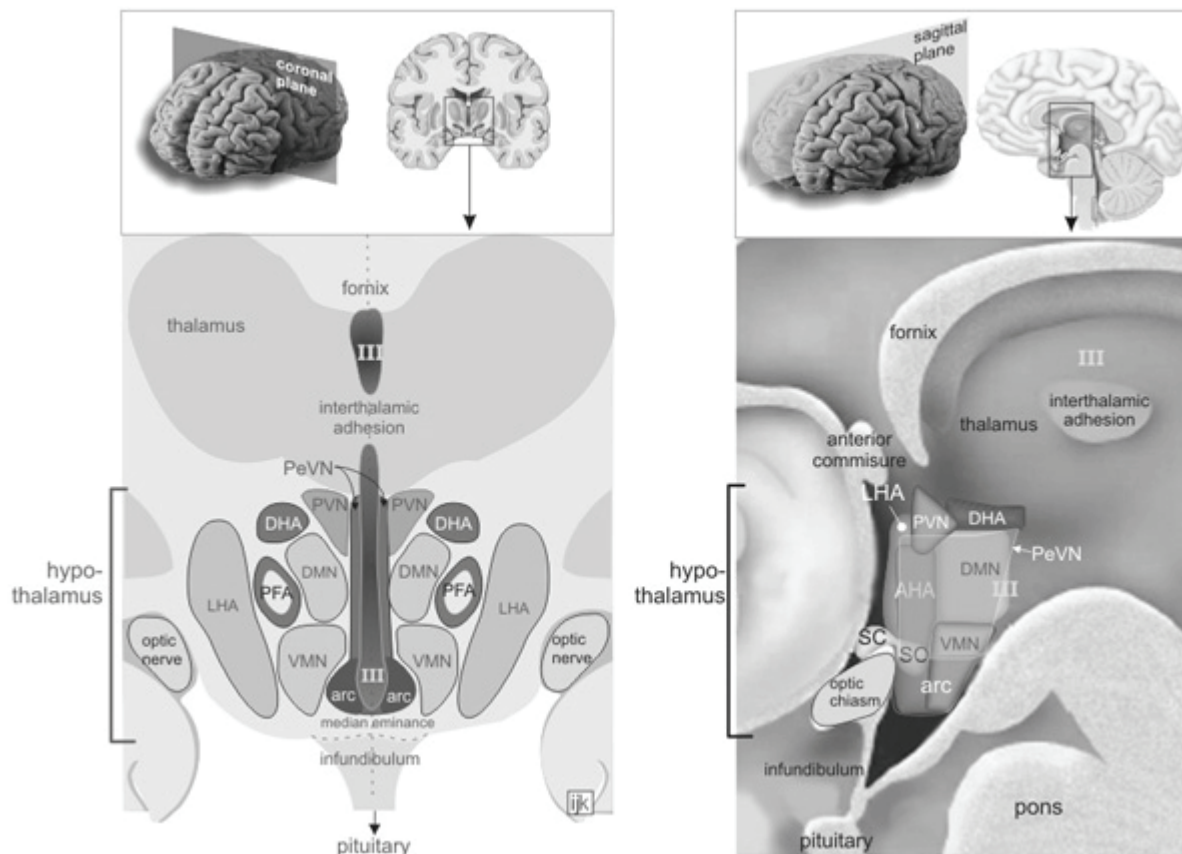
Figure 1. Anatomical localization of the hypothalamic nuclei.

Coronal (left) and saggital (right) section of the human brain. Abbreviations: arc, arcuate nucleus, DHA, dorsal hypothalamic area, DMN, dorsomedial nucleus, LHA, lateral hypothalamic area, PeVN, periventricular nucleus, PFA, parafornicular nucleus, PVN, paraventricular nucleus, VMN, ventromedial nucleus, SO, supraoptic nucleus, SC, surprachiasmatic nucleus. Arc and PeVN are drawn transparently in the sagittal section in order to show the underlying nuclei. From: [40]

Arcuate nucleus (ARC)

The arcuate nucleus (lat. *Nucleus arcuatus*, ARC) is considered as the primary integrative center of the hypothalamus and contains POMC and NPY/AgRP neurons [41]. For the following reasons, the ARC plays a fundamental role in the signalization of peripheral messages to the other structures:

• It is located between the 3rd ventricle and median eminence (lat. *Eminentia mediana*), an area with a relatively porous blood–brain barrier enabling hypothalamic nutrient sensing of extracellular nutrients (circulating in the plasma) for which the blood-brain barrier is impermeable [41].

• It is the only zone of the hypothalamus that expresses fatty acid synthase; therefore, it is sensitive to intermediary metabolites of fatty acid metabolism.

• It expresses key neuronal populations in the regulation of food intake behavior: neurons expressing orexigenic substances neuropeptide Y (NPY) and Agouti-gene related peptide (AgRP), as well as the anorexigenic substance proopiomelanocortin (POMC). POMC is a precursor of α-MSH and cocaine and amphetamine related transcript (CART) which are anorexigenic substances [14]. POMC is sensitive to numerous hormones or neuromediators (Figure 2).
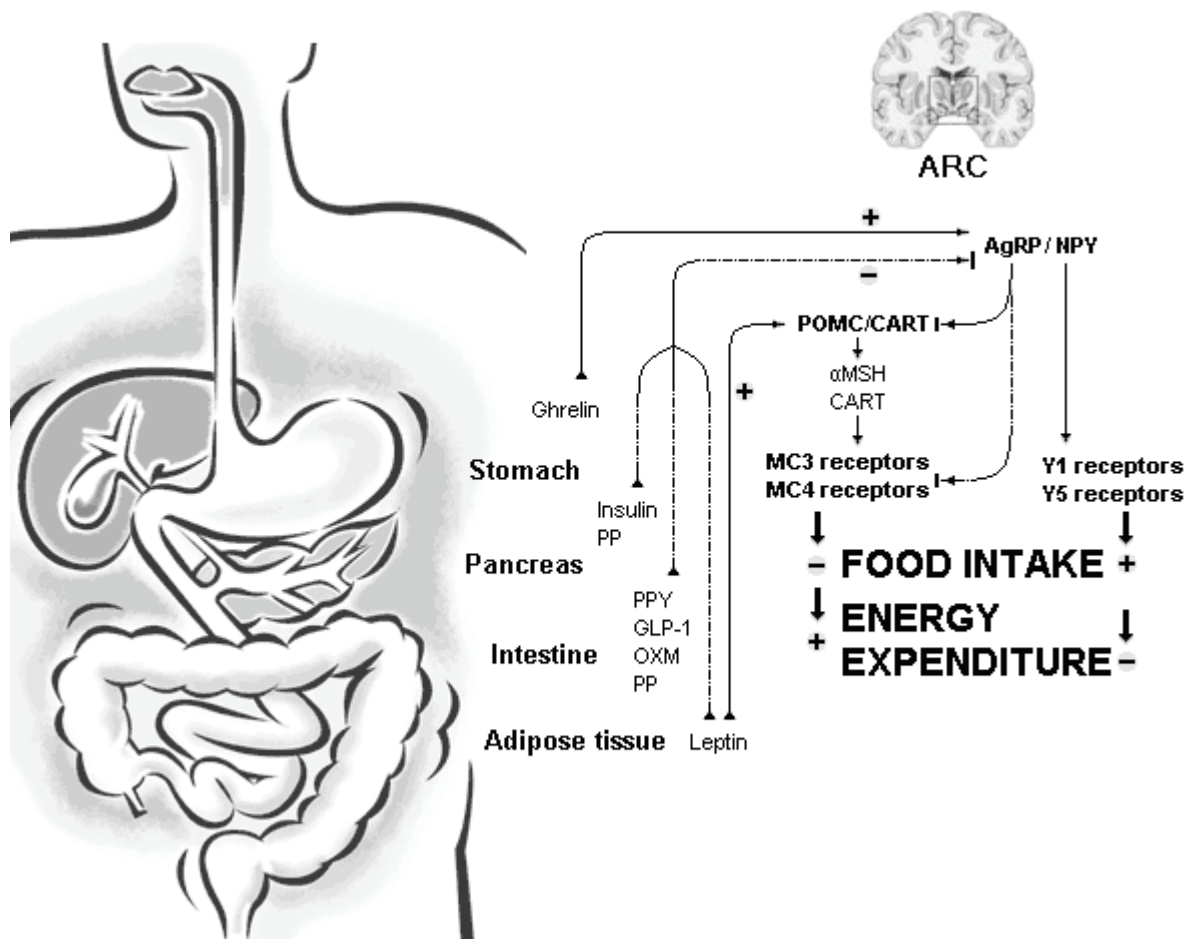
Figure 2. Hormones influencing the arcuate nucleus.

Continuous lines: stimulatory effects, dashed lines: inhibitory effects. AgRP, agouti-related peptide; CART, cocaine-and amphetamine-related transcript; GLP-1, glucagon-like-peptide 1; αMSH, alpha-melanocyte-stimulating hormone; NPY, neuropeptide Y, OXM, oxyntomodulin; POMC, pro-opiomelanocortin; PP, pancreatic polypeptide; PYY, peptide YY. Modified after: [42]

Paraventricular nucleus (PVN)

The paraventricular nucleus (PVN, lat. *Nucleus paraventricularis*) is an integrating center that receives projections of NPY/AgRP and POMC/CART neurons and is rich in endings containing neurotransmitters implicated in the modification of appetite [43].

Ventromedial nucleus (VMN)

The ventromedial nucleus (VMN, lat. *Nucleus ventromedialis*), for a long time considered as the 'satiety center', is rich in leptin receptors [44].

Dorsomedial nucleus (DMN)

The dorsomedial nucleus (DMN, lat. *Nucleus dorsomedialis*) contains insulin and leptin receptors and plays a role in the initiation of food intake [44].

Lateral hypothalamus (LH)

The lateral hypothalamus (LH, lat. *hypothalamus lateralis*), in the past considered the 'feeding centre', is an area involved in the control of motivational state and reward [361]. It contains NPY receptors and glucose-sensitive neurons [43].

2. *Hypothalamic participation in energy homeostasis*

The various nuclei above cited synthesize or are sensitive to numerous neuromediators and neurotransmitters. At the hypothalamic level, these affect food intake and body weight. These data have emerged through many studies where such molecules were administered centrally or their activity was modified by pharmacological or genetic manipulations [2].

In addition, these neurons receive information from the periphery of either hormonal (leptin, insulin, ghrelin) or metabolic nature in particular *via* intermediary glucose sensing neurons whose activity is modulated by variations in glycemia or levels of circulating free fatty acids.

Neurons sensitive to glucose (glucosensing neurons)

The neurons sensitive to glucose are neurons that do not use glucose as an energy substrate, but as a signal modifying cell function and neuronal activity [14]. The importance of these neurons was stressed by the demonstration of obesity induced by aurothio-glucose which selectively destroys gluco-sensitive neurons of the ventromedial hypothalamus. These neurons are disseminated in hypothalamic areas involved in energy regulation and contain leptin and insulin receptors, they are also sensitive to other circulating metabolites like free fatty acids. NPY- and POMC-neurons seem to be prototypes of this class of neurons.

Furthermore, these neuronal populations interact in an antagonistic or synergistic fashion (Figure 2), allowing short- and long-term adaptation. These interactions allow adaptation even in the case of deficit in one of the circuits. However, this adaptation seems to be more precise in situations of energy deficiency than in situations of energy excess.

3. *Hypothalamic Neuromediators /-modulators implicated in energy homeostasis*

Orexigens and anorexigens

A certain number of neuronal populations are engaged in the regulation: NPY/AgRP, POMC/CART, and the orexins (Table 1). Their regulation and their precise roles are not yet perfectly known, in particular in humans.

Table 1. Hypothalamic neurotransmitters involved in the control of food intake.
From: [14]

Neuromediators stimulating food intake	Neuromediators inhibiting food intake
Monoamines • Noradrenaline (α_2) • Gamma-amino-butyric acid (GABA)	**Monoamines** • Noradrenaline (β) • Gamma-amino-butyric acid (GABA) • Serotonin (5-HT) • Dopamine • Histamine
Neuropeptides • Agouti-related peptide (AgRP) • Endocanabinoids • Galanine • Ghrelin • Growth hormone-releasing hormone (GHRH) • Melanin-concentrating hormone (MCH) • Neuropeptide Y (NPY) • Orexins (A and B) • Opiate peptides	**Neuropeptides** • Amyline, Bombesin • Calcitonin-gene related peptide • Cholecystokin (CCK) • Corticotropin-releasing hormone (CRH) • Glucagon-like peptides (GLP-1, GLP-2) • α-melanocyte-stimulating hormone (α-MSH) • Neurotensine, Ocytocine • Cocain-amphetamine regulated transcript (CART) • Somatostatine • Thyrotropin-releasing hormone (TRH) • Urocortine

4. NPY

NPY is a neurotransmitter of 36 amino acids. It is widely distributed in the brain (for review see [45]). The principal hypothalamic site of NPY is the *arcuate nucleus* (where 90% of the neurons also contain AgRP). NPY is the most powerful known orexigen. It also acts by decreasing energy expenditure. Synthesis and release of NPY in the hypothalamus are controlled by hormonal factors: it is inhibited by insulin and leptin and is stimulated by ghrelin and glucocorticoids. The hyperphagic response to NPY is mediated by various receptors distributed over the hypothalamus. Six different receptors have been identified; the isoforms Y1 and Y5 are involved in the orexigenic effect, whereas receptors Y2 and Y4 exert a negative retro-control of NPY-release.

However, the presence of NPY is not essential for the hyperphagic response to a fast, as attested by a normal response of NPY knock-out mice [46].

5. α-MSH, AgRP and MC4-R

The melanocotines are a peptide family deriving from proopiomelanocortin (POMC), which is synthesized in the *nucleus of the solitary tract* and in the *arcuate nucleus* [14]. The melanocortins include ACTH, secreted by the *antehypophysis*, and α-MSH synthesized in the POMC-neurons of the *arcuate nucleus*. These peptides bind to the melanocortin receptors (5 sub-types: MC1-R to MC5-R). MC1-R relays the pigmentogenic action of ACTH and α-MSH on skin and hair. MC2-R is the ACTH receptor and regulates synthesis and secretion of the adrenal glucocorticoids.

MC4-R receptors are expressed in the hypothalamus (NPV and NDM). α-MSH and Agouti gene-related peptide (AgRP) are the ligands for the MC4-R receptor. α-MSH is an agonist of the MC4-R receptor inhibiting food intake and thus has an anorexigenic effect.

This 'MC4-R pathway' brings into play two populations of neurons of the *nucleus arcuatus*: neurons synthesizing POMC and its fragment α-MSH, and neurons synthesizing AgRP [39].

AgRP is a natural antagonist of the MC4-R receptor. It stimulates food intake by blocking the anorexigenic action of α-MSH. POMC- and AgRP-neurons both express the leptin receptor. POMC and AgRP are controlled by leptin in an opposed fashion. These neuropeptides constitute two additional effectors of the inhibitory actions of leptin on food intake. The two neuropeptides are also controlled in an opposed way by fasting and food intake. In MC4-R receptor gene knock-out mice, the over-expression of the AgRP gene provokes major obesity. Mutations of the MC4-R receptor in humans lead to increased food intake and massive obesity. Mutations of the POMC gene cause adrenal insufficiency because of the absence of ACTH (at the hypophyseal level), but also a massive obesity because of the absence of α-MSH (at the hypothalamic level). AgRP and NPY, both orexigens but relayed by different receptors, are synthesized by the same neurons of the *arcuate nucleus*.

AgRP is co-expressed in the majority of NPY neurons, is an antagonist of MC4-R which mediates the anorexigenic effect of α-MSH through pathways different from the orexigenic action of NPY [42].

II.4.2. Extra-hypothalamic regions

The integration of energy homeostasis utilizes many cerebral structures involved in appetite control which have connections with the hypothalamus [47]:

• **Nucleus of the solitary tract** (NTS, lat. *Nucleus tractus solitarius*), receiving information from vagal afferents
• **Parabrachial nucleus** (PBN, lat. *Nucleus parabrachialis*)
• **Thalamus**, which plays a part in hedonic perception
• **Amygdala**, implicated in the processes of conditioning and in learning which visual stimuli are foods [361]
• **Orbitofrontal Cortex** (OFC, lat. *Cortex orbito-frontalis*), playing a major role in specific satiation (please refer to chapter *SSS*).

II.5. Peripheral regulation signals

The central nervous system receives abundant afferent signals, which interact with each other.

II.5.1. Short and long-term signals

1. Short-term signals
These signals are not generated proportionally to body fat mass, but they are directly related to food intake [2]. They include neural and humoral sensory information during food intake, and the digestion and assimilation of nutrients. These signals are principally implicated during the inter-meal period. They intervene *via* volume and duration of food intake which generate them, over the duration of the period of satiety which follows this food intake, but also on satiation in the subsequent food intake.

2. Long-term signals
These factors are primarily hormonal in nature, their intensity is related to adiposity, and their action is delayed compared to food intake [2]. They act by modulating the impact of short-term signals in cerebral areas that control food intake and by exerting direct effects on hypothalamic pathways that control energy balance.

II.5.2. Digestive signals

1. Gastric distension
The arrival of food in the stomach stimulates the mechanoreceptors of the gastric mucosa which transmit the information *via nervus vagus* to the central nervous system [2]. However, this effect is transitory and subtotal fullness is required to elicit a strong signal.

2. Entero-digestive hormones and peptides
The arrival of food in the digestive tract involves the secretion of numerous hormones and peptides which limit food intake. The physiological importance of the majority of these peptides is not yet established. Three of them play an important role in postprandial satiety, which was demonstrated in humans: cholecystokinin, insulin and PYY. The main gut hormones and their actions are shown in Table 2.

Table 2. Main gut hormones and adiposity signals implicated in food intake.

↑, increases feeding; ↓, decreases feeding; PYY, peptide YY; PP, pancreatic polypeptide; GLP-1, glucagon-like peptide-1; GLP-2, glucagon-like peptide-2; OXM, oxyntomodulin; CCK, cholecystokinin; GCGR, glucagon receptor. From: [39]

Influence on Feeding ↕		Receptor	Site of secretion	Other actions
Gut hormones				
PYY (3-36)	↓	Y2	L cells in gut	Delays gastric emptying
PP	↓	Y4, Y5	PP cells pancreas	
GLP-1	↓	GLP-1	L cells in gut	Incretin, decreases blood glucose, delays gastric emptying, neurotrophic effect
GLP-2	-	GLP-2	L cells in gut	Intestinal trophic effect
OXM	↓	GLP-1	L cells in gut	
Glucagon	↓	GCGR	pancreatic αcells	Increases blood glucose levels and insulin secretion
CCK	↓	CCK 1,2	I cell small intestine	Gall bladder contraction, relaxation of sphincter Oddi, pancreatic enzyme secretion
Ghrelin	↑	GHS	stomach	Growth hormone secretion
Amylin	↓	AMY1-3	pancreatic βcells	Decreases blood glucose levels
Adiposity signals				
Insulin	↓	Insulin	pancreatic βcells	Decreases blood glucose levels, stimulates glycogen synthesis
Leptin	↓	Leptin	adipocyte	Regulation of energy metabolism

Cholecystokinin (CCK)

This peptide (for review see [48]) is secreted into the circulation by enterocytes (I cells) in response to the arrival of lipids and proteins in the intestinal lumen. Administration of CCK in rats (intraperitneal)[49], rhesus monkeys (intravenous)[50] and man (intravenous)[51] decreased food intake. This effect is stronger when CCK is administered intraperitoneally. Vagotomy blocks the effects of peripherally injected CCK on satiety, which suggests that the satietogenic message of CCK is relayed to the brain *via* the vagal nerve.

PYY

It is secreted by the digestive tract proportionally to the energy content of the meal; it probably inhibits food intake by activation of Y2R receptors in the arcuate nucleus (for review see [52]).

Insulin

It is secreted peripherically and its secretion by the CNS has been discussed. Its effect is described below.

3. Intestinal nutrient-sensing chemoreceptors

The perfusion of the digestive tract with nutrients before and during a meal induces a premature feeling of satiety and a reduction of food intake. Mixing a meal with guar gum, which increases the duration of contact of nutrients with intestinal cells, prolongs the satiating effect of intake [53]. These experiments show the importance of intestinal chemoreceptors for the duration of postprandial satiety. Only a few studies have suggested the possibility of nutrient sensing in the gastrointestinal tract that could provide specific feedback to the CNS. These chemoreceptors located along the small intestine are specific for each type of nutrient [54,55,56,57].

One study using the 'electronic esophagus' preparation in rats suggested that nutrient tastes detected in the intestines can be recognized centrally based on oropharyngeal gustatory stimulation [55]. Another study in mice [58] suggested the existence of nutrient sensors in the gastrointestinal tract to modulate sweet taste sensitivity. In humans, whether infusion or not of a given food/flavor specifically decreases oral acceptance of that food/flavor has not been investigated on.

4. Nutrient oxidation

The metabolism of energy substrates generates signals which make it possible for the brain to control food intake [59]. The reduction in glucose-utilization by the oxidation of fatty acids or intrahepatic contents of ATP increases food intake. The catabolism of carbohydrates and lipids leads to oxidative phosphorylation and the production of ATP. Thus, it appears that intrahepatic and/or intracerebral oxidation of substrates generates signals which modify food intake in the subsequent meal. A series of observations suggests that hepatic production of ATP is a mechanism that controls food intake [2].

II.5.3. Hormonal signals

Hormonal factors are known to be involved in the long-term regulation of energy balance through the inhibition or the promotion of intake.

The endocrine system complements the nervous system in control and coordination. Hormones, released into the blood and other body fluids by endocrine glands, act either on specific target organs or on certain activities of many organs. Nervous coordination is most often concerned with rapid responses of short duration. Endocrine coordination, however, is usually involved in slower responses of longer duration. Stationary-state regulation, or homeostasis, depends on the action of hormones at many points. Hormonal regulation, however, is not confined to homeostasis [60].

The pervasive regulatory action of hormones is part of a large system of feedbacks. Hormones involved in homeostatic regulation influence their own secretion. For example, the secretion of steroid hormones, which affect the conversion of amino acids to glycogen, is controlled by the adrenocorticotropic hormone (ACTH). In turn, the secretion of ACTH is controlled by the releasing factor CRF. ACTH release is controlled by the concentration of steroids in the blood, so that an increase in steroid concentration inhibits ACTH secretion, which is negative feedback [60].

A similar pattern of releasing factors, by which the nervous system interacts with the endocrine system, exists for other pituitary hormones. In addition, neurosecretory cells (*i.e.* nerve cells specialized for endocrine function) release hormones that act directly on a specific target. Comparative studies show that neurosecretory cells are important in developmental and regulatory functions of most animals [60].

1. Inhibiting hormones

Insulin

Insulin secretion during the postprandial period is stimulated by the arrival of glucose in the portal circulation. The effect of insulin on food intake depends on the amount and the way it is administered (for review see [61]). While injection of Insulin into the hepatic portal vein does not affect food intake, it decreases it when injected into a cerebral ventricle [61]. The direct effects of insulin on satiety in humans are difficult to determine because of hypoglycemia which occurs when insulin is injected peripherally.

Circulating levels of insulin are proportional to the mass of white fat tissue, and the intracerebral administration of insulin induces hypophagia and weight-loss. However, the half-life of insulin is short and insulin secretion adjusts very quickly to metabolic changes. It thus seems a signal reflecting the interaction between immediate metabolic processes and the degree of adiposity [14].

Leptin

The regulation of body-fat mass by a hormonal factor was shown in the early 1950s by the experiments of parabiosis (a surgical technique that puts into contact subcutaneous tissues of two animals, which allows diffusion of humoral factors from one animal to the other) of Hervey

[62,63,64]. These experiments were carried out with a rat made obese by a lesion in the ventromedial hypothalamus and a normal rat. Under these conditions, the normal animal developed anorexia and lost weight. This experiment demonstrates that a hormonal signal is generated by excessive adiposity in the obese rat but that the hypothalamic lesion made the animal insensitive to the signal.

A decade later, Coleman carried out further experiments of parabiosis by crossing genetically obese mice (by autosomal recessive mutation of the *ob* gene – *ob/ob* mice) with normal mice [65,66]. In this case, the behavior of the normal mice remained unchanged whereas food intake and weight decreased in the obese mice. Coleman deduced that the obesity of *ob/ob* mice was the consequence of a defect in the production of a hormonal signal suppressing food intake. 25 years later, the *ob* gene was cloned and the protein which it expresses was synthesized and named leptin [67].

Circulating levels of leptin reflect body-fat mass, which explains why plasma concentrations of leptin rise with obesity. However, with equal adiposity, leptin levels are higher in women than in men and leptin resistance has been observed [2]. Contrary to preceding descriptions, leptin is sensitive to food intake; it decreases during fasting and rises after the meal. This postprandial rise is retarded; it begins 4 to 5 hours after food intake and is proportional to the quantity of insulin secreted. Also physical activity decreases circulating leptin. Thus, leptin is a marker of variation of energy stocks, and its role appears important in situations of energy deficit and excess. Leptin inhibits food intake and increases energy expenditure *via* interactions with specific receptors in the hypothalamus. It activates anorexigenic pathways (POMC) and inhibits orexigenic pathways (NPY/AgRP)[39].

2. Promoting hormone

Ghrelin

It is a peptide principally secreted by the stomach and duodenum. Its plasma level increases before intake and decreases postprandially. Ghrelin increases food intake both in rats and humans. Its plasma-level is decreased in obese subjects and increases after slimming. In the hypothalamus, it has an antagonistic action to that of leptin: it activates NPY neurons and decreases the anorexigenic action of leptin [39].

II.6.   Food intake behavior

II.6.1. Periodicity of food intake

Food intake behavior is characterized by discontinuous episodes of ingestion.

• Food intake follows a circadian rhythm, opposing a period of ingestion, taking place during the active period (or of vigilance), *i.e.* the day for diurnal species like humans, and a period of fast, corresponding to the phase of rest (or sleep). This discontinuous character of food intake, being opposed to the continuous use of energy substrates by the cells, implicates a different orientation of energy fluxes (storage or release of energy substrates from the reserves) during these two phases.

• Food intake takes place episodically in the majority of species. In non-human animals, the interval between two food intakes is one of the factors that control energy level as shown by Le Magnen [68]. In humans, the distribution of episodes of food intake is influenced by the environment, and by social norms which may determine the number of intakes, and even their composition. Food intake, when codified by social or cultural rules, is termed 'meal' [2].

II.6.2. Episodicity of food intake

Food intake includes three phases:
• **Pre-ingestive phase**, characterized by the sensation of hunger
• **Prandial phase**, corresponding to the period of food intake leading to the state of satiation
• **Postprandial phase**, characterized by the state of satiety, which is of variable duration.

Food intake can be regulated both by the quantity of food ingested during an eating bout, which brings about the process of satiation, and by the duration of the inter-meal interval [68], which corresponds to the period of satiety and depends in particular on the action of the short-term factors of satiety described later on. Food intake behavior is also dependent on food availability which represents an environmental regulatory factor.

II.7. Food reward

Reward mechanisms in the brain began with the discovery of electrical self-stimulation by Olds et Milner [69]. The concept of 'food reward' goes back at least to the early 1950s [70]. Evidence from many sources regarding the functional components and brain substrates of food reward has led Kent C. Berridge to formulate a dual concept of food reward based on two distinguishable psychological and functional components [514], often referred to as 'liking & wanting'. These components are 'liking' (*syn.* pleasure, pleasantness or palatability) and 'wanting' (*syn.* appetite, incentive motivation or incentive salience). They can be manipulated and measured separately and have separate neural anatomical structures and neurotransmitter systems [514]. Liking is mediated by opioid and GABA/benzodiazepine systems in ventral pallidum and brainstem primary gustatory relays while wanting is mediated by dopamine in mesotelencephalic systems, nucleus accumbens and amygdala [514]. Further, the core processes of liking and wanting exist without their conscious awareness.

II.8. Unspecific hedonic phenomena

There are unspecific and specific phenomena concerning food intake. The purpose of unspecific phenomena and mechanisms is to secure energy homeostasis, while specific phenomena are thought to secure the covering of nutrient needs.

II.8.1. Hunger

Physiological hunger is the feeling caused by lack of food. It can be accompanied by weakness and an uneasy or painful sensation in the lower part of the chest. This aspect of hunger has metabolic, sensory, and cognitive attributes [71].

The perception of hunger triggers food intake. The nature of the signal was initially identified as a transitory decline in blood glucose and has been shown to be a signal for meal initiation [72,73].

II.8.2. Satiation

Satiation has recently been defined as "the process that leads to the termination of eating, which may be accompanied by a feeling of satisfaction" [42].

The term 'satiation' refers to the progressive process that puts an end to an episode of food intake. It is an anticipatory phenomenon with neurophysiological and metabolic determinants,

acting even while the essential part of ingestants is still in the lumen of the gastrointestinal tract [74].

In recent practice, the term satiation has almost become synonymous with 'meal termination' or the feeling of comfortable fullness [75]. The term satiation stands for the control of meal size [76].

II.8.3. Satiety

Satiety has been defined as "the feeling of fullness that persists after eating, potentially suppressing further energy intake until hunger returns" [42]. Satiety is the phase following satiation [77], *i.e.* the state of inhibition of the feeling of hunger and of eating during the postprandial period. It is opposed to the state of hunger [77]. The term 'satiety' also stands for the control of the post-meal interval [76]. The capacity of food to induce satiety is known as satiating efficiency [78] and this phenomenon is influenced by the total energy and composition of the food consumed [79].

II.8.4. The satiety cascade

The 'satiety cascade' is a concept about the phenomenon of general satiety by John Blundell dating back to 1987 [79]. During food intake, the central nervous system receives and integrates a torrent of peripheral signals, which are collectively named by the term 'satiety cascade' [42] (Figure 3). It initiates and maintains satiety by a series of overlapping mediating processes [80]. Satiation and satiety are influenced separately by the nature and timing of physiological processes.
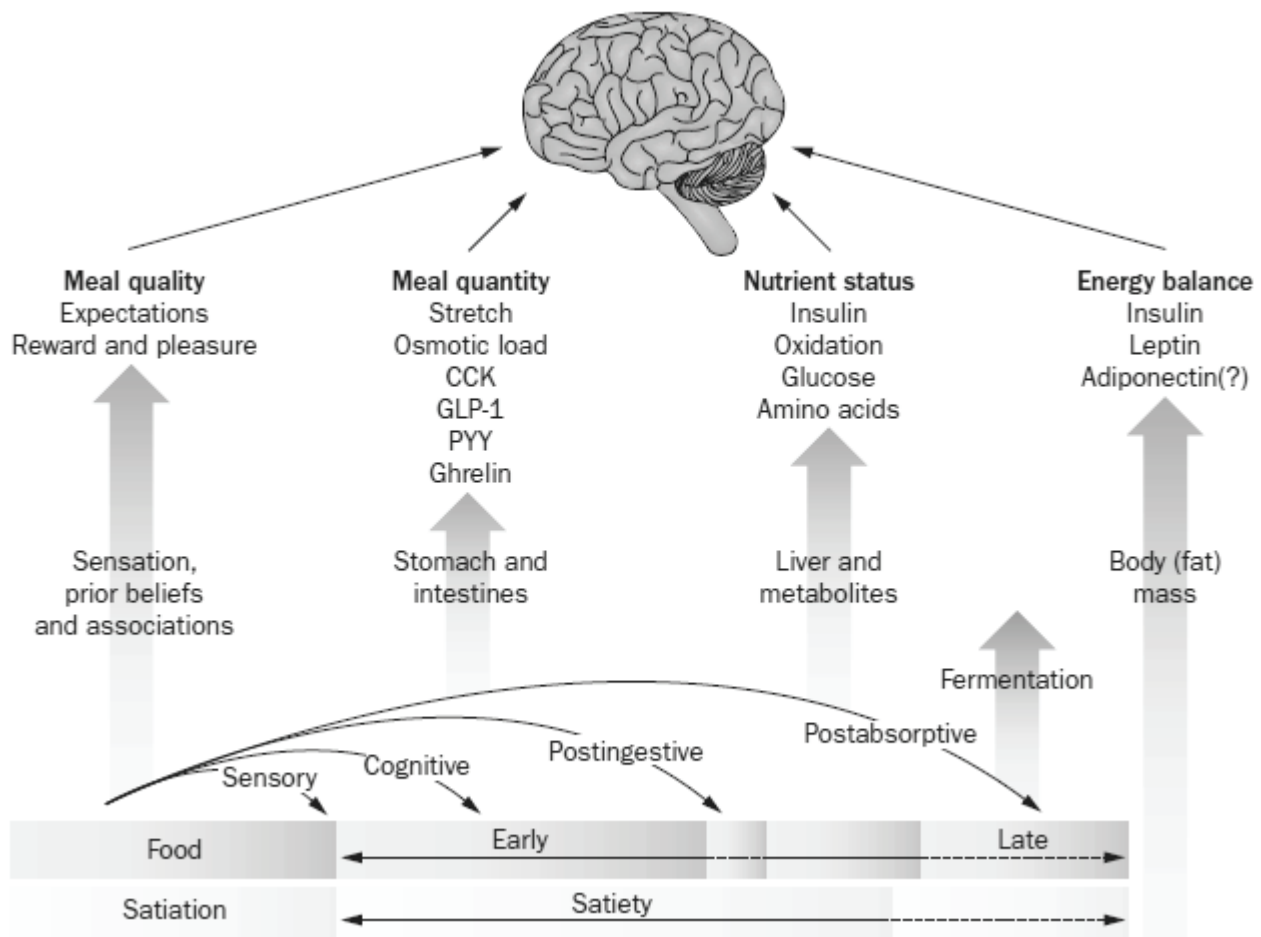
Figure 3. The satiety cascade.

This recent version of the satiety cascade includes the relationship between satiation and satiety, and the principal psychological and physiological processes mediating them. Original concept from: Blundell 1987 [79], design from: Benelam 2009 [42], image from: Blundell 2010 [81]

II.9. Specific phenomena

During the ingestive phase, food intake is controlled by multimodal sensory signals such as aspect, taste, odor and texture of food. It is increased if the food is palatable whereas it stops very quickly if the sensation is unpleasant [2]. This sensory regulation of food intake is modulated by several phenomena:

II.9.1. Specific hungers & specific appetites

There is also the qualitative regulation of nutrient choice, destined to compensate for protein and ionic deficiency which leads a deprived animal to choose foods that will compensate for the specific deficiency. However, qualitative regulation has only partially been evidenced in man [2].

The deficiency of specific anabolic nutrients like minerals or vitamins in the internal milieu must be corrected by increasing intake of the particular substance. While the specific hunger mechanisms that ensure increased intake still need to be elucidated, there is some evidence in animals that nutrient deficiency causes a specific rise in responsiveness to food containing the substance needed [82].

Much pioneering work in this field was done in the 1940s by Curt Paul Richter and E.M. Scott who originally were the first to use the term 'specific hungers' which was later replaced by 'specific appetites'.

Specific deficiencies are implicated in growth failure [83]. Therefore it seems likely that during evolution, species have evolved to develop chemosensory systems that detect 1, deficiency of crucial elements within their internal milieu, and 2, the presence of that element capable of correcting this deficiency within their external environment. In this way, taste was found to play a crucial role in recovery from specific nutrient deficiencies in rats [84] and postingestive feedback has been identified as a major determinant of food preference in ruminants [85]. Similarly, in accordance with the 'self-selection method' food choice adapted to nutritional needs has been observed in neonates [334], children [86,87] and adults [335].

However, it is not entirely clear how a mammalian organism is able to integrate the multitude of specific needs (macronutrients, specific amino-acids, fatty acids, vitamins, salts, oligo-elements etc.) into specific appetites in order to avoid deficiency in any of these vital elements and to what extent the chemical senses are implicated in the genesis of specific appetites.

Specific appetites have been observed for several nutrient types:

1. Salt

As specific appetite for salt in a sodium deficient subject, on the other hand, appears to be based on a genetically determined increase in reaction to the taste of sodium chloride and does not require any learning [82]. Increased salt appetite has been observed in sodium deficient mice [88], domestic fowl [89] and baboons [90].

2. Calcium

An undiagnosed case of severe calcium deficiency led a patient to ingest large amounts of lime off a wall [91].

3. Potassium

Preference changes to dried fruit rich in potassium have been observed in patients with potassium deficiency [91].

4. Vitamins

In the case of thiamine (vitamin B1), it has been suggested that a learning process is involved. The deficient animal tries various kinds of food and concentrates on those that remove the deficiency [82]. Examples for adapted intake behavior are thiamine deficient domestic fowl [89] and riboflavin deficiency in squirrel monkeys [92,93].

5. Amino acids

Rats have been observed to alter their dietary choice patterns during amino acid imbalance and deficiency [94].

II.9.2. PICA

PICA[5] has been defined as the ingestion of nonnutritive substances (mostly inorganic matter) over a period of at least one month [95]. The typically ingested substances vary with age. The main substances consumed by humans are soil or clay (geophagia), ice (pagophagia) and starch (amylophagia). Especially geophagy (ingestion of lime, sand earths) may have a nutritional or physiological regulatory function. In animals, it has been observed among others in primates (chimpanzees [96], macaques), in birds (parrots [97]) and in elephants [98]. In humans, PICA has been observed across all cultures. In humans, geophagia is common in tribal communities of Africa (Kenya, Tanzania), in Australian Aboriginees [99] and in Mexico. PICA is common during

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[5] PICA derives from *Pica pica* – the Latin name of a bird, the magpie, known for its uncommon eating behavior

pregnancy. Further, it has been observed in situations of severe nutritional insufficiency of calcium where instinctive food selection has been observed [91]. However, PICA can also be a symptom of various psychiatric pathologies [95].

II.9.3. Conditioned satiety (CS)

This is one of the three major hedonic phenomena (conditioned satiety, alimentary alliesthesia, and sensory-specific satiety). The phenomenon was first observed in rats and mentioned in 1951 [100] by Jacques Le Magnen who from 1955 on used the term 'caloric appetites' [6][101,102,103,104,105]. It was rediscovered in 1972 (again in rats) by David Allen Booth [106,107], who coined the term 'conditioned satiety' [108]. While the term has been used since to refer to this phenomenon, several synonyms do exist and are still in use ('conditioned satiation' [107,111,112], 'caloric satiation' [113,114], 'caloric satiety' [224] and 'intestinal satiety' [115]). Results of rats have been reproduced in human children [116] and adults [112,117].

Conditioned satiety is a form of learned satiety which requires (repeated) preceding intake of a food with defined flavor. In a (principally) unconscious learning process, the specific olfacto-gustatory pattern of stimulation exerted by a given foodstuff (*i.e.*, its sensory properties) during ingestion comes to be associated with postingestive (gastric distension? stimulation of intestinal chemoreceptors? gastro-intestinal hormone-release like CCK?) and/or postabsorptive events (plasmatic presence of previously absorbed and partly hydrolyzed nutrients and their central recognition?) up to several hours later [118]. Once established, conditioned satiety intervenes in the control of food intake *via* anticipatory limitation of intake [119]. The learned association between flavor and satiating effect of its ingestion are updated after each encounter with the same or a similar flavor (when the same flavor was paired with increased or decreased energy density).

Conditioned satiety is based on the principles of associative learning[7] and classical conditioning[8] [132]. However, in contrast to these, the US-CS-interval (*i.e.*, the time passing between stimulation by the unconditioned stimulus and by the conditioned stimulus) generally exceeds several hours instead of mere seconds to minutes. Albert Stunkard hence argued that satiety is an example of a long-delay conditioning [120]. He [120] and Booth [121] suggested that satiety would be a conditioned reflex.

Booth stated that the term 'conditioned satiety' was chosen, "because the phenomenon is a learned loss of preference for at least some foods which depends on a degree of repletion, which fits the general definition of satiation of appetite for foods" [107](p.34).

He suggested that conditioned satiety induces a relative aversion for the food eaten (relative to other foods) which is confined to the later parts of the meal [108,109], as evidenced through two-bottle forced-choice tests [110] with diluted or concentrated flavored maltodextrin solutions (thus avoiding *per se* aversive sensations induced by carbohydrate monomers)[122].

Conditioned satiety has similarities but should not be confounded with the phenomenon of 'conditioned taste aversion' [124,125] *sive* 'conditioned taste avoidance' (CTA)[126]. CTA induces a food/flavor-specific aversion by pairing with a stimulus having negative consequences (*e.g.*, irradiation [127,128,129] or injection of lithium chloride [130] which both produce strong malaise) resulting in the refusal to consume that food.

The internal signal or signals however, responsible for conditioned satiety (*i.e.*, the internal unconditional stimulus (UCS)[131,132] of satiation/satiety) has yet to be found.

While the intake-reducing *sive* intake-increasing effect of a conditioned satiety has been suggested to be based on the foods' energy density and thus their energy content, a form of conditioned satiety might as well exist for specific macro- and micronutrients. This offers a

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[6] French '*appétits caloriques*'
[7] based on Aristotle's 'law of contiguity'
[8] first described by Ivan Petrovich Pavlov

theoretical framework for the mechanism underlying specific appetites with deficient diets lacking a specific essential nutrient [82,89,91,92,93]. In this light, it was shown that rats develop a CTA for the food deficient in the required nutrient [133].

Booth criticized [134,135,123] that most studies dubbed 'conditioned satiety' were in fact unsuccessful in reproducing conditioned satiety (including his initial publication which coined the term [108]), and instead only induced a general aversion (and not a relative one towards the end of meal) or were biased by flawed protocols [123].

II.9.4. Alimentary alliesthesia (AA)

The pleasure derived from sweet and salty taste is reduced by the respective presence of carbohydrates and salt in the small intestine and does not require stimulation of the chemical senses. It was suggested that the origin of gustatory alliesthesia (*cf* chapter on alliesthesia) for sweet taste lies in the duodeno-jejunal vagal glucoreceptors discovered by Mei [240,136,137], which convey afferent sensory information to the CNS.

II.9.5. Sensory-specific satiety (SSS)

The reward-value of a food eaten diminishes gradually during intake, but leaves other foods with distinct sensory properties, present but not eaten in the same meal relatively unaffected, a fact which was confirmed by objective brain imaging techniques in primates and humans. (*cf* chapter on sensory-specific satiety)

II.10. Integration of signals

It has been stated that because of the delay between the swallowing of food and the digestion of food, the satiety mechanism requires a short-term signal to prevent over-eating. That short-term satiety signal might be induced by hedonic functions like SSS, chemical senses and mechanical feedback related to swallowing and gastric distension [374].

However, despite all the efforts into the study of peripheral and central mechanisms of ingestive behavior in thousands of publications on the anatomy, chemistry and metabolism, physiology and behavioral aspects of feeding, we will lack an understanding of the interactions among signals of different systems [374].

II.11. Environmental and behavioral factors

The physiological regulation of food intake can be modulated by psychological, social and environmental factors which can disrupt its balance, in part explaining the frequency of over- and underweight [2].

Prior experience, as well as educational, family or social conditioning can have an important impact on food-related behavior, by reinforcing or by antagonizing signals related to energy status.

II.11.1. Social, cultural and environmental factors

In humans, social, cultural and family rules condition food intake behavior from early childhood. They intervene by determining the norms and schedule of food intake.

1. Portion size and caloric compensation

Both, the effects of portion size and of the bottomless bowl (a soup bowl that was constantly and secretly refilled by a tube from underneath) were described by Brian Wansink [138,139,140].

Psycho-behavioral conditioning can override sensory control of food intake, especially in children. Children tend to eat what they are served, meal size thus predicts and dictates calories ingested. In an experiment, children did not adjust their intake to the energy density of the meal or to the energy consumed as snacks between meals, indicating that, similar to adults, they display very poor regulation of energy intake and are more responsive to environmental stimuli [141].

Similarly in young adults (undergraduate students) when given access to a buffet, the amount consumed increased with serving sizes [142].

Unlike rats, following an imposed period of overfeeding, young adults did not reduce their mean daily caloric intake to return to their baseline weight before overfeeding [143].

When humans are challenged with overfeeding, underfeeding, or changes in the caloric density of the diet, they fail to demonstrate precise caloric compensation. However, humans appear to be very sensitive to changes in environmental stimuli [144].

2. Ambiance & distractors

The cultural perception of ideal body-shape can influence food intake behavior. Also environmental stimuli like ambient temperature, light, noise, or complex influences like eating in a restaurant and the number of 'co-eaters' influence food intake [145].

3. Physical activity

Importantly, a rise in energy intake does not increase body fat mass if this is accompanied by an equivalent increase in energy expenditure through physical exercise. However, if energy intake exceeds expenditure, this results in a positive energy balance. As an example, Americans have gradually been increasing their mean energy intake since 1970, while their self-reported physical activity remained constant, at least during the 1990s [146].

II.11.2. Psycho-affective factors

Psycho-affective factors (like mood, emotions, anxiety, psychological stress…) can influence food intake, especially in women [147]. In particular, these factors can interact with food-related sensory cues (aspect, odor, taste of food). Thus, 'reinterpretation' of sensory information by limbic structures and the cerebral cortex allows confrontation with former experience, mood, or emotional state. Thereby, sensory signals can take an emotional dimension and arouse feelings which influence food intake, *i.e.*, anticipated pleasure, desire, culpability, frustration, or disgust.

This can lead to extremes like disinhibition (*i.e.*, the mental loss of control over food intake) on the one hand, or dietary restraint (*i.e.*, refusal of caloric intake), on the other [148].

Whenever food sensory pleasure is uncoupled from usefulness for the individual (because it is associated with negative sensations of unwanted weight gain), affective factors can override internal needs and can manifest themselves as eating disorders, responsible for sometimes serious weight anomalies.

II.11.3. Cognitive factors

Even though food intake-related behavior is basically motivated by internal energy needs and metabolic substrates, it remains voluntary behavior, which depends on the conscious decision of the individual. Thus, if internal needs lead to a feeling of hunger and a high level of motivation with respect to food intake, the individual preserves the voluntary capacity not to consume food.

For example, in certain particular situations, urgent behavior has priority (escape of danger, following of a social or professional obligation…) can be privileged and can suppress or delay food intake. The will to lose weight can also lead to the voluntary restriction of food intake. In this cognitive restriction, it is no longer feelings of hunger and satiety that determine food intake, but the conscious decision of being authorized or prohibited to eat.

II.12. Availability and Composition of Food

II.12.1. Food availability

The quantity of food available may reduce (shortage during wartime or environmental catastrophes) or augment (abundance in restaurant buffets or supermarkets) the quantity of food ingested by an individual. The passage from a traditional way of life (food obtained by hunting and gathering, or even by traditional agriculture and farming) to a western and/or urban lifestyle with steady availability and abundance of food in the inner [149] and in the outer environment [150] may therefore increase the quantity of energy ingested and result in increased body-fat mass.

II.12.2. Food palatability or the 'appetizer effect'

Originally, Yeomans found that adding spices (oregano) and varying their amount can modify food intake in the short term [151]. Later it was revealed that this effect is mediated by intrinsic opioids [152].

II.12.3. Sensory Variety and Monotony

Megan McCrory *et al.* argued that in the long-term, high dietary variety including sweets, snacks, condiments, entrées, and carbohydrates can increase energy intake and body fat mass, in part explaining the high and rising prevalence of obesity in the United States of America [153], where citizens are gaining more weight and becoming obese at an ever earlier age [146]. Variety has been recognized as an important factor determining the amount of food eaten and variety-seeking has been found to be induced by sensory-specific satiety (*cf* chapter Sensory-specific satiety)[361].

Monotony in oro-sensory stimulation in monotonous diets on the other hand has been found to reduce food intake [545,154], which may in part be explained through sensory-specific satiety (see chapter SSS) and finds its application in monotonous weight reduction programs [423].

II.12.4. Macronutrient composition

1. *Proteins, carbohydrates and lipids*
The relative amounts of macronutrients in foods influence energy intake because they differ in their energy density: proteins (4 kcal/gram), lipids (9 kcal/gram) and carbohydrates (4 kcal/gram). The principal energy carriers are lipids and carbohydrates. Therefore, high lipid diets deliver more energy per gram than high carbohydrate diets. In addition to their high energy density which is more than double that of carbohydrates, lipids are highly palatable. Lipids have a pleasant texture and reinforce aromas. Moreover, lipids stimulate the secretion of leptin to a lesser degree than do carbohydrates and could thus exert a less inhibitory effect on food intake in the long-term [2].

II.12.5. Aggregate state of foods

The physical state (solid *versus* liquid) and the texture (hard *versus* soft) may influence appetite control and metabolism. The consistency of foods determines the amount of chewing necessary to grind and swallow, which in turn produces feedback from sensory stimulation. Therefore, harder foods produce more sensory satiation than softer ones.

In line with this, two studies [323,324] suggested that fluid calories from beverages are not completely taken into account by the CNS. Another study observed that calories ingested in a liquid form are not well taken in account and could induce a subsequent overconsumption, at least until satiety was conditioned to the fluid [155].

However, this observation has been challenged, in that very few longitudinal cohort studies have investigated soft drink consumption and body weight change [156].

Further, the physical state also determines the duration of gastrointestinal passage. Fluids pass through the stomach quickly and thus do not create a lot of gastric distension. Also, energy rich soft-drinks or alcoholic beverages did not exist in the environment in which humans evolved. The main beverage was non-caloric water, which has have been the main source of fluid intake until very recently in human history, while coconut milk or palm sap depend on regional availability. In addition, (caloric) fruit juices have been available only very recently on a phylogenetic timescale as they require a series techniques (for extraction) and inventions (recipients; selection of juicier fruit varieties – wild fruit is more fibrous than today's hybrids). It is thus unlikely that the primate satiation mechanisms have been selected to readily detect calories in fluids.

II.12.6. Organoleptic properties of food

While non-human primates and other mammalian species eat food "as is", *i.e.* without any processing, humans have learned to modify their foods before intake. Refinement, *i.e.* food processing (grinding, extraction, thermal denaturation) may affect food intake in several ways: On the one hand, it generally leads to nutrient- and thus energy-concentration. On the other hand, heating foods creates new chemical species like Maillard molecules [157], aromatic substances which are known to enhance the organoleptic properties of foods [158,159,160]. In this way, mixing and seasoning of foods can suppress the astringent properties of foods and thus contribute to increased intake (as will be demonstrated in the first study of this thesis [425]. Finally, the more refined a food is, the less fiber it will contain, fiber which are known to expand in the intestines by water uptake.

II.12.7. Physical aggressions

Exteroceptive physical stress (*i.e.* painful stimuli or unpleasant sensory stimuli of external origin, *e.g.* a very noisy environment) can influence food intake. The mechanisms brought into play are only partially characterized. Generally, they implicate conscious psycho-affective and cognitive processes.

Enteroceptive physical stress (which corresponds to aggressions having consequences on the '*internal milieu*') can also modulate food intake. Bacterial or viral infections or other diseases like cancers or inflammatory syndromes are connected with enteroceptive stress. These diseases influence (generally reduce) food intake *via* cytokines and other mediators of inflammation which act at the level of the central nervous system.

III. Sensory Pleasure: Historical Aspects of Hedonics

III.1. Ancient Greece

The first reflections on the role of the hedonic component of sensation and of its dynamics can be traced back to writings of philosophers from ancient Greece, some centuries before the beginning of the Christian era.

Over two millennia ago, the Greek philosopher Aristotle[9][161] wrote down his reflections about the teleonomy of hedonics in his "Περὶ Ψυχῆς" – "On the soul" [162]:

"To perceive then is like bare asserting or knowing; but when the object is pleasant or painful, the soul makes a quasi-affirmation or negation, and pursues or avoids the object. To feel pleasure or pain is to act with the sensitive mean towards what is good or bad as such. Both avoidance and appetite [*i.e.* órexis – in the sense of longing, desire, appetence] *when actual are identical with this: the faculty of appetite and avoidance are not different, either from one another or from the faculty of sense-perception; but their being is different."* [10][163]

What Aristotle wanted to express might be that pleasure has a useful function. Its perception *per se* is capable of guiding an organism and directing it towards the execution of useful behaviors maintaining its balance or reestablishing it. This hedonic principle *de facto* has life-preserving qualities: within natural bounds, pleasure will always be linked with benefit while pain always signals harm or danger. Therefore, at this early stage of western history, this philosopher recognized the principle of pleasure, as well as its bipolarity.

In "*De sensu et sensibilibus*", Aristotle considered the contribution of the chemical senses in food-intake as a function of the individual's state of satiation:

"One class of odours, then, is that which runs parallel, as has been observed, to savours: to odours of this class their pleasantness or unpleasantness belongs incidentally. For owing to the fact that savours are qualities of nutrient matter, the odours connected with these [e.g. those of a certain food] are agreeable as long as animals have an appetite for the food, but they are not agreeable to them when sated and no longer in want of it; nor are they agreeable, either, to those animals that do not like the food itself which yields the odours. Hence, as we observed, these odours are pleasant or unpleasant incidentally, and the same reasoning explains why it is that they are perceptible to all animals in common." [11] [164,165]

Arguably, twenty-four centuries ago, Aristotle was the first to suggest that alimentary pleasure/displeasure played a major role in the control of food intake when he stated that flavors

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[9] (*gr*. Ἀριστοτέλης - Aristotelēs, *ca.* *384 B.C. – †322 B.C.)

[10] τὸ μὲν οὖν αἰσθάνεσθαι ὅμοιον τῷ φάναι μόνον καὶ νοεῖν· ὅταν δὲ ἡδὺ ἢ λυπηρόν, οἷον καταφᾶσα ἢ ἀποφᾶσα διώκει ἢ φεύγει· καὶ ἔστι τὸ ἥδεσθαι καὶ λυπεῖσθαι τὸ ἐνεργεῖν τῇ αἰσθητικῇ μεσότητι πρὸς τὸ ἀγαθὸν ἢ κακόν, ἢ τοιαῦτα. καὶ ἡ φυγὴ δὲ καὶ ἡ **ὄρεξις** ταὐτό, ἡ κατ' ἐνέργειαν, καὶ οὐχ ἕτερον τὸ ὀρεκτικὸν καὶ τὸ φευκτικόν, οὔτ' ἀλλήλων οὔτε τοῦ αἰσθητικοῦ· ἀλλὰ τὸ εἶναι ἄλλο.

[11] § 7. [...] τὸ μὲν γάρ ἐστι κατὰ τοὺς χυμοὺς τεταγμένον αὐτῶν, ὥσπερ εἴπομεν, καὶ τὸ ἡδὺ καὶ τὸ λυπηρὸν κατὰ συμβεβηκὸς ἔχουσιν (διὰ γὰρ τὸ τοῦ θρεπτικοῦ πάθη εἶναι, ἐπιθυμούντων μὲν ἡδεῖαι αἱ ὀσμαὶ τούτων εἰσί, πεπληρωμένοις δὲ καὶ μηδὲν δεομένοις οὐχ ἡδεῖαι, οὐδ᾽ ὅσοις μὴ καὶ ἡ τροφὴ ἡ ἔχουσα τὰς ὀσμὰς ἡδεῖα, οὐδὲ τούτοις)ὥστε αὗται μέν, καθάπερ εἴπομεν, κατὰ συμβεβηκὸς ἔχουσι τὸ ἡδὺ καὶ λυπηρόν, διὸ καὶ πάντων εἰσὶ κοιναὶ τῶν ζῴων· Please refer to § 7 of for the French translation.

and smells of food are pleasant when we are hungry, but when we are sated and not requiring to eat, they are not pleasant.

Epicurus [12][166] even went as far as considering pleasure as the ultimate source of motivation:

"For we recognize pleasure as the first good innate in us, and from pleasure we begin every act of choice and avoidance, and to pleasure we return again, using the feeling as the standard by which we judge every good." [167]

III.2. Modern Times

By the end of the 19th century, philosophers and psychologists began to re-examine the problem of hedonicity. Research in the field of hedonics was probably reignited by Gustav Theodor Fechner[13][168], who studied the implications of hedonics in psychophysical processes. In 1873 [14] [169] he wrote that:

"Forasmuch as conscious drives always stand in relationship with pleasure or displeasure, also pleasure or displeasure can be thought of with conditions of stability and instability in psychophysical relation, and the hypothesis elsewhere to be developed more thoroughly by me can be founded upon, that each psychophysical motion exceeding the threshold of consciousness accordingly be afflicted with pleasure, whenever it approaches full stability beyond a certain limit, accordingly with displeasure, whenever it deviates thereof over a certain limit, whereas between both, exists a certain width of aesthetic indifference as borders that may be designated as qualitative threshold of pleasure and displeasure ..."

For Fechner, pleasure and displeasure seemed to have been both ends of a continuous scale, and in close relation with conscious drives. One is tempted to think that Fechner had the notion of *homeostasis* in mind when he spoke of "the psychophysical motion … approaches full stability" where the pleasure/displeasure dualism has the role of a driving force approaching balance.

In 1920, Sigmund Freud[15] [170] published his essay named "*Jenseits des Lustprinzips*" (Beyond the pleasure principle)[171]. For Freud, the "pleasure principle" determines the aim of life. In his introduction to the pleasure principle, he states that:

"In psychoanalytic theory we assume without hesitation that the course of mental processes is being regulated automatically through the pleasure principle, i.e., we believe, that it is instigated each time by displeasurable tension and that it then takes such a direction, that its final result coincides with a reduction of this tension, thus with an avoidance of displeasure or production of pleasure. When we regard the mental processes in consideration of this expiration studied by us, we bring in the economic criterion into our work. We mean, a representation, which in addition tries to appreciate this economic apart from the topical and the dynamic moment, are the most complete,

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[12] Epicurus (*ca.* *341 – †271 B.C.)

[13] Gustav Theodor Fechner [13] (*1801 – †1887), founder of psychophysics

[14] »Insofern bewußte Antriebe immer mit Lust oder Unlust in Beziehung stehen, kann auch Lust oder Unlust mit Stabilitäts- und Instabilitätsverhältnissen in psychophysischer Beziehung gedacht werden, und es läßt sich hierauf die anderwärts von mir näher zu entwickelnde Hypothese begründen, daß jede die Schwelle des Bewußtseins übersteigende psychophysische Bewegung nach Maßgabe mit Lust behaftet sei, als sie sich der vollen Stabilität über eine gewisse Grenze hinaus nähert, mit Unlust nach Maßgabe, als sie über eine gewisse Grenze davon abweicht, indes zwischen beiden, als qualitative Schwelle der Lust und Unlust zu bezeichnenden Grenzen eine gewisse Breite ästhetischer Indifferenz besteht...«

[15] born Sigismund Schlomo Freud (*1856 – †1939), founder of psychoanalysis

which we can imagine at present, and earn it, to be emphasized by the name of a metapsychologic one.“ [16]

In other words, the pleasure principle mediates all psychic motivations, by executing actions that are incited by unpleasurable tension, which the individual unconsciously tends to reduce by avoidance of displeasure and generation of pleasure. These circumstances made Freud introduce the economic aspect to his metapsychologic theory.

However, on his quest for the purpose of pleasure and displeasure Freud could not find an explanation in the literature. In analogy with Fechner, Freud discusses hedonics by means of quanta. He compares displeasure with excitations capable of producing a quantity of tension, which can be reduced by pleasure, and *vice versa* [17] [171].

The pleasure principle according to Freud is the driving force of the *id* that instinctively strives to fulfil its basic needs, including hunger, thirst, and sex. Inaccomplishment of these needs results in a state of tension. However, with the development of the *ego* and *superego*, the individual learns to temper its quest for pleasure [172].

From 1952 to 1968, Paul Thomas Young [18] [173] studied the role of hedonic processes in the organization of behavior [174], learning and motivation [175], with special emphasis on "psychologic factors regulating the feeding process" [176]. He hypothesized a global "hedonic organization and regulation of behavior" [177] and rendered the hedonic dimension of sensation measurable [178,179].

Only recently, physiologists have begun the systematic study of the physiological role of sensory pleasure in homeostatic behavior [249], starting with Jacques Le Magnen [19] [180,181], who began his investigations on the influence of smell and taste on the regulation of food-intake in 1951 [182], above all in a laboratory animal, the white rat. It was as early as 1956 [183], when he clearly depicted the prominent role of sensory pleasure in the regulation of food-intake, thereby laying the foundations for hedonic phenomena as they are known today:

"Subjectively, the odor and the savor of a usual food are considered to be "pleasant". It is under the aspect of this affective reaction, its evolution during ingestion and its diversity according to the foods, through which human food intake behavior can be analyzed. [...]

The affective judgment with regard to the food odor perceived outside, the appreciation of the complex taste of the same food in the course of ingestion itself, are related to the existence of the state known as hunger. This same odor, this same taste will be considered as "unpleasant" and even nauseous (i.e. capable of causing nausea) in the subject when satiated or in a state of anorexia.

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[16] "In der psychoanalytischen Theorie nehmen wir unbedenklich an, daß der Ablauf der seelischen Vorgänge automatisch durch das Lustprinzip reguliert wird, das heißt, wir glauben, daß er jedesmal durch eine unlustvolle Spannung angeregt wird und dann eine solche Richtung einschlägt, daß sein Endergebnis mit einer Herabsetzung dieser Spannung, also mit einer Vermeidung von Unlust oder Erzeugung von Lust zusammenfällt. Wenn wir die von uns studierten seelischen Prozesse mit Rücksicht auf diesen Ablauf betrachten, führen wir den ökonomischen Gesichtspunkt in unsere Arbeit ein. Wir meinen, eine Darstellung, die neben dem topischen und dem dynamischen Moment noch dies ökonomische zu würdigen versuche, sei die vollständigste, die wir uns derzeit vorstellen können, und verdiene es, durch den Namen einer metapsychologischen hervorgehoben zu werden."

[17] "Dagegen würden wir uns gerne zur Dankbarkeit gegen eine philosophische oder psychologische Theorie bekennen, die uns zu sagen wüßte, was die Bedeutungen der für uns so imperativen Lust- und Unlustempfindungen sind. Leider wird uns hier nichts Brauchbares geboten. Es ist das dunkelste und unzugänglichste Gebiet des Seelenlebens, und wenn wir unmöglich vermeiden können, es zu berühren, so wird die lockerste Annahme darüber, meine ich, die beste sein. Wir haben uns entschlossen, Lust und Unlust mit der Quantität der im Seelenleben vorhandenen - und nicht irgendwie gebundenen - Erregung in Beziehung zu bringen, solcherart, daß Unlust einer Steigerung, Lust einer Verringerung dieser Quantität entspricht."

[18] Paul Thomas Young (*1892 – †1978)

[19] Le Magnen (*1916 – †2002), French physiologist of sensory sciences

The ingestion of the food makes evolve the affective judgment, already in the course of chewing and swallowing, from the positive character of pleasant facilitating ingestion to the unpleasant and nauseous character inhibiting the continuation of consumption. The transformation of the state of hunger and appetite for a food considered with that of satiety which determines the consumed quantity thus carries out by transformation of the affective response towards the complex taste of that food."[20] [183]

Also Carl Pfaffmann[21] [184], who dedicated a major part of his studies to the sense of taste in particular and to chemoreception in general, focused on sensory pleasure in his research. He stated that affective responses to sensory stimulation play a significant role in the reinforcement and guidance of behavior [185], or in other words, that behavior is controlled through the "pleasures of sensation" (1960)[186].

So we have seen that early scientific research already evoked the idea that sensation consists of two components [183,175,186]: one *discriminative*, indicating the nature and intensity of the sensation, and the other *affective*, indicating pleasantness or unpleasantness.

Michel Cabanac originally studied temperature regulation in man and animals (essentially from 1964–1972). He showed that (dis)pleasantness for thermal stimuli (cold, warm) is an important motivator of thermoregulatory behavior and that the pleasantness for cutaneous thermal stimuli is dependent upon the core temperature of the body [283,286,233,293,320,331]. For instance, hypothermia renders warm stimuli pleasant while cold ones become unpleasant. Within physiologic bounds, the affective component of sensation therefore does not only depend on the nature and intensity of the stimulus, but above all on "internal factors" of the body (dubbed *internal milieu* or fr. *milieu intérieur*). Most likely, these circumstances lead Cabanac to the search for parallels in food-intake. In 1966 [284] and 1968 [285], Michel Cabanac, published his first alimentary observations. A series of experiments, involving ingestion *per os* and *via* gastric tubing of sweet (caloric) solutions, showed that only sucrose solutions (*i.e.* caloric solutions) were capable of downshifting ratings of pleasantness of sweet gustatory stimuli from pleasant to unpleasant. Both, saline solutions (of equal osmolarity but non-caloric) and isovolumetric infusions of water (*i.e.* gastric distension) were ineffective in reducing the hedonics of sweet taste. Neither contact of sugar with gustatory receptors, nor the act of swallowing was necessary to produce displeasure for sweet taste. Ratings of pleasantness were also independent of blood glucose levels [283]. In 1971, Cabanac in collaboration with Stylianos Nicolaïdis termed the phenomenon '*alliesthesia*' [233].

In 1975, Mc Farland *et* Sibly reintroduced Freud's economic criterion by claiming the necessity of a trade-off mechanism between the motivational variables of a motivational control system [308].

In the 1990s, Cabanac put rats in situations of motivational conflict where they had to assign hierarchies to homeostatic behaviors (such as thermoregulatory behavior, food-intake, fluid-intake). The rats acted as if they were trying to maximize the pleasure derived from stimuli of very different sensory modalities [325]. He concluded that maximization of plurimodal pleasure (which is behaviorally and quantitatively measurable) serves as an optimizer of behavior and suggested that

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[20] « Subjectivement, l'odeur et la saveur d'un met habituel sont jugés « agréables ». C'est sous l'aspect de cette réaction affective, de son évolution au cours de l'ingestion et de sa diversité suivant les aliments que peut s'analyser le comportement alimentaire humain. [...]

Le jugement affectif à l'égard de l'odeur alimentaire perçue à l'extérieur, l'appréciation du goût complexe du même aliment au cours même de l'ingestion, sont liés à l'existence de l'état dit de faim. Cette même odeur, ce même goût seront jugés « désagréables » et même nauséabonds (c'est-à-dire capables de susciter la nausée) chez le sujet rassasié ou en état d'anorexie.

L'ingestion de l'aliment fait évoluer, au cours même de la mastication et de la déglutition, le jugement affectif, du caractère positif de l'agréable facilitant l'ingestion au caractère du désagréable et nauséabond inhibant la poursuite de la consommation. La transformation de l'état de faim et d'appétit pour l'aliment considéré à celui de satiété qui détermine la quantité consommée s'effectue donc par transformation de la réponse affective envers le goût complexe de l'aliment. »

[21] Carl Pfaffmann (*1913 – †1994), American psychologist and physiologist

sensory pleasure was the brain's 'common currency' in ranking and integrating motivational drives to satisfy physiological needs [309,310].

Based on his observations, he proposed a definition of consciousness [319] as a four-dimensional experience (quality, intensity, hedonicity, and duration), as well as a definition of emotion as any mental experience with high intensity and high hedonic content (*i.e.*, pleasure or displeasure)[330]. Ultimately, he compared sensory pleasure to the four forces of physics (the weak nuclear force, the strong nuclear force, the electromagnetic and the gravitational force) and suggested naming it the '5th influence' since being a mental phenomenon it is without dimension [331,337,338].

Arguably, animals, and as such, humans, innately and continuously seek pleasure and avoid displeasure. Therefore, this 'hedonic striving' may lead to organized behaviors with useful and life-conserving homeostatic consequences for the individual's organism and survival of its species.

However, it has recently been put forward that "the joy of eating can arise not only from the fulfillment of a vital physiological need but also from the sheer gratification derived from savoring appetizing foods" [187].

This statement implicates the idea that under certain circumstances, hedonic signals may be isolated from their finality of signalling the utility of an external stimulus to the organism consuming it.

IV. MEASUREMENT AND QUANTIFICATION OF REWARD

Over the second half of the past century, researchers have established and applied many different methods to estimate states of hedonicity in humans and in animals.

IV.1. Measuring in Humans

IV.1.1. Questionnaires

Various questionnaires have been developed as tools to determine food choice and food preference [188,189,190,191].

IV.1.2. Rating scales

1. Likert Scale

In experiments investigating hedonics, the reported sensation of (dis)pleasure was initially measured using visual numeric scale (VNS) or fixed-point scale (FPS, Figure 4). This scaling technique was introduced by Rensis Likert[22] [192], first presented in his dissertation in 1932 [193]. He developed methods to study attitudes and their influencing variables and created the most widely used scale for attitude measurement, the Likert scale [194,195]. This attitude scale is anchored by two extremes, ranging from favorable to unfavorable, with a neutral midpoint for each statement. The range of the scale depends on its application, in the case of hedonics typically ranging from one to between five and nine although larger scales have also been used [303]; the mid-point of the scale is reserved to reflect an undecided position. A variation of the Likert scale for acceptance testing is the 9-point hedonic scale developed in 1957 [196] and still in use [197].
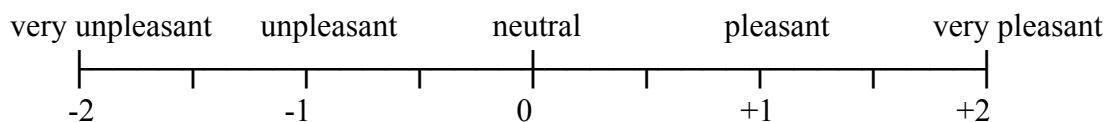
Figure 4. Example of a fixed-point scale (FPS).
Also called "affective arbitrary scale". Also values between marks can be chosen.

2. Visual Analogue Scale (VAS)

Its precursor was developed in the 1920s in the Laboratories of the Scott Company[23] [198,199] by Hayes et Donald G. Paterson [200,201] and named "Graphic Rating Scale" (see [202] for original scale). It was revised by Paterson in 1922 [203,204] and by Freyd in 1923 [205]. The term "Visual Analogue Scale" was coined by Aitken *et al*. in the 1960s [206,207]. It has been used for the assessment of subjective phenomena that range across a continuum of values [208] like feelings [209], pain [210], nausea, fatigue, anxiety [211], hunger [212], and pleasure [213].

It is a hedonic line scale, consisting of a straight horizontal or vertical line, usually of 100 mm in length, anchored by word descriptors depicting extremes (the minimum and the maximum)[214] at the endpoints of the line (Figure 5).

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[22] Rensis Likert (*1903 – †1981)
[23] Walter Dill Scott (*1869 – †1955), Psychologist and Industrial

Subjects give their rating by placing a mark on the line. This method has been preferred in recent studies because of several advantages over fix-point scales: 1, it permits of the use of parametric statistical procedures with small sample sizes, and, 2, subjects cannot compare to their previous ratings. The observer then measures in mm the distance of that mark from one end and uses that figure for analysis [215].

very unpleasant ├────────────────────────────┤ very pleasant
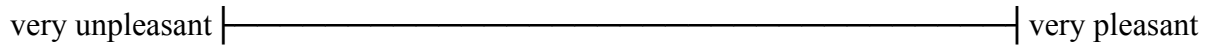
Figure 5. Example of a visual analogue scale (VAS).
The participant gives a rating by placing a mark along the line.

IV.2. Measuring in Animals

IV.2.1. Visualization and frequency of specific behaviors

In animals, classically rats, the subject is prepared with both, oral and naso-gastric or naso-duodenal tubes, in order to give bursts of taste samples of defined volume, concentration and at defined moments in time. In contrast to human subjects, who spit out the sample after evaluation, rats swallow it. The 'hedonic note', as animals are unable to communicate to the observer what they perceive, is interpreted from the characteristic behavioral response-sequence following the oral load, the occurrence of which is counted. Berridge, Grill and Norgren found out that facial expressions of rats tasting sweet and bitter solutions corresponded to positive and negative hedonic sensations, reflecting pleasure and disgust just as in human subjects [216,217,218,219,220,221]. Hedonically positive reactions (Figures 6 and 7), called 'ingestive facial consummatory responses' (*i.e.* paw licking, lateral tongue protrusions, midline tongue protrusions, mouth movements, passive drip) are differentiated from hedonically negative ones (Figures 8 and 9), called 'aversive facial consummatory responses' (*i.e.* gapes, chin rubs, face washing, forelimb flailing, headshakes, locomotion) [254,255,257,256]. The facial expressions and specific postures of the rat, which is sitting in a transparent cage, are recorded by direct observation or *via* video camera (Figure 10) and subsequently frame-by-frame analyzed for quantification of the frequency of occurrence of hedonic signals.
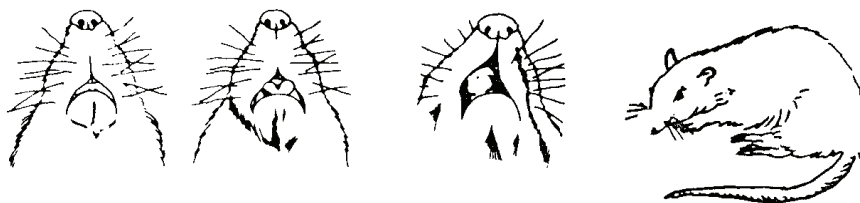
Figure 6. Positive affective facial taste reactions in the rat. (Illustrations by Harvey J. Grill)
Positive (ingestive or consummatory) hedonic reactions (elicited by palatable sucrose): rhythmic tongue protrusion, lateral tongue protrusion, and paw lick (from left to right). Original illustrations from: [222,223,224]
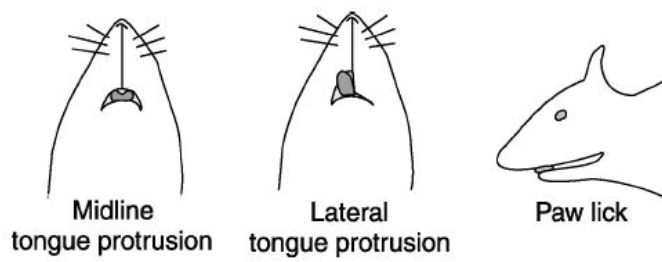
Figure 7. Ingestive facial responses in the rat (Illustrations by Fredrik Sederholm).
From: [329]

Figure 8. Negative affective facial taste reactions in the rat (Illustrations by Harvey J. Grill)
Negative (aversive) hedonic reactions (elicited by unpalatable quinine): gape, headshake, face wash, and forelimb flail (from left to right). From: [222,223,224]
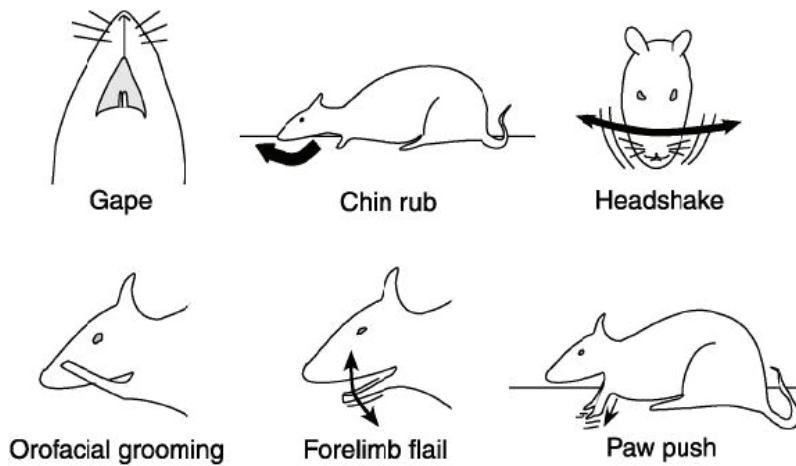
Figure 9. Aversive facial responses in the rat (Illustrations by Fredrik Sederholm).
From: [329]
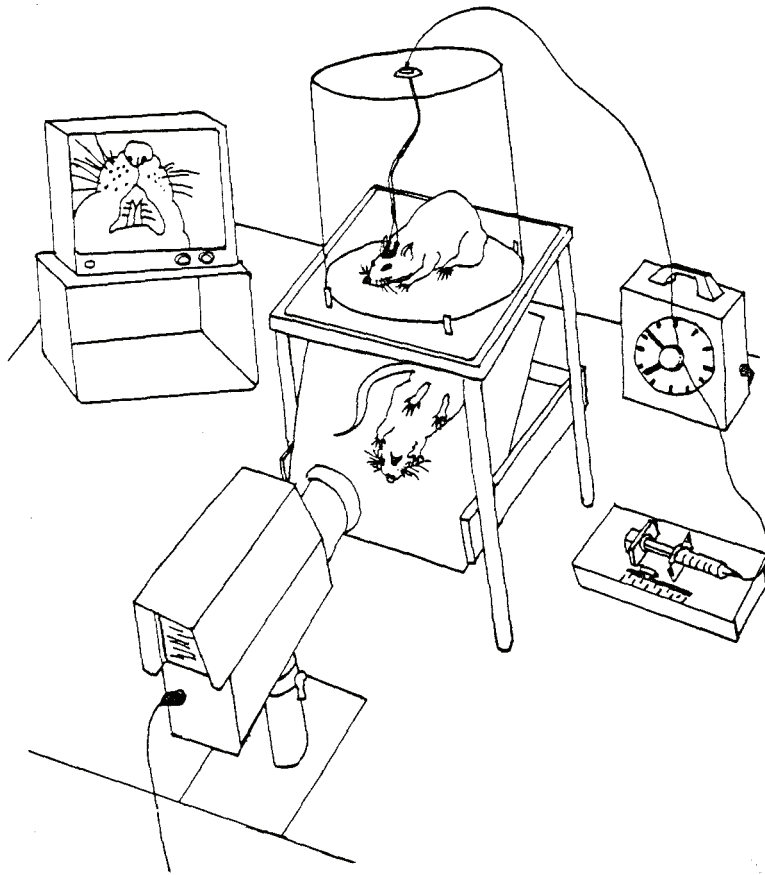
Figure 10. Apparatus for video recording of hedonic taste responses.
Taste stimuli are injected into the mouth via chronic intraoral catheter; video was recorded via a mirror beneath the transparent Plexiglas floor. From: Grill (1985)[223]

IV.3.   Other Measurement techniques for Animals and Humans

IV.3.1. Quantitative Measurement

Palatable foods are preferred to less palatable ones and as result, larger quantities are eaten of the first. Thus, the easiest and most objective way to study hedonics consists in measuring the ingested quantities by means of weight or volume ingested. This technique can be applied in both, animals and human subjects.

IV.3.2. Choice behavior - Motivational Conflict

Cabanac extensively studied the interaction of concurring hedonics from different modalities in motivations, forcing animals [325] or human subjects [225] to gain pleasure (*e.g.* a sweet solution) through a situation of displeasure (*e.g.* cold discomfort) or to have them choose between two pleasurable stimuli. Therefore, the perception of pleasure, quantitatively measurable by choice-behavior (in animals), or by rating of pleasure/displeasure (in man) can serve as a common currency. Integration of various motivations is accomplished by maximization of pleasure [309,310].

IV.3.3. Behaviorism and Reward

1. Working for reward

The rewarding effect of stimuli and behaviours is reflected in the willingness to work to gain access to a rewarding goal. Thorndike stated that behavioural responses to stimuli are more likely to be repeated if they produce satisfying effects [226].

2. Reinforcement

Skinner's theory of reinforcement states that response outcomes determine subsequent behavioral actions and that a positive reinforcer (*i.e.*, the pleasant consequence of a response) increases the probability that response will occur in the future [227].

3. Operant conditioning

Operant (or instrumental) conditioning[24] is a major concept in the experimental analysis of behavior and is applied in behavioral choice and reward measurement [228]. A central principle of Skinner's operant conditioning is the determination of response strength by measurement of the frequency or intensity of behavioral responses (*e.g.* lever presses) [227]. (for more details please refer to subchapter *conditioned satiety*.)

IV.3.4. Facial mimics in newborns

Berridge's extensive comparative studies in newborn non-human mammals and human infants have demonstrated a high degree of conservation of facial hedonic responses through phylogeny [229]. The positive facial response to sweet like the negative hedonic response to sour, bitter, and astringent are innate [230].

IV.3.5. Brain stimulation reward

The contributions of results of electrical brain stimulation and drug self-administration have led to the establishment of the brain correlates of reward. Modulation of motivated behavior by neurochemical manipulations revealed the contributions of peptide and neurotransmitter systems.

1. Central electrical self-stimulation

Self-administration of electrical stimulation to certain brain regions is known as 'brain stimulation reward' (BSR) and has been studied in rats since the 1950s to reveal brain reward circuits [231]. Brain areas where electrode placement successfully triggered self-stimulation include the orbitofrontal cortex, the nucleus accumbens, the lateral hypothalamus, the ventral tegmental area and the brainstem. BSR works by stimulating neural circuits that convey the rewarding properties of natural stimuli and behaviours.

2. Central drug self-administration

In analogy with electrical brain stimulation, the central administration of drugs that modulate dopaminergic circuits can be reinforcing (see [232]). The reinforcing actions of abuse drugs are due to the modulation of DA signalling in the nucleus accumbens. Abuse drugs (such as amphetamine, cocaine and opiates) increase instrumental responding associated with enhanced dopamine release in the nucleus accumbens.

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[24] The term 'conditioning' refers to the transfer of a reflexive or automatic response to an unrelated stimulus/behavior

V. ALIMENTARY ALLIESTHESIA

V.1. Definition and Terminology

The term '*alliesthesia*' describes a common phenomenon that is rarely taught even at university level. The term can only be found in selected scientific dictionaries but not in common or most medical ones. Still, this phenomenon does exist, as it has been thoroughly studied and described within the past 30 years. To date, many publications on *alliesthesia* can be found in the scientific literature[25] [340]. The purpose of this chapter is to give the reader an insight into what *alliesthesia* represents.

The term '*alliesthesia*'[26] [332], derives from Greek words '*alloios*' (άλλοϊος, meaning changed) and '*aisthisis*' (αΐσθησις, sensation). Fusion of these two words results thus in a word meaning 'changed sensation'. It was coined by Michel Cabanac in collaboration with Stylianos Nicolaïdis in 1971 and its first mention is the following [233]:

"In order to avoid using a whole sentence saying that a given external stimulus can be perceived either as pleasant or unpleasant depending upon signals coming from inside the body, it may be useful to use a single word to describe this phenomenon. I hereby propose the word alliesthesia coming from esthesia (meaning sensation) and allios (meaning changed). This word will be used in the remainder of this article."

There are three oeuvres where a definition of the term alliesthesia can be found:

The 'Dictionnaire illustré des termes de médecine'[27] defines alliesthesia as "*variations in pleasant or unpleasant feelings, produced by an external stimulus, depending on the internal state (temperature, body-weight, various constants of the internal milieu etc.) of the subject receiving it.*"

The 'Glossary of terms for thermal physiology' states the following:
Generally, the changed sensation for a given peripheral stimulus resulting from the stimulation of internal sensors; in thermal physiology, the dependence of thermal sensation on both skin and core temperatures (Gk. *alloioo* - to alter; *aisthesia* - sensation); positive alliesthesia indicates a change to a more pleasurable sensation, negative alliesthesia a change to a less pleasurable one [296,304,328].

The Encyclopedia of Neuroscience:
Alliesthesia is the faculty of a sensation to move up and down the affective axis. The word alliesthesia (Greek *Alios* changed and -*esthesia* sensation) is applied to the affective component of sensation, pleasure or displeasure. The amount of pleasure or displeasure aroused by a given stimulus is not invariable - it depends on the internal state of the stimulated subject and on information stored in memory. Factors that can modify the internal state and in turn induce alliesthesia are as follows: internal physiological variables (*e.g.*, deep body temperature or body dehydration modify the pleasure of thermal sensation or taste of water); set points (*e.g.*, during fever

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[25] PubMed: 50; ISI Web of Knowledge: 44 (Search term: alliesthesia OR alliesthesial)

[26] English: alliesthesia (n.), alliesthesic (adj.), French: l'alliesthésie (n., féminine), alliesthésique (adj.), German: die Alliesthesie, *syn.* Alliästhesie (Allio-; -ästhesie), alliesthesisch (adj.), ancient Greek: *aisthisis* [αΐσθησις] – sensation; *alloios* [άλλοϊος] - changed), modern Greek: *aisthisi* [αίσθηση], *allios* [αλλιώς])

[27] Alliesthésie, *s. f.* (M. Cabanac, 1968) (gr. *allos* ou lat. *alius*, autre ; gr. *aïsthêsis*, sensation) [angl. *alliaesthesia*]. Variations de l'impression agréable ou désagréable produite par un stimulus externe en fonction de l'état interne (température, poids, différentes constantes du milieu intérieur etc.) du sujet qui le reçoit.

the body temperature set point is raised and pleasure defends the elevated set point); multiple peripheral stimuli (*e.g.*, mean skin temperature determines the set point for deep body temperature and in turn generates alliesthesia); and past history of the subject (*e.g.*, association of a flavor with a disease or a recovery from disease renders it unpleasant or pleasant). Positive alliesthesia indicates a change to a more pleasurable sensation, negative alliesthesia a change to a less pleasurable one [321,326].

According to these definitions, a given stimulus deriving from the external milieu can be described by its descriptive component, which is objective, consisting in quality (*e.g.* taste: sweet, salty, sour, bitter, umami; temperature: cold, warm; color: red, green, blue *etc.*), and intensity (from very weak to very intense). It is important to note that alliesthesia is not related to intensity. It has been demonstrated that intensity ratings parallel pleasantness ratings: however, they do not correlate [245].

Sensation is three-dimensional, which was first stated by Le Magnen in 1951 [182] and specified in 1992 by Cabanac [311,312,313]: qualitative (nature), quantitative (intensity), and affective (usefulness). A stimulus can also be described by the subjective hedonic sensation it may arouse in the receiving subject (very unpleasurable over neutral to very pleasurable). However, this hedonic sensation is not constant as the same stimulus may elicit varying responses in the same subject over time.

Alliesthesia therefore is the affective part of sensation, which can take any tone of the spectrum from pleasant to unpleasant (it is a bidirectional process: positive alliesthesia means a shift up on the affective axis from unpleasant to more pleasant [241,243,334] and vice versa for the case of negative alliesthesia), and depends not only on the stimulus, but also on internal factors of an organism. Consumption of an external stimulus, initially causing pleasure, modifies the state of internal variables (*i.e.* the 'internal milieu')[28][341], which turns pleasure over neutrality into displeasure, and in turn may stop consumption of the stimulus. The internal state is the key to the concept of alliesthesia.

As an example, a sated subject, tasting a food just eaten to satiety will perceive little pleasure or even displeasure toward this food. If this sated subject waits for some hours and becomes hungry again, and again tastes this food, he might perceive this same food now as pleasant as during the pre-prandial state. It is important to note is that the stimulus is the same at all times, the only change concerns the human or animal being, more exactly some (metabolic, neuronal) parameters within his organism.

It should be noted that alliesthesia is different from both adaptation and from habituation. Adaptation [666], or sensory receptor fatigue, is the phenomenon that describes a reduction in the firing-rate and amplitude of sensory receptors when exposed to a continuous external stimulus (*e.g.* visual adaptation, gustatory adaptation), while habituation [328,666] results in a specific diminution of response to a stimulus after repetitive confrontations of the organism with it through a brain mechanism of non associative learning (Table 3).

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[28] (*fr.* '*milieu intérieur*')

Table 3. Sensory adaptation *versus* habituation *versus* alliesthesia.
Extended, from: [342]

	Adaptation	Habituation	Alliesthesia
Action	peripheral	central	central
Structure	sensory receptor	CNS	internal milieu
perceived	unconscious	conscious	conscious
by stimulus intensity	affected	unaffected	unaffected
by prior exposure	unaffected	affected	unaffected

Furthermore, alliesthesia should not be confounded with allesthesia. While *alliesthesia* represents a physiologic phenomenon, *allesthesia* [343,344] is a pathologic phenomenon that describes sensory disorders. Unluckily, in early works on alliesthesia the term was misspelled as *allesthesia*, most probably a mistranslation from the French '*alliesthésie*' and is present in publications even by its founder [297] and other authors [306,307], which is a major source of confusion.[29]

V.2. Sensory modalities of alliesthesia

Alliesthesia is a general term, not solely applicable on food intake. Alliesthesia is multimodal. The concept of alliesthesia has been shown to extend to the following sensory modalities:

V.2.1. Thermal alliesthesia and Alliesthesia for water

Alliesthesia was discovered in 1966 [283] and first in the thermal sensation [286] where it is most evident. The International Union of Physiological Sciences, which focuses research on temperature regulation, included the definition of thermal alliesthesia in the "Glossary of terms for thermal physiology" in 1973 [296]. This term was restated by this instance in 1987 [304].

Thermal alliesthesia is defined as a change in the pleasantness of temperature stimuli (cold, warm).

The pleasantness of thermal cutaneous stimuli depends on the value and the sign of the difference between actual real deep body core temperature and its regulated (set) value [320,331]. In other words, a warm stimulus feels pleasant to someone who is freezing or excessively cooled. This same warm stimulus will feel unpleasant to the same person, as soon as his core temperature rises above normothermia. Therefore, thermal alliesthesia plays a role in the regulation of body temperature: the regulated value of the internal milieu is the deep core temperature of the body. The sensor has been shown to lie within the hypothalamus [328]. In this light, fever results from regulation on a higher set-point [320,331]. That negative thermal alliesthesia participates in behavioral thermoregulation can be seen in the fact that it exerts its role via thermal discomfort of cutaneous temperature sensitivity [269].

Thermal alliesthesia also plays a role in the control of thirst and water-intake. Hyperthermia favors preference (positive alliesthesia) for cold water and results in negative alliesthesia for warm water [246]. Dehydration results in positive alliesthesia for water. Water temperature influences fluid-consumption, which is lower for warm drinks (negative alliesthesia) and higher for cool drinks (positive alliesthesia). Cooling of water (like flavoring) increases water-intake. Negative alliesthesia

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[29] Anecdotal: when the author first talked about *alliesthesia* to his thesis director in Vienna, he opened the *Pschyrembl*, the standard medical dictionary, and pointed at the term '*allesthesia*', as alliesthesia was then still absent

for warm water results in reduced fluid-intake if only warm water is available, leading to dehydration, hyperthermia, hypovolemia, and heat stroke [250].

V.2.2. Olfactory and gustatory alliesthesia

Olfactory alliesthesia signifies a change in the pleasantness of olfactory stimuli and gustatory alliesthesia a change in pleasure derived from taste. Together, the term 'olfacto-gustatory alliesthesia', as found in early studies, meaning alliesthesia for alimentary stimuli, was replaced in 1984 [249] by the more general term 'alimentary alliesthesia'[30]. Alimentary alliesthesia comprises olfactory alliesthesia (*i.e.* within the olfactory modality) and gustatory alliesthesia (alliesthesia of gustation) [321,326].

V.2.3. Visual and auditory alliesthesia - Environmental alliesthesia

Alliesthesia even extends to the visual modality [263]: the pleasantness of a given color has been described to be a function of circadian rhythm, *i.e.* from day- to nighttime. Although less evident, it does exist. Daytime exposure to bright or dim light influences color preference in the evening. 'Warmer' colors are preferred after dim exposure, due to a higher set-point of core temperature after dim light. After bright light exposure, core temperature is lower and skin temperature higher during sleep [263].

Visual and auditory modalities (*i.e.* environmental conditions) are subject to alliesthesia. Actually, strong visual and auditory stimulations become more and more pleasant during the day in a state of vigilance while they become more and more unpleasant in a state of fatigue and *vice versa* [275]. The state of vigilance and fatigue may correspond to a change in the internal milieu.

V.2.4. Alliesthesia for sexual cues

Sexual exhaustion in male rats has been proposed as a case of alliesthesia. For the individual engaged in sexual behavior, its only purpose is its execution. Repeated execution of copulatory acts may reduce the reward value of the female or of the execution of copulatory reflexes. In the absence of sexual consummatory behavior, negative alliesthesia diminishes over time.

On the other hand, the Coolidge effect [345], a phenomenon in which males show renewed sexual interest in a novel female following copulation to satiety with another female, could be an example of dishabituation or could be related to negative sexual alliesthesia. However, these interpretations are based on behavioral observations. Measurements of hedonic correlates would be necessary to confirm or rule out the hypothesis that sexual behavior is in fact a case of alliesthesia. Also human studies support these interpretations [267]. In this light, the Coolidge effect may be seen as a form of sexual-specific satiety (see chapter SSS).

V.3.   Origin of Alliesthesia

For the appearance of alliesthesia, at least two sensors and an integrative centre are required: the peripheral sensor detects the environmental stimulus and the internal sensor senses the internal state of the subject. The integrative centre is a 'comparatory device' which has 'prerecorded' a set-value for the regulated internal parameter concerned. It must be capable of comparing the set value with the real actual value. If alliesthesia is to play a role in physiological regulation, the preceding device must be connected to an 'adaptatory device' which in turn can arrange adaptation of the actual value

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[30] Alimentary alliesthesia, *i.e.* alliesthesia for olfactory and gustatory food cues, from fr. *alliesthésie alimentaire*

to approach the set value. There are three possible situations: 1, the actual value measured equals the set value: in this case, no response is necessary to guarantee homeostasis of the regulated parameter; 2, and 3, the actual value is above/below the set value: in these cases, the 'comparatory device' communicates a signal containing the amount of difference (delta, Δ) and its sign (+/-) to the 'adaptatory device'.

In temperature regulation (and thermic alliesthesia), hypothalamic sensors [346,347,348,349] measure deep body core temperature, compare it to the set value (normally 36.5°C, elevated in fever, lowered in hypothermia), and, if they do not match, communicate the signed (+/-) difference to motivational brain regions, which in turn interpret the incoming signals, aroused by an external stimulus, as a function of this signed difference and arouse positive or negative sensation. If the external stimulus is appropriate to correct the internal 'trouble', CNS hedonic pathways will make this stimulus feel pleasant and appetizing. If the stimulus worsens the situation, it is perceived as unpleasant, if the stimulus is neither beneficial nor noxious, it will be perceived as hedonically neutral. The physiological regulatory response will be autonomic (vasodilatation, sudation/shivering) and behavioral (approach/withdrawal from a source of heat, un/covering...).

The control of food intake follows the same principle, but is more complex, as instead of one regulated parameter (core temperature), there may be many more, although there may be principle ones like plasma glucose (representing metabolizable energy), degradation products of proteins or brain-gut peptides (leptin, NPY...).

Alimentary alliesthesia was demonstrated in subjects prepared with naso-gastric or naso-duodenal tubes in order to exclude olfacto-gustatory stimulation in 1970 [289]. The 'food'-stimulus, consisting of either a sweet (*e.g.* sucrose) or salty (NaCl) solution of defined concentration, was infused through the tube directly into the stomach or the upper duodenum. Instead of food-boli arriving successively and over the normal time-span of a meal (15 to 45 min), the solutions were infused at once (as a 'load' bolus). The experimental evaluation itself consisted in presenting taste- or odor-samples to the subject prior to the load, which served as a reference-value and then every 5 to 10 min during the ensuing 2 h. Taste samples, consisting of sweet or saline solutions of various concentrations, were not ingested but spat out after giving a hedonic note and the mouth was then rinsed [234,235,285].

V.4. Mechanism(s) of Alimentary Alliesthesia

Gastric infusion of a sucrose solution was able to turn the sensation of sweet aversive [239], although no sensory signal was transmitted to the CNS from olfactory and gustatory receptors *i.e.* the first and second order peripheral analyzers. The 'vagal intestinal glucoreceptors', located in the upper small intestine (duodenum and proximal jejunum)[240], *i.e.* the third order peripheral analyzer, therefore are implicated in giving feedback on concentration and quantity of ingested carbohydrates. The signal elicited by the concentration of glucose in the digestive tube is conveyed *via* afferent sensory fibers of the vagal nerve to the CNS. The decrease, but not elimination of negative alimentary alliesthesia by vagotomy [261] suggests that another subordinate mechanism may involve the release of duodenal or other gut hormones which carry the signal to the CNS, not *via* neural pathways but *via* the blood plasma. Furthermore, the existence of 'nutrients-sensing intestinal receptors' [55] has been proposed, which could be one way of sensing and communicating the presence of nutrients to the CNS, supposedly providing some specific information on intestinal content. In contrast, hepatic glucoreceptors do not seem to be a signal for negative alimentary alliesthesia, as direct injection of glucose into the *arteria mesenterica superior* did not cause it [236], nor do postabsorptive signals as 1, negative alliesthesia occurs before complete absorption from the gastrointestinal tract, and 2, because injection of glucose into a peripheral vein is ineffective. In the CNS, the amount of ingested carbohydrate (*e.g.* glucose) seems to be computed from the frequency and duration of incoming signals from intestinal glucoreceptors

[137]. However, the time course of negative alimentary alliesthesia for carbohydrates and NaCl (delayed onset of 0-15 min, gradual growth during 30 min, peak at 45 min *post ingestion*, and disappearance 2 hours after intake) suggests that this phenomenon contributes to general satiation and subsequent satiety, thus ensuring abstinence from food-intake during the post-prandial absorptive period.

V.5. Internal signal implicated in Alimentary Alliesthesia

Important studies showing that alimentary alliesthesia is indeed post-ingestive but preabsorptive, and that the duodenum and not the stomach stands at the origin of alliesthesia are presented in the subchapter on animals.

V.5.1. Hepatic receptors

The hepatic glucoreceptors, first described in 1963 by Russek [350,351,352] are not responsible for the internal signal that triggers negative alimentary alliesthesia for sugar because injection of glucose into the *arteria mesenterica superior* in humans is not followed by negative alliesthesia in response to sweet gustatory stimuli [236].

V.5.2. Intestinal receptors

In 1968, negative gustatory alliesthesia for sweet was produced by sucrose directly delivered into the stomach by deglutition or intubation. However, gustatory alliesthesia for sweet stimuli did not follow mechanical (infusion with water) or osmotic (infusion with saline) stimulation of the stomach and did not correlate with blood glucose levels [285]. These findings suggested that the internal mechanism of alliesthesia 1, involved neither gastric stretch- nor osmoreceptors, and 2, had to be found between the lumen of the upper gastrointestinal tract and the blood circulation.

In 1977, it was postulated that duodenal nervous chemoreceptors sensing nutrient concentration were at the origin of olfactogustatory alliesthesia [239] in humans, because:

1, olfactory and gustatory alliesthesia occurred after gastric glucose infusions;

2, glucose solutions produced a more intense and more rapid alliesthesia when directly injected into the duodenum than into the stomach;

3, maximal negative gustatory alliesthesia for sweet stimuli occurred with the highest infused concentration, *i.e.* smallest volume;

4, maximal negative olfactory alliesthesia for the odor of anchovy and meat extract occurred after the most concentrated gastric load.

Concentration dependency points more to chemoreceptors (present in the small intestine) while volume dependency would have pointed more to mechanoreceptors registering distension (present in the stomach);

5, gastric mannitol (a nonabsorbed and nonmetabolizable sugar) was followed by strong negative alliesthesia for alimentary stimuli, proving that the signal of alliesthesia is preabsorptive.

It has been reported that duodenal infusions of sweet molecules elicited stronger alliesthesia than did gastric infusions [239]. Thus, the intensity of alimentary alliesthesia depends on the site of administration.

In 1978, sensory vagal neurons have been discovered in the small intestine (duodenum and upper jejunum) of cats. The endings of these neurons, located in the villi beneath the epithelial layer, were named 'vagal intestinal glucoreceptors' and are activated by the perfusion of glucose or other

carbohydrates. Their activity (*i.e.* discharge frequency) depends on the carbohydrate infused and on its concentration. They cannot be activated by intestinal contractions/distensions, stroking of the mucosa, over-distension of the bowel, perfusion with alkaline/acid solutions, or by osmotic pressure (ineffectiveness of isoosmolar KCl, NaCl). They belong to the vagal sensory component (their number is reduced by unilateral selective sensory vagotomy)[240]. Therefore, it has been proposed that they send feedback on the nature of ingested foods to the CNS and are thought to generate the internal signal for gustatory alliesthesia for sweet stimuli (not for salty).

It has also been suggested that cholecystokinin (CCK) is responsible for alimentary alliesthesia because CCK-8 (synthetic octapeptide of cholecystokinin) could suppress the intake of a sucrose solution in water-deprived rats. This effect was independent of sucrose-metabolism because it occurred before absorption of sucrose from the gastrointestinal tract [300]. In fact, the contribution of CCK in producing negative alliesthesia is a possibility as vagal afferent neurons are a target of CCK for the inhibition of food intake [353].

These studies suggest that the origin of the internal signal of alliesthesia might be situated in the duodenum.

V.6.   Specificity of Alimentary Alliesthesia

V.6.1. Olfactory alliesthesia

All of the experiments on olfactory alliesthesia have been carried out in human subjects.

In 1970, negative olfactory alliesthesia was observed for the odor of orange syrup (*i.e.*, an odor with 'sweet significance') after oral intake of a glucose solution [287].

In 1973, negative olfactory alliesthesia was shown to be specific for odors related to food (meat, cheese, fish, honey) because only they and not odors of substances unrelated to food (lavender, bleach, ink {reconfirmed in 1974 [297] and in 2008 [277]}) or of food-associated products (tobacco, wine, coffee) were followed by negative olfactory alliesthesia after eating an *ad libitum* meal (composed of bread, butter, ham, French fries, concentrated milk and an orange) [295].

In 1974, negative olfactory alliesthesia appeared for the odors of both, sweet (orange syrup) and fatty foods (peanut butter, pork fat, butter) after a gastric load of glucose, but not after an isocaloric gastric load of peanut oil [297]. This suggests that negative alliesthesia is not related to the energy content, but requires the presence of glucose in the digestive tract. Inversely, gastric glucose did not produce olfactory alliesthesia only for sweet odors, but also affected fatty stimuli as well, suggesting that olfactory alliesthesia is unspecific to the nature of macronutrient ingested, or that it affects all alimentary odors, independently of the macronutrient ingested.

It has been proposed that the salivary response, which is related to hedonic responses, reflects negative olfactory alliesthesia. Oral ingestion of a glucose solution specifically reduced stimulus-induced salivation (SIS) induced by a honey-flavored olfactory stimulus but not by lemon juice or meat-flavor extract [302].

V.6.2. Gustatory alliesthesia for primary sense

The first protocol that evidenced gustatory alliesthesia for sweet oral stimuli in humans was established in 1966 [284]. It showed for the first time that ingestion of a sucrose solution diminished pleasantness of sweet sucrose taste.

In 1970, it was observed that gastric infusion of a hypertonic solution of glucose or sodium chloride via gastric tubing induced negative gustatory alliesthesia for sweet, and NaCl for salty taste, but not *vice versa*, indicating that gustatory alliesthesia is specific for sweet (sucrose) and salty (NaCl) tastes [289].

In 1976, it was shown that negative gustatory alliesthesia for sweet taste (saccharose) occurs equally after the intake of glucose or of beefsteak with oil, which is mainly composed of proteins, and to lesser degree of lipids, but not after the intake of carbohydrates [238]. This result suggests that gustatory alliesthesia for sweet stimuli is not specific to carbohydrates as the presence of proteins in the digestive tract evoked the same response.

In 1992, the facial consummatory responses of rats to the sweet taste of sucrose after gastric loads turned aversive only after high caloric, but not after low caloric gastric loads of carbohydrates (glucose), proteins (casein hydrolyzate), and lipids (oil), and produced negative gustatory alliesthesia of equal magnitude, showing that the intestinal signal for alimentary alliesthesia is unspecific for macronutrients [256].

From these results, it can be concluded that gustatory alliesthesia 1, is specific for sweet and salty tastes, 2, is non specific for the macronutrient ingested, and 3, depends on the caloric load ingested.

V.6.3. 'Flavor alliesthesia'?

In 1982, a study reported that negative alliesthesia for a sweet (vanilla pudding) or a non-sweet (mashed potatoes) flavor occurred after oral preload (being solid/liquid, sweet/non-sweet, and high/low in energy content) of processed cereal and dairy products (cake, bread, or milk). It was greater after high-caloric and solid preloads. However, this alliesthesia was unspecific for sweet versus non sweet flavors, as both flavors ingested produced equal alliesthesia for both flavors tasted [245]. A single observation from 1974 described a case of positive alliesthesia from one day to another [334], *i.e.*, over a longer time-span than is usually monitored. However, in both cases the foods were ingested orally and therefore orosensory feedback, *i.e.*, a participation of sensory-specific satiety cannot be ruled out.

V.7. Time-course and Intensity

The temporal pattern of gustatory alliesthesia was examined in human subjects. After ingesting a fixed amount of sucrose solution, either by deglutition or by circumvention of their chemical senses via naso-gastric/naso-duodenal intubation, subjects had to rate the pleasantness of a sweet gustatory stimulus at 3 minute intervals during the course of two hours. Negative gustatory alliesthesia appeared at 5 to 10 min after ingestion (Figure 11, upper curve) and successively became more prominent over the two hours following ingestion. This effect was absent after mechanical or osmotic stimulation of the stomach. In this study however, no correlation with blood glucose level was detected (Figure 11, lower curve) [284]. In another study, negative gustatory alliesthesia for sweet stimuli in subjects receiving intragastric glucose loads appeared 15 min after the load, increased up to a maximum at about 55 min, and then decreased [235].
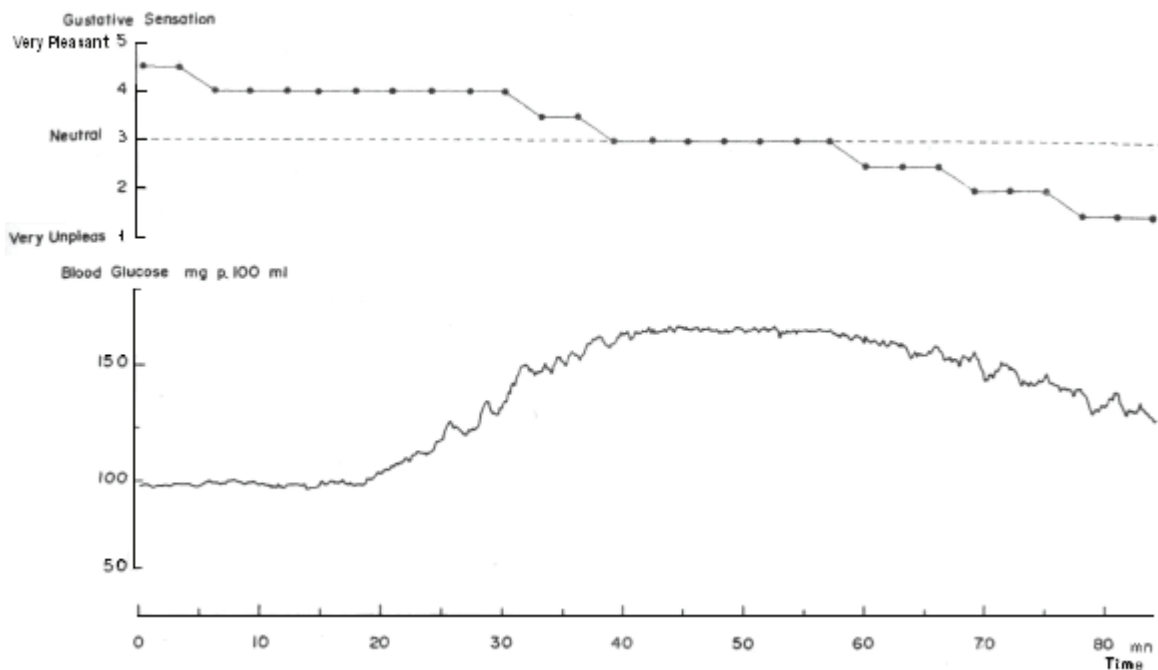
Figure 11. The time course of negative gustatory alliesthesia.
Shift in the pleasantness of a gustative sweet sensation (upper curve) and level of blood glucose (lower curve) when all successive test samples (20% saccharose in 50ml) were ingested. Each point on the upper graph represents a test; both curves represent data from one subject. From: [284]

Negative olfactory alliesthesia for food-related stimuli after eating a standard meal *ad libitum* reached its nadir within 60 min after the end of intake of the meal (its onset remained unmentioned), then decreased and disappeared within the next 60 min (*i.e.* 2 hours after the end of the meal) [295]. The duration of negative olfactory alliesthesia is therefore about 2 hours, marked by the return to the pre-prandial level [234].

Negative alimentary alliesthesia appeared 15–20 minutes after ingestion, then built up and reached its nadir 40–50 minutes after ingestion. Its duration was independent of the ingested dose, but the lesser the amount of glucose ingested, the earlier the decrease occurred [291]. In 1977, a study again reported the nadir of negative alliesthesia at 45 min after the gastric load, after which negative alliesthesia decreased [239].

Several studies [294,299,301,306,307] expressed results as "maximal alliesthesia" (*i.e.* the mean of the most negative values of all subjects tested for a set of stimuli-concentrations at a given moment). This suggests that 'mean alliesthesia' did not reach significance in all cases.

In summary, gustatory alliesthesia has been demonstrated to follow a characteristic temporal pattern in human subjects. The strength of its nadir depended upon carbohydrate concentration, and its duration upon carbohydrate quantity (*i.e.* the caloric content). The pattern was unrelated to plasma glucose levels. In contrast, osmotic or mechanic stimulation of the stomach was uncapable to produce alliesthesia.

V.8.   Influencing factors

V.8.1. Food-related factors

1. Caloric content
In humans, it was also shown that the importance of negative gustatory alliesthesia is related to the amount of glucose ingested [235].

Orally ingested sweet caloric (glucose) and non caloric (cyclamate) solutions were equally effective in inducing negative gustatory alliesthesia for sweet taste in humans [292]. In college

students, the high-caloric versions of an either solid (yellow-cake versus saccharin-cake) or liquid (sugar-milk versus saccharin-milk) oral preload produced stronger negative alliesthesia for both the sweet (vanilla pudding) and non-sweet (mashed potatoes) flavor [245].

In contrast, a study using *Gymnema sylvestre* extract (which reduces perception of oral sweetness) before drinking a milkshake preload of 240ml (with sucrose, aspartame, or without sweetener) failed to demonstrate negative gustatory alliesthesia. Furthermore sweetness perception (reduced by *Gymnema sylvestre*) and gustatory pleasantness for sucrose (from before to 60 min after preload) was unrelated to caloric density [303]. In accordance with this study, it has been observed that a meal induced similar negative flavor alliesthesia for sucrose- and aspartame-sweetened drinks (but not for mineral water or orange-flavored mineral water) [323]. Therefore, the studies on the influence of energy content of foods on alliesthesia have not led to unequivocal results.

In rats, five sweet taste-stimuli (glucose, cyclamate, saccharin, aspartame, mannitol), orally administered in concentrations adjusted to equalize sweetness, aroused similar ingestive facial responses. However, oral ingestion of sucrose was followed by facial responses typical of negative alimentary alliesthesia only after an isovolumetric gastric load of glucose and mannitol, but not after cyclamate, saccharin, and aspartame. Artificial non-nutritive sweeteners, molecules which do not exist in a natural environment, therefore did not produce gustatory alliesthesia for sweet taste [260].

In summary, negative gustatory alliesthesia seems to be unrelated to ingested metabolizable energy, but rather to the concentration or the amount of sweet molecules present in the small intestine.

2. The nature of food

Also the aggregate state of foods can influence alliesthesia: solid preloads provoke greater negative alliesthesia than liquid preloads for the flavor of vanilla pudding and mashed potatoes [245]. However, caution should be exercised in interpreting such results as an effect of alliesthesia whenever foods were orally ingested because of the influence of sensory-specific satiety. Only by excluding olfacto-gustatory stimulation can such results be considered purely due to postingestive events.

3. Macronutrients

In humans, negative olfactory alliesthesia appeared for the odors of sweet and fatty foods after a gastric glucose load but not after an isocaloric gastric load of peanut oil (1974)[297].

This suggests that negative olfactory alliesthesia is unspecific to the nature of macronutrient ingested, or that it unselectively affects all alimentary odors, independent of the macronutrient ingested because gastric glucose did not produce olfactory alliesthesia specifically for sweet odors, but also affected fatty stimuli.

In cats, the activity (*i.e.*, discharge frequency) of vagal intestinal glucoreceptor-neurons depended on the specific carbohydrate (the most active being glucose) the intestine was perfused with, and increased with carbohydrate concentration. Neither salt (KCl and NaCl) stimuli of the same osmolarity, nor mechanical stimulation could elicit a similar response [240].

In rats, negative gustatory alliesthesia to oral sucrose of similar magnitude was observed after high-caloric gastric loads (3g glucose, 3g casein, 1.4 ml oil). No negative alliesthesia was observed after gastric injection of water and high-caloric gastric loads (1g glucose, 1g casein, 0.6 ml oil), showing that the intestinal signal for alimentary alliesthesia is unspecific in rats [256].

V.8.2. Intrinsic and environmental factors

1. Plasma glucose level

Positive gustatory alliesthesia for sweet taste can be induced by the injection of insulin. The taste of sugar solutions is perceived as more pleasant 36-48 min after insulin than after isotonic saline. The hedonic changes induced by insulin correlated negatively with blood sugar at 30 min after insulin and positively with blood sugar at 50 min after insulin. It was concluded that insulin, rather than a physiological satiety signal, seemed to be an unreliable emergency response [241,243].

2. Ambient temperature

Environmental ambient temperature (tested at between 0°C and 40°C) affected pleasure ratings for tastes (sucrose-solution, isotonic NaCl solution), food odors (bacon, concentrated meat extract, anchovy, cheese) and non-alimentary odors (lavender, bleach) differently. While pleasure for non-food stimuli was unaffected by ambient temperature, an increase in ambient temperature moderately decreased pleasure for food-stimuli. A cold environment almost completely suppressed negative alliesthesia for sweet stimuli. The return to 20°C restored negative alliesthesia. These observations were independent of the temperature of the solutions tasted [299].

3. Gender and preference for sweet taste

Gender and individual preference for sweet taste can influence alliesthesia. Hungry and sated men and women rated sweetness and pleasantness of a lime drink (sweetened with four concentrations of sucrose) and their personal preference for sweet taste. Only women displayed negative gustatory alliesthesia when sated, but not men. Women rated the same solutions as sweeter than did men [259]. In this study however, the meal composition was not standardized and the criterion for satiety/hungriness (having/or not eaten during past 2 h) was relatively crude. Furthermore, Laeng *et al.* mistranslated alliesthesia as "other taste" instead of the correct "changed sensation".

4. Mood

The affective state can influence gustatory alliesthesia: Seasonal Affective Disorder (SAD) patients in whom a combined glucose tolerance–alliesthesia test was done in winter (before and after 1 week light therapy) and in summer, perceived the taste of high sucrose concentrations (10, 20 and 40%) as more pleasant when depressed in winter than after 1 week light therapy, with as well as without a glucose load. A comparison between winter-light and summer showed no differences in hedonic ratings when euthymic. When depressed in winter, SAD patients also exposed faster post-glucose glycemic and insulin responses to oral glucose, maybe as a result of accelerated gastric emptying [264].

5. Smoking

Smoking can influence gustatory alliesthesia. Smokers usually gain weight after quitting smoking. Oral and transdermal nicotine does not modify initial pleasure for sweet taste, but accelerates the onset negative gustatory alliesthesia for repeatedly ingested sweet stimuli, indicating a lowering of the body-weight set-point by nicotine. Quitting smoking eliminates nicotine from the organism. If nicotine artificially lowers the body-weight set-point, body weight gain may be due to a rise in the set-point [268].

6. Disease

Sickness and inflammatory states can influence gustatory alliesthesia. Decreases in food intake frequently accompany inflammation. Changes in taste perception could contribute to this modification of feeding behavior. In rats, lipopolysaccharide (LPS)-induced sickness reduces fluid

intake but does not change taste response to unpalatable (bitter: quinine) or palatable (sweet: sucrose or saccharin) substances. LPS increases aversive reactions and decreased hedonic responses to mixed (bittersweet: sucrose + quinine) taste. This increase in 'choosiness' could play a role in the adaptation to sickness [333].

7. Bodyweight
Surgery & body-weight
Gastro-intestinal weight-loss surgery (bariatric surgery [354] and duodenal switch [355]) modifies negative gustatory alliesthesia. Although hedonic ratings for sweet decrease only insignificantly after surgery, negative alliesthesia and satiety are three times faster after surgery (*i.e.*, times to reach negative gustatory alliesthesia and satiety are three times shorter)[270].

Weight-loss & dieting
Losing significant weight erases negative gustatory alliesthesia: after a 10% loss of body-weight, gustatory and olfactory alimentary sensations stay pleasant after the ingestion of glucose. The initial sensory response returns after return to the initial weight. The affective component of olfactory and gustatory perceptions is related to body weight, which is regulated with a set-point. The mechanism of this regulation is the negative feedback that adjusts the pleasure evoked by taste and odor of food. The regulating mechanism of body mass is termed "*ponderostat*" [288]. Dieting can reduce pleasure for sweet tastes. Female dieters rate sucrose solutions tasted prior to and after ingestion as less pleasant than nondieters. Oral ingestion of glucose was followed by negative gustatory alliesthesia for sucrose solutions in both, dieters and nondieters [248]. Dieting and weight loss in obese female subjects reduced the time to reach hedonic indifference (from 22 to 16 min), as well as the onset (from 33 to 24 min) of negative gustatory alliesthesia for sweet tastes, while maximum or minimum hedonic ratings remained unaffected. The observed accelerated onset of negative alliesthesia was interpreted as a response to a lowered body-weight set-point [271].

Weight gain & obesity
In 1970, it was shown that obesity can erase negative gustatory alliesthesia because ingestion of glucose did not cause shifts in pleasure for sweet tastes from pleasant to unpleasant, indicating decreased sensitivity to internal signals in obese persons [290].

In contrast, in 1972, no differences in alliesthesial reactivity between obese and normal-weight persons were observed [292]. It was suggested that the ponderostat of obese subjects was adjusted to a higher level.

In support of this, is has been observed that dynamic obesity eliminated negative gustatory alliesthesia in obese women, who showed gustatory alliesthesia of smaller amplitude than normal-weight women. If obese subjects are differentiated into 'static' obese (stable body-weight) and 'dynamic' obese (recent weight-loss), normal negative alliesthesia is observed in static obese (identical with normal-weight subjects) and zero alliesthesia in dynamic obese beneath the body-weight set-point, suggesting the existence of a '*ponderostat*' [237].

Massive overfeeding cures can cause the disappearance of negative alliesthesia: in men in Cameroon following the traditional fattening cure named "Guru Walla" (2 months of extreme overfeeding resulting in weight-gains of 10-20 kg), ingestion of glucose was followed by zero gustative alliesthesia for sweet after weight-gain. So, not only weight-loss, as previously reported, but also excessive weight-gain results in a disappearance of alliesthesia [305].

8. *Eating disorders*
Anorexia nervosa

Alimentary alliesthesia persists in anorexia nervosa, although it is associated with major weight-loss: a glucose load was followed by significant negative alliesthesia. [306] While in normal subjects, glucose-induced negative alliesthesia is known to disappear upon loss of weight, it persisted in anorexia nervosa despite major weight loss [307][31].

V.8.3. Modulation by drugs manipulating reward-circuits

1. *Serotonin agonists & antagonists*

The serotonin agonist dexfenfluramine influences motivational ratings and food consumption. However, it did not affect glucose-induced negative gustative alliesthesia in lean subjects. In the obese, negative gustative alliesthesia was neither present nor reinstated by dexfenfluramine. Serotonin mechanisms seem to affect control of eating by suppression of the subjective motivation to eat, not by a reduction in pleasantness of sweet tastes, leading to a reduction in food intake in lean and obese subjects [252].

On the other hand, the serotonin antagonist cyproheptadine did not affect affective ratings for sweet gustatory stimuli in fasted subjects, but reduced glucose-load induced negative alimentary alliesthesia [253].

Thus, equivocal results have been reported on the influence of serotonin on alliesthesia.

2. *Opioid antagonists*

The opioid-antagonist naltrexone has a strong action on alimentary pleasure by decreasing the hedonic rating for sweet sucrose solutions and by a strong potentiation of intragastric glucose-induced alliesthesia [306]. Commentary: note that alliesthesia was misspelled as "allesthesia" in this and the following paper.

In anorexia nervosa (AN) patients (in contrast to normoponderal subjects), naltrexone neither decreases preference for the taste of sucrose after intragastric glucose nor enhances glucose-induced negative alliesthesia. As the basal plasma β-endorphin level is 6x higher in AN than in normal subjects, impaired activity of the endogenous opiate system might be a reason for food refusal and body-weight loss in AN. While glucose-induced negative alliesthesia disappears on weight-loss in normal subjects, it persists in AN, despite major weight-loss. [307]

V.9.   Behavioral equivalent in animals

Behavioral correlates suggesting the existence of alliesthesia in animals were observed in fish and in rats.

V.9.1. Fish

It has been suggested that alliesthesia may explain the food-searching behavior in a fish species, *Gasterosteus aculeatus Linnaeus*[32]. Feeding behavior consists of the acceptance and rejection of food items. Prey rejection is a measure of state change during feeding. Not only general satiety, but also sensory stimuli from preceding encounters with food determine subsequent behavior upon exposure to food [298].

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[31] NB: alliesthesia was misspelled as 'allesthesia' in this article, not to be confused with the pathologic symptom
[32] the three-spined stickleback

Discovery of a food object influences searching behavior. Searching behavior after acceptance, termed 'area restricted searching', is characterized by a reduced tendency to move away from the site of eating and by increased searching intensity. Searching behavior after rejection, termed 'area avoided searching', is characterized by an increased tendency to move away from the site of the prey and a decrease in search-intensity [356].

Area restriction/avoidance subsequent to eating/rejection was compared with previous behavior/experience during same feeding session. The motivation to eat/reject was not simply due to increasing satiation with cumulative intake over a session. Short-term positive/negative motivational after-effects were present after eat/reject encounters. While eat encounters increased the probability that subsequent prey would be eaten, reject encounters reduced that probability [357]. However, while the existence of alliesthesia has been confirmed in mammalian species and in *vertebratae* in general, it can be doubted that true alliesthesia (which requires perception of hedonics) exists in fish.

V.9.2. Rats

In the rat, facial consummatory responses reflect ingestive and aversive perceptions and can be used as a behavioral correlate of gustatory alliesthesia in rats.

The typical procedure is injection of a liquid via a gastric or duodenal catheter after which a sweet solution is periodically (every 5 min) injected into the oral cavity over a timespan of 1 to 2 hr to see if and when aversive facial responses occur.

In one study, sucrose was injected into the mouth every five min for one hour, glucose or water were injected into the stomach. While facial consummatory responses were ingestive prior to all loads, aversive consummatory responses were observed only after gastric glucose loads, not after water. The extent of the reversal of consummatory response depended on the concentration of the gastric load, and was independent of its volume and of the amount of injected glucose [254].

In another study, weight-loss suppressed negative alliesthesia after the gastric glucose-load in response to sweet oral stimuli. After the rats had recovered their initial weight, the gastric load was again followed by negative gustatory alliesthesia, paralleling responses in humans and suggesting the existence of a *ponderostat* [255].

When the rats were vagotomized, weak and delayed negative gustatory alliesthesia for sweet stimuli occurred after the duodenal load, paralleling results in humans, thus suggesting that the vagus nerve is its afferent pathway [257].

Rats equipped with electrodes in their lateral hypothalamus (LH) increased electrical self-stimulation during food restriction and reduced it during subsequent re-feeding. Weight-loss activates an opioid mechanism that facilitates LH self-stimulation. The association of the LH with feeding and its connections with gustatory structures suggest that food restriction promoted self-stimulation is related to positive alliesthesia [258].

Rats receiving a gustatory stimulus of sucrose intraorally were injected with cholecystokinin (CCK) intraperitoneally (IP). While ingestive responses were observed before IP CCK, negative alliesthesia was observed after IP CCK. After weight-loss, IP CCK was not followed by negative gustatory alliesthesia for sweet stimuli. After the rats had recovered their initial weight, IP CCK was again followed by negative alliesthesia [262]. In another study, after vagotomy, IP CCK was not followed by negative alliesthesia while a sham operation resulted in strong negative alliesthesia, suggesting that CCK mediated the duodenal preabsorptive signal for alimentary alliesthesia, with the vagus nerve as the afferent pathway [261].

IP injections of epinephrine and glucose were followed by anorexia but failed to induce negative gustatory alliesthesia. The dissociation of alliesthesia from anorexia suggests that distinct mechanisms are responsible for alliesthesia and for food intake [315].

Food-restriction in rats is accompanied by positive alliesthesia for the taste of alcohol [266].

Behavioral markers of an aversive taste (gapes and chin rubs) present in the oral cavity increased at the end of oral intake of a sweet sucrose stimulus, indicating that the taste perceived by the rat turned aversive towards the end of infusion, contributing to the termination of ingestive behavior, which is compatible with negative gustatory alliesthesia. [329].

V.10. Innate or acquired?

Observations in human newborns suggest that olfactory alliesthesia is either 1, acquired during the milk-intake during the first 3 days of life, 2, acquired in a late stage of the prenatal period or 3, 'innate' (*i.e.* genetically imprinted).

A first report from 1974 described alliesthesic reactivity patterns towards simple foods in a six hour old newborn: it opened its mouth when smelling certain foods but not with others; it actively rejected food using its tongue if feeding was continued beyond specific satiation [334].

A study confirmed that human neonates show olfactory alliesthesia at least as early as the 3rd day of life. The shift in motivational state from hunger to satiety is marked by their behavioral and autonomic responsiveness to artificial and food-related odors as a function of stimulus-familiarity. Facial movements and autonomic responses (respiration rate: RR, heart rate: HR) to 5 olfactory stimuli (familiar milk, unfamiliar milk, protein hydrolysate, vanillin, control) were recorded in 3-day-old neonates during sleep, one hr before and after bottle-feeding. Olfactory detection discriminating between odors and control stimulus was indicated by RR. Neonates reacted with higher HR change when smelling their familiar milk postprandially. Postprandially, aversive facial movements were more often caused by the odor of familiar or unfamiliar milk than by the other olfactory stimuli [265].

However, these results dubbed alliesthesic seem to be more due to sensory-specific satiety, because of 1, oral intake of the milks, and 2, because of the flavor specificity of the hedonic decline.

V.11. Functions and finality

V.11.1. The ponderostat
It has been suggested that alimentary alliesthesia is implicated in the regulation of body weight. The concept of the '*ponderostat*' is based on findings about the influence of dynamic body weight on alliesthesia. The ponderostat is thought to register the difference between the actual value and the set point of a regulated variable. It will assess the internal feedback after food intake and in turn inform the conscience of the individual on this difference through hedonic sensations [233,293].

V.11.2. The function of alimentary alliesthesia
The time-course of alimentary alliesthesia suggests that alliesthesia does not act in the short term and thus does not induce satiation (*i.e.* stop intake), but rather sustains abstinence from intake during the post-prandial period (*i.e.* satiety phase). Among hedonic phenomena, alliesthesia seems to play an intermediate role in limiting food intake, as its onset and maximum occur later than those of sensory-specific satiety, but before conditioned satiety, which requires repeated intake and combines sensory properties of a food with its postingestive effects even several hours after intake (see subchapter on *Conditioned satiety*).

Another fact that supports this view is the relative unspecificity of alliesthesia for macronutrients and flavors. Satiation can be very specific (*i.e.* towards the sensory properties of a given food). Eating one food to satiation leaves the possibility of hedonic acceptance of other uneaten foods in the same meal (see chapter *Sensory-specific satiety*). Taken together, the finality of alimentary alliesthesia seems to be the monitoring of abstinence from food-intake during the postprandial period.

VI. SENSORY-SPECIFIC SATIETY (SSS)

VI.1. Definition

Sensory-specific satiety (SSS) has been defined as "the phenomenon in which the decrease in the palatability and acceptability of a food which has been eaten to satiety are partly specific to the particular food which has been eaten" [372]. This decrease has been shown to extend to all sensory properties of foods: most notably to aroma and flavor, but also to consistency (*i.e.*, texture, shape, mouth feel)[359], and to visual aspects (look and color)[360].

VI.2. Standard test procedure

The standard test procedure to demonstrate SSS is as follows. Moderately hungry normal weight, non-dieting individuals have to rate the perceived pleasantness of the flavor of small portions of several sweet and savory foods. Following these initial ratings, one of the foods is offered as a test meal and eaten *ad libitum*, which is likely to lead to specific satiation. Thereafter, the sample foods are re-rated (once, or at intervals over 1 or 2 hours) to screen for changes in preference. In addition, after the last rating, subjects are asked to select a food out of the sample set as a second course in order to determine if the food consumed in the first course influenced subsequent food choice [368].

VI.3. Historical aspects

The first observations were made by Jacques Le Magnen in 1956 [604] in rats fed a complete synthetic diet with one of four different flavors added (citral, eucalyptol, benzylacetate or benzaldehyde). Although the nutritional composition was identical, rats ate more in the same meal when the four odors were presented successively than when only a single flavor was added.

Given that the rats continued eating *ad libitum* with each new odor presentation showed that the sensory properties of foods are an important determinant of satiation. However, Le Magnen underlined that these factors interact with gastrointestinal feedback to the CNS because the additional amount eaten declined across the successive segments of the meal, related to a progressive increase in gastrointestinal content [605].

Le Magnen's finding attracted little scientific attention at that time [606], but came under the spotlight when it was reexamined in 1981 in humans by Barbara Rolls *et al.* who named it 'sensory-specific satiety' [358]. Le Magnen noted the discrepancy between his original term 'satiation' and the in his eyes inaccurate term 'satiety' [606]. In B. Roll's experiment, subjects had to taste (without swallowing) and rate subjective pleasantness (also referred to as 'liking' or 'palatability') of eight foods (chicken, beef, walnuts, chocolate, cookies, raisins, white bread, tinned potatoes) before and after eating one of these foods *ad libitum*. The pleasure of the taste of the food eaten to satiation decreased more than that of the other foods tasted but not eaten. This specific decrease in pleasantness of the flavor of the eaten food correlated with the subsequent intake of uneaten foods in an unexpected second course. B. Rolls assumed that there might exist "an inbuilt mechanism which helps to ensure that a variety of foods, and thus of nutrients, is consumed" [358].

VI.4. Sensory modalities

The specificity of SSS has been shown to be based on the sensory properties of the foods. Accordingly, taste-, smell-, texture- and appearance-specific satieties have been identified [413]. Although SSS is mainly sensory, and partial SSS can be produced solely by sensory stimulation without any ingestion (smelling or chewing a food for as long as it would have been during a

meal)[390], full SSS requires intake. Feedback from the oral cavity, esophagus, stomach or proximal duodenum may therefore contribute to full SSS.

VI.4.1. Flavor-specific satiety

SSS was shown to be specific to the food eaten [358] but might also affect other uneaten foods with similar sensory properties: after eating a sweet food to satiation, the pleasantness of the taste of other sweet-tasting foods were reduced while that for savory (salty, spicy) foods were unaffected or even increased, and inversely when a savory food was eaten [358,416]. Hence, sensory-specific interactions between foods similar in savoriness or sweetness have been reported [362,383,391]. Similarly, eating a food with a specific flavor also reduced liking for a different food if it had a similar flavor (pasta with tomato sauce *vs*. ground beef with tomato sauce; blueberry-flavored whipped cream *vs*. blueberry puree; chicken *vs*. chicken bouillon)[382]. Consequently, crossovers between flavors have been reported [594], in that flavor similarity of a previously consumed flavor decreased the probably of the same flavor subsequently being chosen [440].

VI.4.2. Olfactory and taste sensory-specific satiety

Olfactory SSS and taste SSS have been described. Partial olfactory SSS and taste SSS can be produced by smelling or chewing samples of a food for approximately as long as the food would normally be eaten in a meal. Olfactory and taste SSS do not require food to enter the gastrointestinal tract and do not depend on the ingestion of calories [390]. Olfactory SSS in humans has also been evidenced by *f*MRI where activation of the orbitofrontal cortex area specifically decreased when subjects smelled banana odor after eating bananas to satiation, while the pleasantness of vanilla odor was unaffected by the intake of bananas [400,401].

VI.4.3. Texture-specific satiety

The specificity of SSS was proved to extend to the sensory modality of touch. Changing the shape of food (affecting mouth feel) by successively offering different shapes of pasta decreased the pleasantness of the shape eaten compared to the shape not eaten [359].

In another study [391], the pleasantness of texture was rated for eight test foods of which one was eaten *ad libitum*. The foods eaten were the hard and soft versions of a savory food (ham and cheese sandwich on baguette *vs*. white bread) or of a sweet food (apples *vs*. applesauce). SSS for the eaten food was specific for texture**.** After comparing the contribution of texture (the hardness dimension) to SSS, the term 'texture-specific satiety' was proposed.

VI.4.4. Appearance-specific satiety

The specificity of SSS extends to the sensory modality of vision [359,360,388]: After eating sugar-coated chocolates of one color, the pleasantness of the taste of the eaten color declined more than that of uneaten colors and led to higher caloric intake (by 14%) than with the preferred color, although there was no difference in taste [359].

VI.4.5. Motivation-specific satiety

SSS for the sight and taste of food is also motivation-specific because in hungry and thirsty humans, the pleasantness of the sight and taste of food but not water is decreased by ingesting it to satiety, and *vice versa* [360].

VI.5. Mechanism

VI.5.1. Intensity perception: adaptation and habituation

The decrease in the palatability of foods that accompanies consumption might be due to peripheral sensory adaptation in the smell and/or taste receptors reducing the intensity of flavor perception. Some studies found that the decrease in the pleasantness of the taste of particular foods did not correlate with changes in the intensity of the taste of those foods [360,415]. It is a known fact that foods can still be tasted and smelled after they have been eaten to satiation [364]. Also, it would not be adaptive if food consumption led to a decreased ability to taste foods. In this way, decreases in the pleasantness of odors after intake, but no changes in perceived intensity were found [607]. Hence it has been suggested that SSS involves a change in the reward or hedonic value of food [360,364] rather than being simply due to sensory adaptation [364]. In support of this, perceived intensity, assessed through recognition thresholds for sucrose and salt, has been observed to be higher during satiety- than during fasting periods, while thresholds for bitter taste showed no difference [608].

These data show that the specific decreases in pleasantness observed in SSS are not due to simple sensory adaptation. A central mechanism, probably related to neuronal habituation in the OFC (see below), was shown to be implicated in the genesis of SSS [372].

VI.5.2. Sensory vs. postabsorptive effects

SSS seems to be primarily related to the sensory stimulation accompanying ingestion as opposed to the postabsorptive effects of foods because changes in the pleasantness of foods occurred rapidly and since the magnitude of these changes did not increase over time as would be the case after nutrient absorption [371].

VI.6. CNS mechanisms

The cerebral correlates of SSS have been objectively demonstrated in two macaque species, the rhesus monkey (*Macaca mulatta*), the cynomolgus monkey (*Macaca fascicularis*), and in the squirrel monkey (*Saimiri sciureus*) through invasive electrophysiological studies [365,369,372, 388,389,409,420,394] and in humans through functional imaging techniques (*f*MRI, PET-scan [400,401,414]).

VI.6.1. CNS studies in non-human primates

1. Electrical activity along the gustatory and olfactory pathways

The electrical activity of single cells has been recorded while monkeys were eating particular foods to satiety to track multimodal sensory processing (taste, smell, view, touch and temperature).

Feeding a primate to satiety with glucose modified neither the gustatory responses to prototypical stimuli (glucose, NaCl, HC1, quinine, glutamate) in the gustatory receptors [372], nor in the nucleus of the solitary tract in the brainstem (1st relay), in the taste thalamus (2nd relay), or in the rostral insula and adjoining frontal operculum (primary taste cortex) [609,361,372,369,610]. Taste processing up to the primary taste cortex consists in tuning the taste signal [372], and representing the identity and intensity of taste inputs [389]. Electrophysiological studies showed that the information coded by single neurons becomes more specific as it passes through the gustatory system until neuronal responses become specific for the food tasted in the secondary taste area of the caudolateral OFC [369]. In the primary taste cortex, electrical neuronal activity also

reflected fat texture, oral viscosity, and temperature, in some neurons combined with taste [612]. However, before reaching the OFC, the signal does not reflect food intake related changes.

While in the absence of food intake, continuous exposure to odors may engender olfactory desenzitation and olfactory adaptation [610], SSS was not reflected in neuronal activity at the early stages of olfactory processing in olfactory sensory neurons (ORNs), in the olfactory bulb (1st relay) and in the olfactory cortex (composed of anterior olfactory nucleus, piriform cortex, amygdala, olfactory tubercle and entorhinal cortex)[610].

2. Orbitofrontal cortex (OFC)

Afferents from primary gustatory, olfactory (*via* thalamus), visual and somatosensory cortices [394] converge onto the orbitofrontal cortex, a region in the prefrontal cortex [372].

In the OFC, neurons with unimodal responses to gustatory [611], olfactory and visual stimuli were found in close proximity and some single neurons responded in two modalities (*e.g.*, to taste and olfactory inputs) [372]. Some of these multimodal neurons had corresponding sensitivities in two modalities (*e.g.* to sweet taste and fruit juice odor) [372], thus representing a sensory image [617] of the sensory properties of specific foods [372,420]. The olfactory responses of some neurons reflected association with taste, forming representations of flavor [389].

While a primate was being fed to satiety with glucose [372] or blackcurrant juice, the activity of single neurons in its caudolateral OFC specifically decreased to zero for the food ingested [369] but continued for foods which had not just been eaten, *i.e.* they reflected SSS [372,614]. This objective neurophysiological evidence of change was paralleled by the primate's behavior, which turned from acceptance to rejection [369]. These responses of OFC neurons seem to reflect the reward value of foods (sensory pleasure or incentive to consume) since cessation of firing paralleled behavioral SSS [361,365]. OFC neurons responded to foods in a sensory-specific pattern after feeding to satiation in several modalities and the sensory-specific responses of these multimodal neurons were observed across all modalities [388]. SSS is thus represented in the caudolateral OFC because this sensory-specific neuronal response in the synapses was not observed earlier in the pathway [369,420]. As SSS was reported with food-related odors, once an odor is experienced in a food-related context, that odor might acquire the ability to modify ingestion [426].

In addition, sensory-specific responses of the OFC to the oral texture (mouth feel) of fat [394], to umami tastants (like monosodium glutamate [387]) to behavioral satiety have been described.

Olfactory SSS is represented in the OFC because olfactory OFC neurons that were responsive to the odors of foods (like blackcurrant juice) selectively decreased their responses to the odor of the food eaten [388]. Most neurons with selective responses to the sight of food displayed a sensory-specific reduction in their visual responses to foods when the primate looked at the food after satiation [388]. Neuronal gustatory responses to water decreased to zero while water was drunk to satiety (1989)[369]. Thus, SSS has been demonstrated for the sensory properties of water.

Also protein taste (*umami*) [33] [613,387,389,392,402], texture like fat texture (odor and mouth feel of fat), astringency (*e.g.* tannic acid) [409] and the sight of food [389] have been demonstrated to be represented within the OFC, where sensory-specific reductions for these properties have been demonstrated.

3. Electrical activity in Lateral hypothalamus (LH) and substantia innominata

The caudolateral OFC sends projections back to the lateral hypothalamus [614], to neurons with food-related responses, whose responses to the taste of food showed specific decreases to a food just eaten to satiety [365,372]. In the hungry primate, some neurons in the lateral hypothalamus and in adjoining substantia innominata responded by specifically increasing or decreasing their firing rates to the taste or to the sight of glucose or to both [615]. The responsiveness of some neurons to

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[33] Japanese 旨味 or うまみ, from '*umai*' meaning brothy, meaty, savory, delicious

glucose gradually decreased during ingestion of glucose and was accompanied by a decrease in behavioral acceptance. Thus, when feeding to behavioral satiety with one food, the neurons ceased responding to the sight and/or the taste of that food [615]. However, these neurons still responded to different foods the monkey was offered, but which had not been eaten, reflected by its acceptance [361,365]. These hypothalamic neurons are thus involved in the feeding responses which occur when an animal sees or tastes food [615]. Responses of these neurons thus mimic the reward value of food. SSS is rather related to brain areas controlling motivation and the reward value of foods than to changes in sensory processing of responses to foods [361].

The metabolic centre in the hypothalamus seems to play a central role in the formation of differential appetites. However, it is not known how the hypothalamus computes the amount of a food eaten before ingestion is limited by SSS [390]. Possibly, it integrates the nutrient composition of a given food with its unique pattern of sensory stimulation (*i.e.* flavor) through a hormonal-neuronal feedback-mechanism which is represented by *conditioned satiety*.

4. Globus pallidus, visual cortex & amygdala

Satiety did not modulate neuronal responses of the globus pallidus (pertaining to the extrapyramidal motor system and to the basal ganglia) which responded when swallowing and during mouth movements [615]. Similarly, satiety did not influence responses of neurons in the inferior visual temporal cortex [609] which responded when the monkey looked at the food [615] or in the amygdala [361]. Information on which visual stimuli are foods is sent from the inferior temporal visual cortex and amygdala to the hypothalamus [361].

VI.6.2. CNS studies in humans

Single-neuron recording studies in non-human primates showed electrical changes in activity of OFC neurons which correlated with progressive behavioral satiation for the food eaten. However, they provided no direct evidence on brain activity related to the subjective pleasantness of food [414]. *f*MRI and PET-scan are indicators of neural activity related to SSS [415]. An *f*MRI investigation demonstrated that olfactory activation of the human OFC was related to SSS because responses to the odor of the food eaten to satiety decreased, whereas there was no similar decrease for the odors of foods not eaten [400,401]. In another *f*MRI study, specific decreases in activation of the human OFC to a liquid food stimulus correlated with its subjective pleasantness when it was eaten to satiety, providing a neural correlate of SSS [414].

Therefore, the specificity of the phenomenon of SSS can be traced back to the cellular level which underlines its concept and theory. Cognitive factors, like a word label presented with an odor, may influence the pleasantness of the odor and the activation produced by the odor in the OFC [420].

VI.6.3. Brain systems mediating Liking & Wanting

1. Opioid system
Although it has long been known that hedonic experience is transmitted by the opioid brain system, SSS was not modified by oral naltrexone in normal-weight men in the short term [376].

2. Dopaminergic system
The mediation of incentive salience (*i.e.*, motivation or 'wanting') involves dopamine systems in the mesotelencephalon, nucleus accumbens and amygdala [616]. In this way, one study in rats demonstrated that changes in dopamine efflux in the medial prefrontal cortex and nucleus accumbens, monitored by *in vivo* microdialysis, reflected the sensory-specific difference in food

intake. This suggests that in addition to opioid-mediated palatability, the relative incentive salience of foods might be a determinant of SSS [397].

VI.7. Temporal pattern and duration

VI.7.1. Short-term SSS

Sensory-specific satiety was shown to follow a characteristic time course (Figure 12). The greatest decline in pleasantness usually occurs two minutes after the end of intake. However, duration of intake with a given food may vary among subjects. After this, pleasure for flavor and aroma of the food eaten remain relatively unchanged for at least two hours, with a tendency of recovery [371].
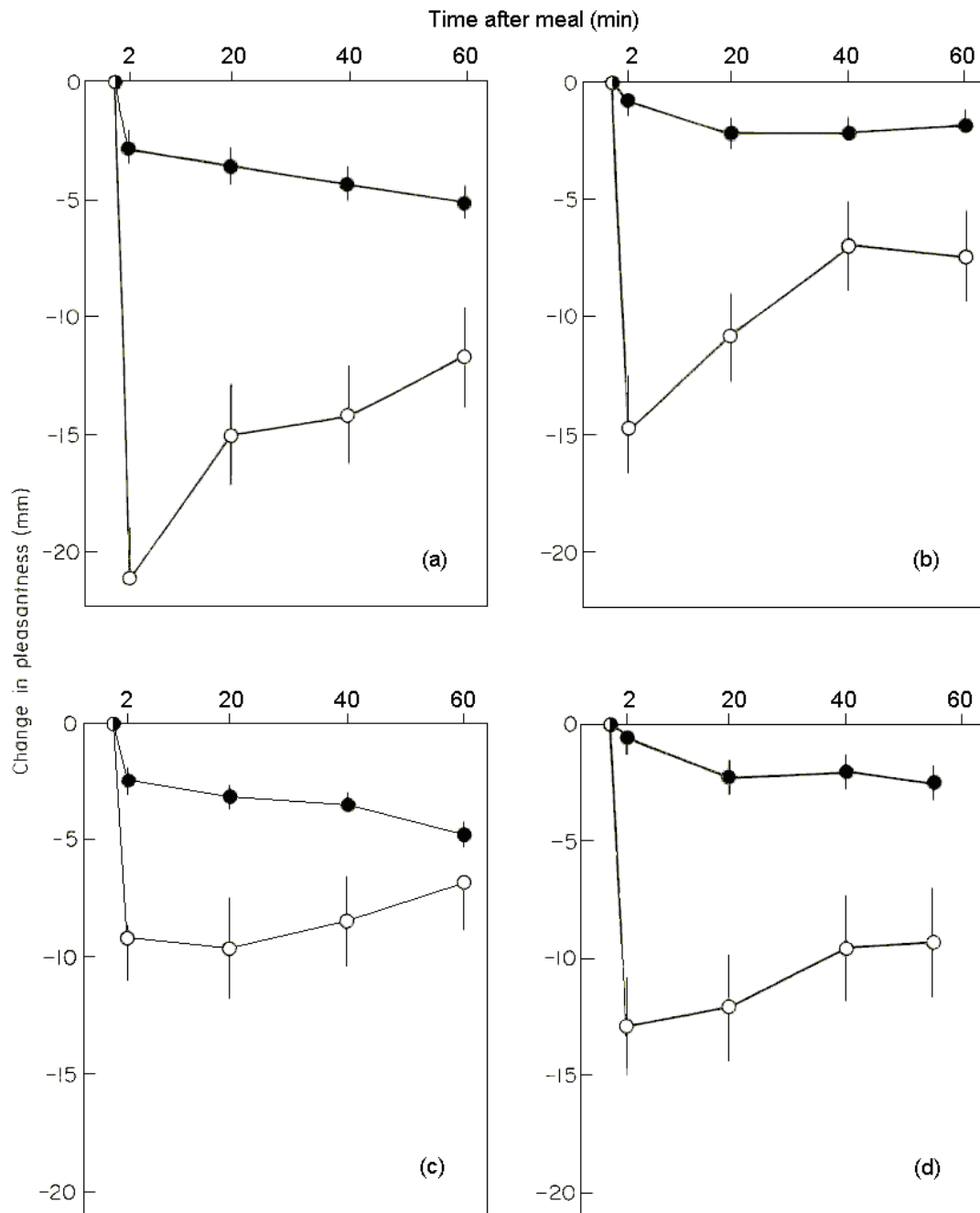
FIGURE 1. Mean ($\pm$ *SEM*) changes in the pleasantness of (*a*) taste, (*b*) texture, (*c*) smell and (*d*) appearance of the eaten food (cheese on crackers) at 2, 20, 40 and 60 min after consumption of the first course, ●, uneaten foods; ○, eaten food.

Figure 12. The time course of sensory-specific satiety.
From: [371]

VI.7.2. Long-term SSS

An observation made in Ethiopian refugees has been interpreted as a long-term form of SSS. These refugees found the taste of three new foods (wheat bread, lentil stew and wheat germ milk) more pleasant than that of three foods (millet pancake, beans and milk) they had been eating for six months, whereas newly arrived refugees who had been eating all foods for only two days rated all six foods as equally palatable [363].

It has been hypothesized that SSS reflected the long-term acceptability of foods (*i.e.*, eaten daily without becoming 'tired' of them). Studies by the armed forces during the 1950s showed that liking

for most foods decreased when consumed repeatedly. However, the rate of decline depended on the specific food [618]. A study about the long-term acceptability of tea found preference for the weak version [393], suggesting that more prominent sensory properties of foods produce stronger SSS.

Limiting food group variety to a chosen snack food over eight weeks produced long-term SSS for that food because hedonic ratings of the chosen snack food decreased over time, more than for other snack foods not eaten [423].

However, the repeated presentation of the same food stimuli over weeks or months suggests that *conditioned satiety* (and not just pure SSS) is involved – results should therefore be interpreted cautiously. Further investigation is needed to separate these two phenomena on the long term. Furthermore, it has been stated that long-term satiety is activated by the chemoreception of nutrients and peptides from the gastrointestinal system and liver, and by intrinsic CNS mechanisms [374]. In this way, hedonic changes to long term exposure to food flavors may rather be attributed to a change in food preference. Accordingly, postingestive nutrient actions could alter flavor preferences through a conditioning process as a function of nutrient type and concentration. Food preferences may thus result from interactions between orosensory and nutritional properties of food [619].

VI.8. Influencing factors

SSS has been shown to be specific to the sensory properties of foods. However, SSS may at least in part be influenced by the physico-chemical properties of foods or by intrinsic factors of the subject.

VI.8.1. Weight & Volume

The volume of orange gelatin dessert and chocolate pudding consumed was reported to have a greater effect on taste pleasantness ratings and subsequent intake than did the calorie contents [368]. In another study, a milk-based liquid food of varying energy content and volume was consumed by women on three days. Doubling the volume of the food (without changing the energy content) decreased pleasantness ratings of the liquid food and increased SSS. Doubling the energy content (without changing the volume) had no additional effect on the decrease in ratings or on SSS. Thus, the volume of the food consumed has a greater influence on pleasantness of food than does its energy content and affects termination of eating through SSS [412]. These results suggest that volumetric feedback is very probable, as the importance of SSS is more related to quantity/volume [384,407,412].

VI.8.2. Caloric content

Several studies have shown that SSS is not clearly related to the energy-content of foods [407,412,413]. In one study, female subjects were served low- or high-calorie versions of tomato soup or orange jelly as a 1st *ad libitum* course. After one hour, they were offered cheese on crackers as a 2nd course to eat *ad libitum*. Despite differences in energy density, they consumed similar amounts in low- and high calorie situations and did not compensate for energy differences of the 1st course in the 2nd course. Furthermore, the calorie content of tomato soup and orange jello did not affect the development, time course and magnitude of SSS for appearance, smell, texture and taste. This study showed that very low-calorie foods can produce SSS and suggests that the sensory properties of foods are more important than calories for the hedonic response to foods during intake [367].

In another study, one of three preloads (tomato soup, melon, cheese on crackers) of two energy levels (50 or 200 kcal) were eaten just before two different 2nd courses (macaroni and beef

casserole, grilled cheese sandwiches) to examine the effects of calories, energy density, and SSS on food intake. Soup reduced intake in the 2nd course more than other preloads, which could be accounted for by the low energy density of tomato soup, but soup reduced intake more than did the melon preload which was matched for energy density. SSS did not explain why a liquid food was more satiating than (semi)solid foods [373].

In a third study, subjects ate the same amounts of high- (sucrose) and low-calorie (aspartame) versions of orange gelatin dessert or chocolate pudding and did not compensate caloric intake 1-2 hr later. No differences were found in SSS between these high- and low-calorie foods [368].

A fourth study found that decreases in liking for a preload (pasta with tomato sauce, whipped cream, chicken) were greater in high calorie versions of the preloads 2 min and 90 min after consumption. In a subsequent *ad libitum* lunch, less weight and calories of food were eaten after high calorie preloads [382].

The development of SSS was not affected by the energy content of potato chips (full-fat potato chips *vs*. chips made with olestra, a non-absorbable fat replacer) for two 10-day sessions [405].

In summary, the studies cited demonstrate that on the very short term, *i.e.*, in a first course, the energy density of the food eaten to specific satiation has little impact on SSS.

VI.8.3. Macronutrients

When the sensory properties of foods were similar, macronutrient composition did not have an impact on SSS [407,413]. SSS was also reported to be unrelated to specific macronutrients [382].

1. Carbohydrates, protein, lipids
Foods with different macronutrient compositions were not found to reflect specific hedonic changes as the drops in liking were unrelated to specific macronutrients of preloads. Eating a high-protein preload decreased the weight of food eaten more than did eating a high-fat or a high-carbohydrate preload and decreased total caloric intake more than did eating a high-fat preload. Macronutrient intake was not differentially affected by the macronutrient composition of a preload. It was concluded that SSS is more related to the sensory characteristics of a food than to its macronutrient composition [382].

2. Protein
When SSS was tested for foods varying in macronutrient composition, the amount of SSS produced by a meal depended on the food eaten. There was a trend for high-protein foods, which were least liked, to decrease more in liking than did low-protein foods [380]. However, food preference may have been a confounder in this study.

High-protein versions of foods (strawberry yogurt or ham/bacon sandwich) were found to produce more SSS than low-protein versions, *i.e.* the decreases in liking were greater for the high-protein versions [386].

3. Lipids
The development of SSS was not affected by the fat content (full-fat *vs*. fat replacer olestra) of potato chips eaten over 20 days because pleasantness of taste and texture of both types of chips declined after consumption compared to uneaten test foods (turkey, strawberry yogurt, cookie and carrot) [405].

A fat-specific satiety has been described in a study comparing the effects of three different oils (high in linoleic, γ-linolenic and oleic acid) during two weeks. Fat-specific satiety with linoleic acid *versus* oleic acid was shown after 2 weeks with each kind of oil. However, fat-specific satiety was not related to taste perception of the oils, since subjects were unable to detect specific fatty acids in the oils used [408]. Because of the long time-span (two weeks) of repeated exposure to these foods,

the findings of this study may rather be the product of conditioned satiety. Another study reported that taste (sweet or savory) had a stronger effect on SSS than did fat content, and concluded that factors other than fat content had the greatest effect on SSS [416].

VI.8.4. Variety and Monotony

SSS is thought to be a promoter of variety in food choice and intake because it increases the amount of food eaten in a meal when different foods are offered. SSS was still operational after eating four different courses in a meal and general satiety still did not occur [362]. Similarly, the variety of sensory qualities within a food influenced SSS because low-variety meals dropped more in liking than did intermediate and high-variety meals [380]. Increasing food variety can increase food and energy intake and in the short to medium term alter energy balance [413]. Successively offering a food with a variety of flavors (cheese sandwiches with salt, non-nutritive lemon, saccharin or curry) increased energy intake by 15% when all three flavors were presented successively compared with intake of the favorite flavor [359].

In this way, SSS was considered a mechanism that linked increased dietary variety with increased food intake in animals and human beings, suggesting that the oral habituation theory is a unifying construct for the effects of variety and SSS [407].

Limiting variety of sweet and salty snack foods (crumb cake) across four days reduced the hedonics of the limited food [424]. Limiting snack food variety in overweights for eight weeks produced SSS for that food because liking of the chosen snack food decreased more than for uneaten snack foods. Limiting food group variety over an extended time could be used as a technique for weight loss [423].

VI.8.5. Aggregate state of foods

Consuming whole fruit reduces ratings of satiety more than does the consumption of fruit juice, but little is known about the effects of different forms of fruit on subsequent energy intake. Preloads of food in different forms (apple, applesauce, and apple juice with and without added fiber) influenced subsequent satiety and energy intake. Eating apple reduced energy intake by 15% and decreased energy intake compared to applesauce and both juices. Fullness ratings were greatest after the solid preload (apple > applesauce > both juices). Whole apple increased satiety more than applesauce or apple juice. Adding naturally occurring levels of fiber to juice did not increase satiety. This suggests that solid fruit affects satiety more than does pureed fruit or juice [620].

Tomato soup had greater satiating efficiency than did two other preloads (melon, cheese on crackers) on a second course (macaroni beef casserole or cheese sandwiches). [373]. While SSS did not explain this effect, it might be that fluid foods influence SSS differently than solids.

VI.8.6. Preference

In one study, the amount of SSS produced by a meal depended on the food eaten. Buttered rolls and cola drink dropped the least in liking. Initial liking within a food influenced SSS. Less-liked meals dropped more in liking than did well-liked meals [380]. Hence, initial preference for a food can influence SSS.

VI.8.7. Information on nutrient composition

Knowing the caloric values of the foods did not influence intake or taste pleasantness ratings [368]. Similarly, the development of SSS was not affected by the provision of nutrition information for potato chips [405].

VI.8.8. Dietary restraint and obesity

Restrained subjects showed patterns of SSS similar to those of the unrestrained subjects for cheese and crackers or cookies versus nine other foods [379]. Heightened responsiveness to sensory properties of foods may not be generalized in restrained eaters.

In humans, taste affects SSS, and differences between lean and obese humans with regard to taste may contribute to the development of obesity [410]. Preliminary results suggest that in comparison with lean women, obese women have reduced SSS both to food eaten and food just tasted [601]. Overweight African-American women, compared to overweight European American women, show an elevated and sustained desire for sweet foods tasted for 30 min [602]. No differences in SSS between obese and normal-weights were observed for *ad libitum* sandwiches and snacks (low-fat sweet, low-fat savory, high-fat sweet, high-fat savory). Thus, obese and normal-weight people may not differ in their sensitivity to SSS [416].

VI.8.9. Alcohol

Alcohol had no effect on the development of SSS following intake of a lunch. Alcohol promoted food intake but neither *via* the additive effects of alcohol and palatability nor through increasing the pleasantness of the taste of foods [419].

VI.8.10.   Age

1. Children
SSS has been observed in human infants, as early as 3 ½ months of age. At this point, children are in the process of being weaned from their mothers' milk and the only solid foods they had been fed are cereals (oats, barley or rice) prepared with water for three weeks. Only the children exposed to carrot flavor through their mothers' milk during a week ate less of the carrot-flavored cereal than of water-prepared cereal. This may be a form of SSS because the infants became less responsive to a flavor they had been repeatedly exposed to recently [398].

A study, based on Clara M. Davis' work on the self regulation of food intake [621,622,623,624], provided evidence of the existence of SSS in young children (aged 2 ½ to 5 yr)[366] in an *ad libitum* lunch. The patterns of preference did not differ with the caloric density of the food eaten. Children displayed much clearer caloric compensation than adults [366]. Similarly, mothers of 6–11 month-old infants fed protein hydrolysate formula milk judged that they enjoyed broccoli/cauliflower less than did infants fed milk-based formula milk, because the hydrolysate milk contains similar flavor notes (*e.g.* sulfur volatiles) with *Brassica* vegetables (*e.g.* broccoli) and thus developed SSS for the similar flavor in milk which also affected solid foods [430].

2. Elderly persons
Decreased SSS has been reported in the elderly [403,404,417]. SSS in elderly persons (65–82 yr) was modified in comparison to adolescents and young and older adults. The pleasantness of taste of the eaten food *versus* uneaten foods did not decrease nor did the pleasantness of the texture or the desire to eat yogurt decrease. SSS was pronounced in adolescents and diminished in elderly [377]. Consumption of a varied diet depends in part on SSS. SSS was absent in elderly people over 65, which could explain why the elderly consume more monotonous diets [381]. Changes in chemosensory systems linked with changes in gustatory or olfactory function to food choice or intake in the elderly are factors of appetite and intake decline with age [395]. However, it is unclear

whether diminished SSS in the elderly reflects neuronal degradation (*i.e.*, a pathological process) or physiological involution.

VI.8.11. Eating disorders & pathologies

1. Anorexia nervosa

Anorexic patients display normal SSS. Smaller portions are sufficient to become satiated on a specific food and limit food intake. Despite normal SSS, anorexics selected the eaten food again in a self-selection meal when that food was low in calories, because the other choices were higher calorie foods. In anorexics, SSS can be overridden by knowledge about the calorie content of foods. This may represent a deficit in subjective assessments of appetite or a denial of such feelings and how such basic processes can become destabilized by disordered eating practices and psychopathological fears about fatness and body shape [370].

2. Bulimia nervosa (binge eating disorder)

Bulimic patients did not display sensory-specific satiety, although their food intake did not differ from controls. Bulimics fail to show sensory-specific satiety to normal amounts of food when eaten *ad libitum* or as a fixed load. Failure to perceive a decrease in the pleasantness of a specific food could enable bulimics to eat beyond normal limits of satiety during binge episodes. Bulimics showed inappropriate adjustment to preloads [370]. In women suffering from food craving and binge eating, a protein-rich meal was suggested to induce craving for sweet foods *via* SSS [396].

In complement to the preceding paragraphs, it has been observed that anorexic patients demonstrated SSS only after a high-energy salad and bulimic patients only after a low-energy salad [378].

3. Cancer

It has been suggested that SSS is part of the mechanism implicated in anorexia (*i.e.*, the early onset of satiety) in cancer patients [429].

VI.8.12. Innate versus acquired

Odor plays a major role in food flavor perception, suggesting that the identification of odors as food-related and liking for food-related odors are learned responses. Pleasantness for odors was increased when paired with sucrose and decreased when paired with quinine, suggesting that acquired liking for odors depends on the motivational state. As SSS was reported with food-related odors, once an odor is experienced in a food-related context, that odor might acquire the ability to modify ingestion [426].

VI.8.13. SSS in rodents

After oral infusion of sucrose until behavioral satiation, positive hedonic reactions in Grill et Norgren's taste reactivity test [222] were reduced more by oral sucrose than by oral milk. Thus, behavioral correlates of SSS were observed in the rat. SSS reduced positive hedonic reactions but did not increase aversive reactions [375]. The existence of SSS in rats was also supported by a two-bottle choice test (sucrose *versus* maltodextrin) where the previously eaten food was less frequently chosen [421].

Rats developed SSS for a glucose solution versus carbohydrate powder and laboratory chow when these were ingested orally. However, this preference was still maintained when ingestion was intragastric. As this bypassed oropharyngeal stimulation, SSS was eliminated as an explanation for

this specific satiation [466]. This might thus be a case of alliesthesia, known to be specific for sweet solutions.

In this way, one study reported a volatile (duration < 20 min) SSS effect after a sucrose/corn oil emulsion preload on subsequent *ad libitum* intake in that the sucrose preload specifically reduced subsequent sucrose- but not corn oil intake and *vice versa*. However, rats with corn oil preload consumed more corn oil after 20 min than sucrose which is contrary to SSS [384].

Another study ruled out SSS as an explanation for the relatively smaller test meal intake after a high carbohydrate preload because the test meal (evaporated milk) was sensorially distinct from the intragastric preloads (equicaloric corn oil or sucrose) [399]. However, this result might rather point to a metabolic/intestinal cause like alliesthesia which has been shown to be stronger in the presence of carbohydrates in the small intestine.

In rats with lesioned gustatory insular cortices, SSS was intact for either food pellets or maltodextrin solution (obtained by lever pressing, chain pulling, respectively) as only gustatory memory was affected [406]. In contrast, bilateral lesions of the basolateral amygdala (thought to be implicated in aversive learning) of rats disrupted SSS in the same setting [411]. This was supported by the results of a study in AMPA receptor (expressed in the amygdala) knockdown mice in a plus maze paradigm: the mice were insensitive to SSS [418].

VI.9. Purpose and functions

VI.9.1. Meal termination

Several studies focused on subjective reasons given for meal termination.

In college students, the most common reason for ending a meal was "feeling full" (39/64), while hedonic reasons ("food stops tasting good"/"tastes less good") were rarely chosen (6/64). The other reasons ["everyone else is finished" (social reason), "had all I'm allowed" (restrained eaters), "food is all gone" (externality reason) and "some other reason" (open alternative)] together made up less than one third (19/64). When 36 of them ranked their reasons by importance, only 22 of them included the hedonic alternative (while all 36 chose fullness), and only 2/22 ranked its importance above the median. Although hedonic shifts occurred during a meal, they seem to have little influence on meal termination [625]. Therefore, this study did not find a major impact of hedonic changes on meal termination.

In contrast, another study suggested the decrease in pleasantness of food eaten to reflect food specific satiety as a reason for stopping intake of that food [385]. After eating cheese on crackers *ad libitum*, subjects recorded their main reason for stopping from seven imposed replies (everyone had finished eating; ate as much as I am allowed; food tasted less pleasant; food was all gone; felt full; got tired of eating the food; or a different reason given by the subject) which they had to rank by order of importance. One hour later, subjects were offered to choose the same food, a different food, or no 2nd course. Reasons for stopping ingestion were again recorded by those who selected a 2nd course. The most common reason given for stopping ingestion in the 1st course was "got tired of eating that food" (40%), most likely reflecting sensory fatigue, which stands for SSS, and for the 2nd course "I felt full" (48%), reflecting general satiety arising from gastric fullness.

Similarly, in a third study, male and female undergraduate students had to complete the statement "I usually stop eating when" with one of four alternative responses and an open alternative. Here, the most popular response was fullness but listed only in half of the questionnaires. Men and women exhibited differing patterns in responses. The second most popular response for men was "food is all gone" (external factors) and in women "the food stops tasting good" (hedonic factors) [626].

Obese male and female subjects following a weight loss program selected "I felt I had eaten enough" as the main reason for meal termination (39%), probably reflecting their effort for weight loss. The second most frequent reply was stomach fullness/repletion (13%).

Gender differences revealed a greater tendency for women to terminate eating for environmental reasons than men (9 *versus* 11%) [627].

The most recent study sought to determine whether non-obese women use orosensory cues to limit short-term intake of high-energy density foods. Subjects consumed one of two equicaloric versions (high sugar or high fat) of high-energy rice puddings for breakfast in four study conditions where they had to eat until satisfied, satisfied based on taste, satisfied based on fullness and during TV-distraction. While decreases in rated taste intensity were reported for both puddings, those who ate until satisfied based on taste had the lowest intake, showing that SSS can limit meal intake in normal-weight women [628].

Together, these studies show that SSS can be a reason to end a course of a specific food, as it was reflected in the reasons whenever subjects were not fully sated, rather than being the cause of final meal termination, as gastric fullness, reflecting general satiety at the end of meal, was the most common reply.

VI.9.2. Variety searching

In 1986, BJ Rolls stated that when confronted with a variety of different foods, the safest strategy for an animal to ensure adequate nutrition is to consume a widely varied selection of foods. In humans, when more than one food is available, there is a natural tendency to switch between foods rather than just consume the most preferred food [364]. This was illustrated by studies conducted by Davis on newly weaned infants [621,622,623,624] who, from 6 to 11 months of age at the start of the study, had little experience with the foods offered and were protected from adult influences during the study. At meal times they were offered a variety of natural, nutritious foods. During the first week they tried most of the foods, and after that definite likes and dislikes emerged. Despite preferences, within any one meal they tended to consume several solid foods and a drink. Thus, their strategy was selection of a varied diet rather than only one preferred food. The children grew normally and developed no nutritional deficiencies. Davis concluded that "such successful juggling and balancing of the more than 30 nutritional essentials that exist in mixed and different proportions in the foods from which they must be derived, suggests the existence of some innate, automatic mechanism directing food selection, of which appetite is a part".

It has been argued that even wild predators will choose a varied diet over a specific attractive and abundantly available prey as long as they find other foods. It has been suggested that a special 'switch' mechanism might reduce the responsiveness of a predator to a given prey that forms a large part of its diet [364].

These examples suggest that the oro-nasal stimulation associated with consumption leads to decreased intake of that food, or in other words, satiety is specific to the sensory properties of foods.

Rolls used the term 'nutrient-specific satiety' to reflect on whether macronutrient composition might influence hedonic changes during intake, *i.e.* if macronutrient needs directly influence intake. There was no significant difference among changes between uneaten foods with the same composition as eaten foods on one hand, and foods with different nutrient composition on the other. When four successive courses of sandwiches with very different fillings were offered, intake was about one third more than when the same filling was consumed throughout [584]. Even though the sandwiches differed in appearance, texture, smell, flavor, and nutritional composition, they were still the same type of food, *i.e.* sandwiches.

VI.10. SSS and the other hedonic phenomena

VI.10.1. SSS versus alimentary alliesthesia

In 1984, Marc Fantino advanced the hypothesis that alimentary alliesthesia may participate in specific sensory satiety [464]. As outlined by Barbara J. Rolls in 1986 [364], sensory-specific satiety and alimentary alliesthesia are often either confused or explained as one being part of another, but in fact, they are distinct. While alliesthesia originates from postingestive preabsorptive signals, sensory-specific satiety is sensory in the first place, originating mainly from olfacto-gustatory stimulation. In contrast to general hunger and satiety, the theory of sensory-specific satiety (or better: -satiation) describes the specific hedonic changes that take place during ingestion of a specific food or food flavor in contrast to uneaten foods. Specific satieties therefore play an important role in the regulation of food-intake and nutritive homeostasis.

VI.10.2. SSS versus conditioned satiety

D.A. Booth also underlined that conditioned satiety is distinct from sensory-specific satiety in that "conditioned satiety is associative, dependent solely on prior contingency of consequences to cues from food and from context, that can be remembered over days and is evoked immediately the conditioned combination of sensory and somatic or social cues is reinstated, with no immediately prior exposure to that food being required" [123]. Sensory-specific satiety on the other hand "is non-associative, dependent solely on immediately prior exposure to the sating food stimuli", but also "may have a non-associative component (habituation) and learnt social component such as norms for the amount eaten of a particular food within a meal" [123].

However, a link between SSS and conditioned satiety is to be considered: while the action of sensory-specific satiety is immediate, and as sensory-specific satiety leads to partial satiation, it has been shown that the sensory-specific effect can be prolonged in settings of monotony [363]. Arguably, as sensory-specific satiety produces satiation and is thus involved in the medium-term regulation of intake, it is difficult to separate the influence of conditioned satiety in repeated intakes from sensory-specific satiety. A long-term decrease in pleasure for eaten foods should not be interpreted as a result of sensory-specific satiety alone (which diminishes specific neuronal responses towards a food eaten in the short term – partial recovery after only two hours), but rather as a 'CS × SSS interaction'. Probably, complete distinction between CS and SSS phenomena might not be possible because of complex circuits and interactions at the level of the CNS.

While olfacto-gustatory stimulation is sufficient to produce partial SSS, postingestive events are necessary for the full installment of SSS.

On the other hand, negative alimentary alliesthesia is independent of orosensory stimulation.

The specificity of gustatory alliesthesia for salty and sweet tastes suggests differential mechanisms implicated in these. It has been suggested that vagal duodenal glucoreceptors convey the internal signal for gustatory alliesthesia for sweet tastes, but a different yet undiscovered mechanism (maybe the activation of ion channels or plasma osmolarity) has to exist for salty taste.

Conditioned satiety (*i.e.*, learning the energy content of food flavors) does not seem to have a big influence on SSS.

Repeated consumption of two versions of potato chips with different energy content (full-fat vs. chips with olestra) over 20 days did not differentially affect SSS [405].

VII. EXPERIMENTAL SECTION

Evidence from the introductory chapters has illustrated that hedonics is one of the main drivers of food intake and satiation. In the absence of cognitive constraints (*e.g.* eating foods supposed to be healthy or low in calories to lose weight), humans are guided in their food choices and intake by hedonic sensations which they search to optimize (*e.g.,* preference to eat palatable foods and avoidance of unpleasant foods). It has been suggested that hedonic food perception is an integral part of the physiologic control of food intake. There are intrinsic (*i.e.* organism-related factors like nutritional and energy needs) and extrinsic factors (*i.e.* environmental ones like the availability of food quantity and variety, season of the year, visual, olfactory and taste aspects of food…) that ultimately determine actual food intake. Finally, based on hedonic perceptions, several hedonic phenomena (sensory-specific satiety, alimentary alliesthesia, and conditioned satiety) that are involved in hedonic cross-meal changes have been described over the past 70 years. All these phenomena rely on the sensory properties of the food which allow the identification and recognition of specific foods. Numerous studies have shown that modification of the sensory properties (like taste, smell, mouthfeel or visual aspects) of foods with similar nutritional properties (macronutrient and energy content) can increase/decrease food intake in the short- and in the long term.

The main purpose of the series of experiments presented in this thesis was to modify the sensory properties of foods (mainly olfactory/gustatory) and to examine the impact of these manipulations on hedonic sensation (essentially sensory-specific satiety) as well as specific appetite and specific food intake. According to this, four study protocols were designed.

VII.1. First study: Seasoning

VII.1.1. Introduction

Hedonic liking (flavor pleasantness), wanting (specific appetite) and salivation [302] are parameters that were previously reported to reflect dynamics in appetence. In this first study, the influence of modifying the olfacto-gustatory properties of a food on these parameters was evaluated while eating in a series of three experiments.

Several elements have guided both the choice of the protocol and the methodology: the sequence of food selection and intake; the food choice among the proposed foods (the study was conducted on simple foods and not on an entire meal); the identification of the hedonic mechanisms involved during short term intake with simple foods. These elements will be discussed after the presentation of the study and its objectives.

1. Presentation of the study

To our knowledge, not many studies have successfully isolated the influence of olfacto-gustatory modifications *per se* without manipulating the nutritional content of the foods (same food with same composition and caloric content).

In a study on the impact of sensory variety on food intake, single modalities of the sensory properties of various foods (equal in nutrient composition) were manipulated [359]: the visual aspect of chocolates (which only differed in color but not in taste)[359], the textural aspect of shapes of pasta [359] and the flavor of cream cheese sandwiches (seasoned with salt, or non-nutritive lemon, saccharin or curry flavor)[359]. In these three experiments, subjects had to consume all three manipulated foods successively in the variety condition, and calorie consumption was compared to intake of the preferred food. Therefore, it was not clear if only a single manipulation in each modality (instead of three) of the sensory properties led to increased intake. Further, the dynamics of hedonic ratings (*i.e.*, SSS) were not explored between courses. Finally,

while condiments used in the sandwiches were non-caloric, they had very distinct flavors (sweet *versus* salty).

Therefore, in the present work, we applied a different protocol to see if in fact a single manipulation of the flavor of a food could increase intake with simple foods and were in fact related to the sensory properties *sensu strictu.* The study was conducted in 180 subjects.

In the 1st experiment, the study layout applied was destined to provide evidence on several points:
- to determine the time course of gustatory hedonic changes for eaten versus uneaten foods,
- to examine the relationships between food choice-related olfactory pleasure and food intake-related gustatory pleasure, *i.e.* to see if the components liking (*i.e.* palatability) and wanting (*i.e.* the incentive or motivation) were related,
- to examine the salivary response of the cephalic phase. Given that the odor of savory foods causes more salivation, salivation may reflect the individual preference for a food smelled, and the aroma of less liked foods may elicit less or no saliva flow. Furthermore, salivary flow may reflect sensory habituation mechanisms [499].

In the 2nd experiment, an unexpected second course was offered to the participants, destined to further elucidate the following points:
- to obtain additional hints on the prevailing hedonic phenomenon,
- to learn how much, in terms of absolute food weight, food volume and energy will spontaneously be eaten when offered a sensorily distinct food,
- to further track the specificity of olfactory hedonic dynamics for eaten in relation to uneaten foods.

The purpose of the 3rd experiment was to examine the impact of seasoning (*i.e.*, changing the food's sensory properties by condiments) and to examine if indeed this manipulation could modify the food's hedonic value, and in case it does, if this would extend food intake, and thus increase the total amount and energy ingested by offering the same food as chosen and eaten to satiation in the first course in an unannounced second course.

The condiment added depended on the food group:
- salt and pepper with vegetables (cucumber, tomato),
- whipped cream with fruit (pineapple, banana),
- torrefaction and salt with nuts (peanut, pistachio)

2. Objectives of the study

The objectives of this three-level study of olfactory self selection of simple foods were therefore to re-examine Rolls's study with special focus on the evolution of SSS of eaten and smelled foods in order to observe the impact of manipulations of the olfacto-gustatory properties of foods eaten to satiation. Additional objectives were:

1. to study cross-meal hedonic odor and flavor dynamics of chosen and ingested foods relative to foods smelled but not eaten,
2. to study the relationship between cross-meal odor and flavor hedonics,
3. to examine the relationship between hedonic odor and flavor perception and specific appetite,
4. to examine the relationship between salivary response and hedonic flavor perception,

5. to examine whether initial pleasantness may predict quantity or energy intake,
6. to determine whether AA or SSS plays a more prominent role in short-term intake control
7. to study and compare hedonics with an unexpected second food and test its impact on total *ad libitum* intake,
8. to study the hedonics and total intake of a food just eaten when its flavor was manipulated by seasoning and offered again,
9. to investigate reasons for stopping intake (RSI) with specific foods chosen from three food groups in all courses of the three experiments.

3. *Choice of the protocol and methodology*

Sequence of sensory food selection and food intake

In wild-living primates, a typical bout of intake consists in the following phases:

1. Search for and localization of food
2. Food selection or food choice
3. Food intake
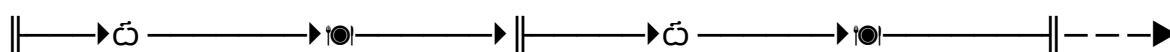
foraging ▶ food selection ▶ food intake ▶ foraging ▶ food selection ▶ food intake

1, The search for and localization of food may mainly rely on the memory of previous food encounters, and on the sense of vision for shorter distances.

2, Food selection or food choice is based on sensory abilities. Once a food source is located, and whenever more than one food is available simultaneously (*e.g.* in abundant tropical environments), food choice may be more closely related to the chemical sense of olfaction[34] which is considered a 'distance sense'[35].

The aim here was to have participants entirely rely on their chemical sense of olfaction for the selection of foods by their olfactory organoleptic properties. In order to avoid the majority of distracting influences during food choice, visual cues were eliminated by blinding subjects with face masks (like the ones used to sleep during Nordic summer nights or on transcontinental flights). Therefore, blinded participants were twice presented the whole series of six foods one after the other after which they had to decide which odor they liked best and which elicited most salivation.

3, Food intake: The proximity sense[36] of gustation together with flavor perception may be closely related to the limitation of intake. Oro-sensory stimulation during chewing may lead to specific satiation and, if not satiated, to a search for a different food. Food intake, after having eaten one or several foods, may lead to general satiety.

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[34] Advantages of olfactory food choice during prehistoric times: selection of an optimal diet (selection of essential nutrients and of fruit at their zenith of ripeness and thus at optimum micronutrient concentration; avoidance of superfluous nutrients, monotony, antinutrients, nutrient deficiency and toxins; olfactory pharmacopeia to rid intestinal parasites and to counter bacterial infections)

[35] Ger. *Fernsinn* (fern – distant, Sinn – sense)

[36] Ger. *Nahsinn* (nah – near, Sinn – sense)

Among these three phases of food-related behavior, the present study focused on chemosensory food selection and food intake.

Food stimuli & manipulations

The nature of a food stimulus may have an impact food intake and therefore, the stimuli used in studies may influence the outcome. Early studies investigating alimentary alliesthesia and conditioned satiety mainly used prototypic stimuli (aqueous solutions of NaCl, sucrose…), in the latter in two-bottle forced choice tests (varying nutritional content paired with different flavors) in their experimental settings. Later experiments on alliesthesia and on sensory-specific satiety mostly used snack foods or complete meals and sophisticated prepared foods (flavored yoghurts, pasta, chocolate, flavored jelly, fruit juice…). However, simple foods without any preparation are infrequently used as food stimuli).

Therefore, one purpose of the present experiment was to test hedonic responses to simple foods of several food groups. Food groups were chosen to be hedonically acceptable even when eaten without condiments or without cooking: fruit (pineapple and banana), fruity vegetables (cucumber and tomato) and nuts (peanut and pistachio).

Determination of the predominating hedonic phenomenon

Sensory-specific satiety (SSS) has emerged as the mechanism that explains the specificity of the search of variety with regard to food intake in primates. Since SSS acts on satiation it impacts food intake earlier in a food bout.

Alimentary alliesthesia (AA) in contrast plays a role later in the meal and during the post-meal period (since it reflects a change in the internal milieu after food ingestion) and thus in satiety. Study protocols investigating AA have related the phenomenon to signals from the upper small intestine and have only demonstrated specificity for sweet, salty [289] and to food-related stimuli in contrast with food-unrelated ones [295,277]. AA is the faculty of a sensation to move up and down the affective axis. The concept of AA thus also in part concerns SSS.

Conditioned satiety (CS) is based on an unconscious learning process, in which the central nervous system comes to associate the sensory properties of foods with their respective energy content and supposedly with their post-ingestive metabolic effects). As CS is based on the principle of conditioning, it may influence food intake with habitual foods, eaten in conditioned contexts.

Past studies did not always return unequivocal results regarding the importance of AA and SSS. As SSS is based on sensory events, it may be more transient and thus easier to manipulate than AA. One purpose was thus to apply a protocol capable of isolating SSS from AA and CS.

Reason for stopping intake (RSI)

While decrease in pleasantness of foods eaten may be one reason (*i.e.*, hedonics) to stop eating, there may be many other intrinsic (*i.e.*, subject-related) and extrinsic (*i.e.*, food-related and environmental) reasons. In fact, subjective reasons for meal termination given by subjects have been assessed in only a few studies. Of these, however, only a single study investigated the specificity of intake (*i.e.*, reasons for ending a course)[631] but rather on reasons for ending a meal [630,632,633,634,635]. Therefore, in all the three present experiments subjects were asked to give up to five reasons, rank-ordered by importance, for stopping eating after each course. Subjects were encouraged to focus on their bodily sensations when doing so.

VII.1.2. Article

Please refer to the Annex for the original PDF of the publication:

Does modification of olfacto-gustatory stimulation diminish sensory-specific satiety in humans?
Romer M, Lehrner J, Van Wymelbeke V, Jiang T, Deecke L, Brondel L.
Physiol Behav. 2006;87(3):469-77. [425]

VII.1.3. Main results & Discussion

In this study, as reported by many other authors, a decrease in olfactory-gustatory pleasure after ingestion of various foods was observed (1st course of all three experiments).

Two original findings were noted. Firstly, the decrease in hedonic ratings for an eaten food was accompanied by increases in olfactory pleasure for non-eaten foods (experiment two). Secondly, flavor-pleasure was fully reversible by seasoning the eaten food (experiment three).

A number of elements can be brought up in reply to the study's objectives:

- Cross-meal hedonic odor and flavor dynamics of eaten foods relative to uneaten ones (objective 1). Participants indeed chose their preferred food only based on olfactory cues. This was reflected by the fact that the chosen one of the six foods smelled significantly better than the other five options, which was the case for each of the six groups and in all three experiments.

  Hedonic flavor dynamics of eaten foods (objective 1). During intake, the pleasantness of the flavor, which was investigated every two minutes, gradually decreased. The last mouthful rated was mostly near or below the indifference mark, *i.e.* hedonically neutral or even unpleasant.

  Cross-meal hedonic odor and flavor dynamics of eaten foods relative to uneaten ones (objective 1). After intake, however, pleasantness of flavor and odor did not correlate any more. This dissociation might reflect different habituation mechanisms[37] for the olfactory- and the gustatory system. We hypothesized that the habituation effect was more prominent in the olfactory system. Actually and although not quantitatively measured, many participants reported a decrease in perceived olfactory intensity for the aroma of the food just eaten to satiation; some even did not perceive the odor at all anymore. This might explain the dissociation of hedonic values as non-perceived odors were rated as hedonically neutral while flavor was still slightly pleasant or already unpleasant. However, it is known that flavor is the combined stimulation of oropharyngeal taste receptors and olfactory receptors in the upper nasal cavity *via* the retronasal route. The present results and previously reported evidence [637] point to at least two functionally distinct groups of ORNs. This suggests that information transmitted to the CNS by the orthonasal group is not the same as that transmitted by the retronasal group. This would explain why the odor of a food just eaten to satiation was not perceived any more orthonasally, while the flavor was still perceived retronasally very clearly.

- A relationship between hedonic odor and flavor dynamics of chosen foods (objective 2). The high olfactory hedonicity was reflected by the equally high hedonicity of the flavor for the first mouthfuls. In fact, both hedonicities closely correlated at the beginning of intake. That

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[37] habituation mechanisms may be evoked since in the chapter SSS it was mentioned that the olfactory signal elicited by a food odor stays unchanged throughout the central olfactory pathway until the OFC

an attractively smelling food also procures palatable taste is notable insofar as the concept of alliesthesia states that the pleasure of food-related stimuli reflects the usefulness to the internal milieu of its consumer. In this context, Goff *et* Klee [636] found that many volatile aroma substances of foods are in fact nutrients (*e.g.*, essential amino acids, essential fatty acids, vitamins). Goff *et* Klee stated that although a single fruit or vegetable synthesizes several hundred volatiles, only a small subset generates the flavor fingerprint that helps animals and humans recognize appropriate foods and avoid poor or dangerous food choices. While the human genome encodes only a few dozen functional taste receptors, it encodes several hundred olfactory receptors. The latter have evolved to allow recognition of specific foods and their compositions. The question that arises is whether there are specific olfactory receptors or clusters of several olfactory receptor neurons (ORNs) capable of detecting nutrients, either by direct receptor activation, or by a specific activation pattern of several ORNs. If so, this would mean that the CNS would have the innate capacity of directly sensing chemical compounds with alimentary significance.

- A relationship between odor and flavor cross-meal hedonics (objective 2) was noted. Therefore, the present finding makes sense in the animal model: in a hungry state of need and thus appetence, a specific food smells pleasant – when given the choice the most pleasant of the foods available is chosen – and this food also tastes pleasant while eating. During consumption, the pleasantness of the flavor gradually decreases. This in turn will make the animal lose interest in the food it is eating and reduce the likelihood of choosing the same food again in a second course.

  Olfactory pleasantness of the five foods not eaten was not reduced by intake of the chosen food. Rather, in some cases, it rose slightly from the preprandial level. This dynamic could in fact promote diversification of food choice in a meal. However, no specific fixed patterns of preferred associations (*e.g.* preference for savory foods after sweet foods: subjects chose banana after eating pineapple which are both sweet, or vegetables after nuts) were observed.

- A relationship between hedonic odor and flavor perception and specific appetite (objective 3) was noted. In fact, both odor and flavor hedonics correlated with specific appetite. Also a more recent study about alliesthesia reported significant correlations between food pleasantness and wanting [277]. Specific appetite is just another term for specific appetence or wanting, the latter being part of Berridge's concept of 'liking and wanting'. According to this concept, both are strongly related and difficult to distinguish mentally. However, both aspects are based on distinct neurological pathways, structures and neurotransmitters [514]. To conclude this finding, the consumer wants what he likes, and will thus choose and ingest foods that are hedonically attractive and avoid those that are not. Again, if hedonics is a reflection of the utility of a stimulus to the consumer, this finding makes sense in physiological terms.

- Odor and flavor hedonics correlated with the salivary response (objective 4). Numerous studies conducted by the group around Epstein have established a link between saliva flow and habituation and studies by the McSweeney group [536] between salivation flow and SSS. It has been shown that habituation plays a role in salivary responses and motivated responses to food [638,499,639,640,641]: humans habituate to repeated food cues and recover their response when a new food cue is presented. Furthermore, salivation is regulated by the autonomous nervous system and therefore is an involuntary reaction. As such, the odor of a food stimulus capable of eliciting saliva secretion relative to other olfactory food stimuli that do not may be preferred by the animal. It might be that along with

sensory pleasure, stimulus-induced salivation might indicate the utility of a food stimulus to the animal during the preprandial state.

- Initial pleasantness as a predictor of quantitative or energy intake (objective 5). It might seem at first sight that the better a food tastes, the more of it will be eaten, making initial pleasantness a predictor of food intake. However, in the present study, initial pleasantness did not correlate with the amount eaten or with energy intake. This can be due to several factors: 1, the fact that each participant chose the most pleasant food among those available and initial pleasantness was always high (between 'pleasant' and 'very pleasant'); 2, the energy content of foods did not impact the importance of SSS (*i.e.* the relative hedonic delta value) because pleasantness decreased similarly in low energy foods (like cucumber) and in high caloric ones (like nuts, sweet fruit), a finding in line with previous observations [367]; 3, quantities eaten before satiation occurred depend on the pleasantness of the food and on ingested volume which reflects gastric distension; 4, quantities eaten depend on homeostatic needs (it is evident that a trained sportsman will eat more than a slim woman, even though both report the same level of pleasure for the same food.

- The roles of AA and SSS in short term intake control (objective 6). The specificity of a decrease in OP of the food eaten relative to uneaten foods is in favor of olfactory SSS. The FP of each food eaten *ad libitum* decreased. As the remaining five foods were only smelled but not tasted between sessions, taste-SSS can only be assumed but not confirmed. Thus, observations suggest that SSS rather than AA is responsible for hedonic variations. This is of importance, as SSS intervenes earlier in a meal it is thus able to limit food intake before complete satiation. SSS enables satiation to operate with a high degree of specificity. Also, this shows that stimulation of the entrance of the GI tract produces strong afferent feedback on actual food intake. Of course, this does not exclude integration of orosensory cues with feedback from gastric, duodenal and jejuna receptors. Studies in animals with esophageal, gastric or duodenal fistula [642] have shown that animals continue food intake, suggesting that integration of orosensory signals with feedback from the GI tract are necessary, including for complete specific satiation (*i.e.*, SSS). Therefore, an interaction between gastric and oropharyngeal factors in the brain is required, where gastric and intestinal factors mediate satiation signals by modulating the reward value of oropharyngeal factors (*i.e.*, the chemical senses). The level of specificity observed throughout this study was food-specific and not specific to elementary taste modalities like sweet or salty. Therefore, the observed changes in OP can principally be attributed to SSS and not to AA.

- The impact of an unexpected second food on hedonics and intake (objective 7). Ingestion of the first olfactorily chosen food was accompanied by a gradual decrease in pleasantness until hedonically neutral or unpleasant. Olfactory choice of a second food out of the six offered showed that the pleasantness of both the odor and the flavor was at the same high level as in the beginning of the meal with the first food. This rebound in pleasantness was accompanied by the intake of a significant amount (Table 4) and energy (Table 5) of that food, suggesting that SSS promotes diversification of food intake.

- The effect of seasoning a food just eaten on: 1, hedonics and 2, total intake (objective 8). 1, flavor pleasure for the chosen food of the first course gradually diminished during ingestion towards hedonic indifference. However, seasoning the same food led to a return of flavor pleasure to its initial pre-ingestion level. 2, seasoning a food just eaten to satiation led to 80% additional intake. For percentages of each food refer to Tables 4 and 5. This may be related to the sensory phenomenon of SSS because seasoning, although it does not modify

the macro- or micronutrient composition, modified the flavor of the food just eaten to satiation, and thus modified the cerebral representation of that food.

Table 4. Quantitative intake in all courses including additional intake in each group. (Study 1)

	QUANTITY (gr)																		
	EXP.1			EXP.2							EXP.3								
				1st course			2nd course			add.	1st course			2nd course			add.		
cucumber	158.6	±	107	131.9	±	70	236.6	±	203	179.4%	176.9	±	124	158.6	±	87	89.7%		
tomato	366.8	±	285	335.1	±	233	163.6	±	109	48.8%	244.9	±	215	197.8	±	201	80.8%		
pineapple	271.1	±	187	105.8	±	43	65.6	±	49	62.0%	185.5	±	89	146.6	±	32	79.0%		
banana	288.1	±	166	226.3	±	163	59.1	±	43	26.1%	121.6	±	60	83.9	±	30	69.0%		
peanut	80.9	±	92	61.8	±	54	442.0	±	313	715.2%	20.0	±	19	20.8	±	16	104.0%		
pistachio	76.5	±	42	105.1	±	79	452.0	±	216	430.1%	15.4	±	13	35.8	±	27	232.5%		
controls A	0.0	±	0	0.0	±	0	0.0	±	0		319.0	±	234	45.9	±	47	14.4%		
controls B											176.3	±	134	29.4	±	28	16.7%		
6 test-groups	207.0	±	192	161.0	±	152	236.5	±	243		127.4	±	136	107.3	±	109	84.2%		

Table 5. Energy intake in all courses including additional intake in each group. (Study 1)

	ENERGY (kcal)																		
	EXP.1			EXP.2							EXP.3								
				1st course			2nd course			add.	1st course			2nd course			add.		
cucumber	19.7	±	13	16.4	±	9	106.9	±	114	651.7%	22.0	±	15	19.7	±	11	89.7%		
tomato	64.0	±	50	58.5	±	41	189.4	±	157	323.8%	42.8	±	37	34.5	±	35	80.8%		
pineapple	151.7	±	105	59.2	±	24	117.1	±	70	197.9%	103.8	±	50	82.0	±	18	79.0%		
banana	257.7	±	149	202.3	±	146	118.1	±	135	58.4%	108.8	±	54	75.0	±	26	69.0%		
peanut	451.7	±	515	344.9	±	303	213.7	±	196	61.9%	111.7	±	108	115.9	±	92	103.7%		
pistachio	439.9	±	239	604.6	±	453	77.8	±	37	12.9%	88.4	±	72	205.6	±	154	232.5%		
controls A	0.0	±	0	0.0	±	0	0.0	±	0		450.1	±	616	66.9	±	85	14.9%		
controls B											303.3	±	355	59.2	±	123	19.5%		
6 test-groups	230.8	±	287	214.3	±	302	137.4	±	134		79.6	±	69	88.8	±	94	109.1%		

- Reasons for stopping intake (RSIs) of a specific food reported by participants (objective 9; [600]).

  Reported RSIs according to the courses and experiments are displayed in Table 6. Whenever two courses were available (experiment 2 and 3), 'fullness & satiation' was reported more frequently after the second course while 'hedonic decrease' was reported more frequently after the first course. This suggests that prior to complete satiation, sensory reasons are more important than gastric sensations in ending a course. Indeed, subjects spontaneously ingested important additional quantities in the 2nd course (see Tables 4 and 5). The mid-meal dominance of hedonic reasons to end a course is in line with the concept of SSS and its proposed role as promoter of variety searching. Unpleasant sensations ('Numbness, pain & itchiness') were reported least frequently after the second course of experiment 3. In fact, many fresh foods (like vegetables) contain compounds which may, during ingestion, provoke unpleasant or even painful sensations (stinging of pineapple and horse radish; feeling of numbness with cucumber; sticky sensation with bananas; burning from the acid of tomato). These unpleasant sensations towards the end of *ad libitum* intake during the first course reported by the subjects, seemed to vanish completely when simple condiments (according to the foods, salt, pepper, sugar, cream, roasting) were applied (experiment 3, 2nd

course). This is notable as this effect may assist in limiting food intake with simple foods. However, this effect can be reduced by addition of condiments.

Concerning the six foods (*cf* Table 7), fullness was reported most frequently with both sweet fruit (pineapple and banana). This effect can neither be attributed to ingested quantity (higher for tomato) nor to ingested energy (higher for the nuts). As both were sweet, some alliesthesic feedback from Mei's intestinal glucoreceptors may have been involved. Hedonic decrease was reported most frequently with cucumber and pistachio, which can be explained by neither ingested quantity nor energy, nor by sensory differences to the other food of the same group (tomato and peanut). Unpleasant sensations ('Numbness, pain & itchiness') were reported most frequently after eating pineapple. It is known that pineapple contains the protease enzymes bromelain which are protein-digesting enzymes. The reported itchiness after intake thus stems from digestion of oral mucosa tissue by these enzymes. The results from Table 7 suggest some food-specific patterns as reasons for stopping ingestion. This may partly be due to differences in texture and content of astringent compounds.

Table 6. Frequency of reasons for stopping intake according to experiment and course. (Study 1)

CATEGORY		EXP.1	EXP.2		EXP.3	
course	*1st*		*1st*	*2nd*	*1st*	*2nd*
n	48		48	44	48	48
Hedonic decrease		28	23	18	29	13
Fullness & satiation		24	15	24	18	22
Numbness, pain & itchiness		14	15	26	19	10
Change in taste-modality		11	16	10	13	14
Hampered swallowing		10	14	12	6	0
Oral residues		9	11	6	5	3
Oro-pharyngeal dryness		7	9	4	2	3
Sensory satiation		6	12	5	13	11
Consistency & chewing		3	13	7	9	7
Sweat & heat		3	2	0	0	0

Table 7. Frequency of reasons for stopping intake according to the six foods (Study 1).

CATEGORY	cucumber	tomato	pineapple	banana	peanut	pistachio
Hedonic decrease	16	9	9	12	10	20
Fullness & satiation	8	8	12	12	7	7
Numbness, pain & itchiness	6	6	11	2	3	4
Change in taste-modality	11	8	11	4	1	3
Hampered swallowing	4	3	1	2	11	5
Oral residues	0	5	3	0	9	8
Oro-pharyngeal dryness	0	0	0	3	10	5
Sensory satiation	6	4	7	9	2	2
Consistency & chewing	4	4	2	6	4	4
Sweat & heat	0	0	1	0	4	0

VII.2. Second study: BMI

VII.2.1. Introduction

The first study demonstrated a specific and consistent drop in pleasantness of the aroma and the flavor of each of six simple foods when eaten to satiation versus the remaining five foods in a large population balanced for BMI, gender and age. The question arises if these person-specific variables may influence food intake. The next step was therefore to screen this population for differences in the measured parameters among these different subgroups to know the impact of anthropometric variables on hedonics, SSS and food intake.

The second study was therefore destined to reanalyze the data of the first study taking into account the first course of the three experiments in order to determine whether overweight persons have a different hedonic reactivity (*e.g.* a reduced sensory-specific satiety) from normal-weight subjects towards simple foods, chosen and eaten *ad libitum* and to evaluate the influence of age and gender. The analyses were done in 144 subjects.

There were three main objectives:

- Several studies have suggested that the BMI of subjects might influence hedonic perception of foods in that overweight subjects may display higher preference for sweet, salty [643] or energy dense foods [644]. Obese persons might differ in their hedonic reactivity to food (reduced negative alliesthesia and SSS) for a food as it is eaten. Therefore, we compared slim, normal weight, overweight and obese subpopulations in the hedonic and intake-related parameters studied.

- Gender may affect food choice and intake. It may be that women are more sensitive to food selection and more susceptible to cognitive restraints which may lead to mental food restriction. These findings suggest that hedonic dynamics might reflect to some degree gender differences in food intake. Thus, data from male and female participants were compared.

- Age may impact food hedonics in that it may influence food sensory preference. Some studies suggest differences in SSS between different age-groups (children , teenagers, young adults, older adults, aged persons)[498,377]. Sensory-specific satiety has been reported to be reduced in elderly persons [377] and may lead to a monotonous diet, which in turn may favor calorie depletion and nutrient deficiency.

VII.2.2. Article

Please refer to the Annex for the original PDF of the publication:

Sensory-specific satiety with simple foods in humans: no influence of BMI?
Brondel L, Romer M, Van Wymelbeke V, Walla P, Jiang T, Deecke L, Rigaud D.
Int J Obes (Lond). 2007;31(6):987-95. [437]

VII.2.3. Main results & Discussion

- BMI (objective 1): although a large, well-balanced representative population was studied, no notable food intake-related differences were discovered: overweight persons showed similar hedonic dynamics to slim persons. This was reflected in food intake: overweight persons did not consume more food than did slim participants, neither by means of food weight nor by energy.

- Gender (objective 2): in this study with simple foods, no differences in hedonic perception between women and men could be found. Also, only when all six foods were taken together men consumed more weight, volume and energy than did women. However, separate analysis could only reproduce this main effect in tomato (only for weight and volume) and both varieties of nuts (only for energy). The differences found in weight and energy of foods ingested between male and female subjects could be attributed to body weight and thus to higher energy requirements in men.

  Concerning gender, results point to similar hedonic control of food intake in men and women of similar BMI. Higher mean intakes in men are in line with the literature and common sense stating that men eat more than women of similar BMI.

- Age (objective 3): similarly, no differences in reported hedonic sensory experiences or in food intake were found between teens and subjects over forty in the studied population.

  Concerning age, quite astonishingly, the studied population of persons over forty performed similarly to teenagers. Similar hedonic reactivity might reflect functioning of the organism in good health. That two subpopulations of very different age-segments (teens and over forties) ingested similar amounts may suggest 1, similar nutrient and energy requirements, 2, similar energy expenditures. This is puzzling as teenagers in their late growth phase may have very different needs than persons over forty years of age.

It should be retained that the hedonic experience (initial and total decline in pleasantness for the aroma and flavor) was similar in all compared subgroups.

This suggests 1, that overweight, and its associated consequences contrasting with an organism at normal weight, did not modify hedonic psychophysics with simple foods, and 2, that although subgroups displayed similar global perceptions, the amounts eaten varied substantially between foods and between subjects. Resulting from 1, and 2, if different amounts ingested were accompanied by similar initial, final pleasantness and drop in pleasantness of the flavor, the rate of decline in pleasantness over time must have been different. Therefore, the slope of decline predicts food intake in that a steep slope is related to a short meal or little intake (whichever of these two is represented on the abscissa)(Figure 13).
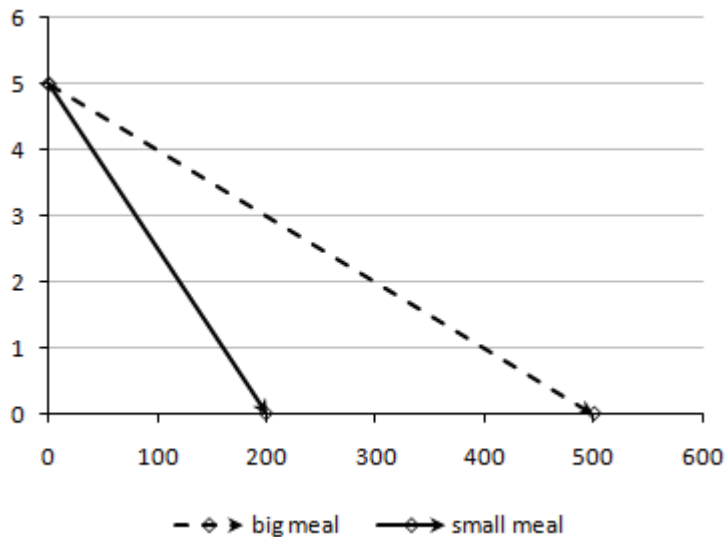
Figure 13. Schematic visualization of two meals with same hedonic characteristics
(initial and final pleasantness; delta) but different intakes (in gram or kJ) or intake durations (in sec).

In conclusion, the question on why obese persons had similar intakes to lean persons remains unsettled. Obesity results from a long-term positive energy balance (*i.e.*, eating beyond energy needs over a long time). Once a higher BMI is reached, the initial dynamic obesity can become chronic and the proposed ponderostat will register that new level of adiposity as normal weight. However, the higher corpulence would still require more daily energy intake than a person with normal range BMI if adipocyte energy stores are not metabolized. One inclusion criterion of this study was stable body weight over the past three months. Therefore, similar intakes cannot be explained by higher intakes in normal weights or lower intakes in obese persons.

It is known that the organism establishes energy balance more accurately over several meals. At least medium- to long-term studies (*e.g.*, over weeks to months) under the present protocol would be necessary to examine the evolution of body-weight, intakes and hedonics.

Further, food intake may have been limited similarly in obese and normal weights by astringent taste. Indeed, many subjects reported the appearance of unpleasant and astringent oral sensations as a reason for stopping eating in the first study. Astringent compounds (*e.g.*, tannins) are present in many plants and foods and may contribute to the limitation of intake.

VII.3. Third study: Monotony & Variety

VII.3.1. Introduction

1. Presentation of the study

In the first study, modification of the sensory properties of a simple food eaten *ad libitum* by adding condiment to the food just eaten in an unexpected second course, led to two related events: 1, a rebound of pleasantness derived from the flavor of the food eaten, and 2, important additional intake of food and energy (around 80% additionally). These observations led to the design of this third study.

While in the preceding studies simple foods were used as food stimuli, in this study a standard western two-course meal with prepared dishes was simulated in the laboratory. The first course consisted of French fries (condiments were tomato ketchup and mayonnaise) and the second one of brownie cakes (condiments were vanilla cream and whipped cream). Therefore, as in the first study, the sensory properties of a food eaten *ad libitum* were modified by the addition of condiments.

The general objective was, as in the first study, to examine the influence of renewal of olfacto-gustatory sensory stimulation on SSS and food intake. Furthermore, the impact of several kinds of renewal of olfacto-gustatory sensory stimulation (simultaneous and successive) on hedonics, additional intake of food quantities and calories were studied to complete observations of the first study where the manipulations consisted in a single sequential sensory renewal.

2. Objectives of the study

The hypotheses were that in the present study with cooked foods 1, both levels of variety (*i.e.*, sequential and simultaneous) would lead to increases in olfacto-gustatory pleasure and in turn increase food intake in comparison with the baseline monotony situation, and 2, simultaneous sensory variety would lead to more additional intake than successive variety because of simultaneous access to the offered condiments (enabling repeated "switching" between flavors according to personal preferences).

The main objectives of the present study were to re-examine the link between SSS and increased consumption of a varied meal and to study how small amounts of variety may influence SSS for a given food ingested during a meal. The following were the specific objectives:

1. study of the dynamics of flavour pleasure in the three different situations
2. study of the influence of successive and simultaneous variety on the amount of food eaten
3. study of the dynamics of olfactory pleasure in the three different situations
4. study of the reasons for stopping intake (RSI) in each course

3. Choice of the protocol and methodology

Most of the results were reported in the article. However, some were measured but were omitted in the publication. Flavor pleasure was evaluated every two minutes during intake (as in the first study). Olfactory pleasure was evaluated before, between and after the courses of the meal for eight food samples of which some were eaten (French fries, brownies, tomato ketchup, mayonnaise, vanilla cream, whipped cream) and some that were not (fresh tomato, ham, fresh banana) in order to study hedonic changes after each course and during intake. Finally, reasons for stopping eating

(RSE) after finishing a course were assessed. However, this time, participants had to rank the three most important RSEs which they had to pick from a list of ten predetermined reasons. The ten categories derive from the free replies most frequently reported obtained in the first study with simple foods (see Table 8 for the list of reasons [not included in the publication]). Additionally, they had to rank three free-choice open option reasons which they had to give.

Table 8. List of the ten predetermined reasons for stopping intake (Study 3)

_____

1. Hedonic decrease
2. Gastric fullness
3. Trigeminal - Oral numbness, pain & itchiness
4. Change in taste-modality
5. Hampered swallowing
6. Oral residues
7. Oro-pharyngeal dryness
8. Tiredness of the aliment (Sensory satiation)
9. Consistency & chewing
10. Sweat & heat

_____

VII.3.2. Article

Please refer to the Annex for the original PDF of the publication:

Variety enhances food intake in humans: role of sensory-specific satiety.
Brondel L, <u>Romer M</u>, Van Wymelbeke V, Pineau N, Jiang T, Hanus C, Rigaud D.
Physiol Behav. 2009;97(1):44-51.

VII.3.3. Main results & Discussion

The following results were obtained:

- Objective 1: Flavor pleasure of the food eaten *ad libitum* decreased during both courses and in all three situations (monotony, successive and simultaneous variety) which may be attributable to SSS. However, as the foods from the rating set were only smelled but not tasted, taste-SSS can only be assumed. As in the first study, initial FP for the second course returned to a high level comparable with initial FP of the first course. This rebound again

can be attributable to the renewal in sensory stimulation by the different flavors in both courses. Changes in FP are reported in Figure 14 for fries and brownies. It can be observed that FP diminished little between the first mouthful and 25%, more between 25% and 75% and again little between 75% and last mouthful (*i.e.*, when the level of hedonic indifference was reached).

In the successive variety situation, in each of the two courses only one condiment (1st course: tomato ketchup, 2nd course: vanilla cream) was successful in raising FP from its previous level. The most obvious reason for this is that the other two condiments (mayonnaise and whipped cream) were both rich in lipids and thus may have delivered a sensory image associated with fat (in terms of SSS) and calories (CS). As the first course was quite fat (fries deep-fried in oil), these fatty condiments most likely were not perceived as pleasant.

In the simultaneous condition, it was not possible to evaluate the increase in FP linked to the introduction of condiments since these were eaten in a consumer-specific random pattern. However, FP decreased more slowly than in the monotony condition and intake was higher than in the monotony condition but similar to the successive condition.
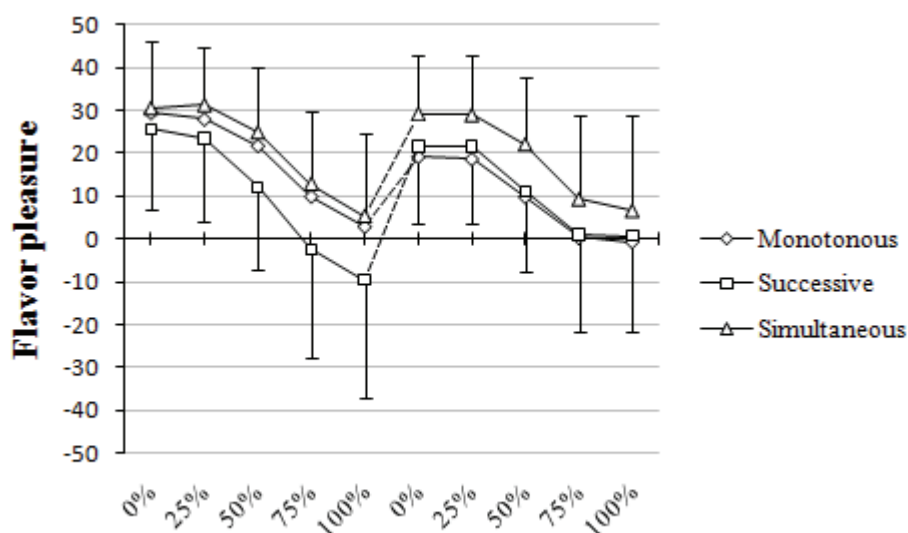

Figure 14. Development of flavor pleasure (FP) for French fries and brownies during intake.
Values are expressed as percentages of eaten quantity (0%–25%–50%–75%–100%) because eaten quantities were *ad libitum* and thus differed between subjects. Values are given in mm (VAS).

- Objective 2: The restoration of FP correlated with an increase in total intake in the successive variety (food weight +41%, food energy +40%, see Figures 15 and 16) and simultaneous variety (weight +35%, energy +24%, see Figures 15 and 16) condition *versus* the monotony condition.

  When courses were analyzed separately and with inclusion of the condiments eaten (all of which contained metabolizable energy), in the 1st course (French fries), both quantitative and energy intakes were significantly higher in both variety conditions than in the monotony condition with no significant difference between successive (+23% gr, +24% kcal) and simultaneous variety (+25% gr, +26% kcal). In the 2nd course (brownies), only quantitative intakes were significantly higher in both variety conditions than in the monotony condition, with no significant difference between successive (+87% gr) and simultaneous variety (+62% gr). Energy intake in the 2nd course was higher in the successive condition than in the monotony and simultaneous variety conditions (68% and 37%, respectively).

  Therefore, the initial hypotheses could be partly confirmed. First, both variety conditions could increase the amounts of food eaten. Second, there was (except for energy intake in the

2nd course) no difference in intake between the two variety conditions. This suggests that offering various flavors (in the form of condiments or sauces) in succession has the same effect on food intake as offering them simultaneously.

A possible explanation for result might be a pre-experimental conditioning effect of food-condiment combinations, *i.e.* conditioned satiety, as subjects were familiar with the foods and condiments offered. In summary, the results are in line with the results of previous studies on monotony and variety. The higher additional intakes during the second course can be attributed to food texture: the dryness of brownies facilitated intake when offered with juicy creams.

Furthermore, offering a dessert (2nd course) had a global effect on additional intake in each condition: monotony (+37% gr, +63% kcal), successive variety (+56% gr, +86% kcal) and simultaneous variety (+48% gr, +61% kcal).
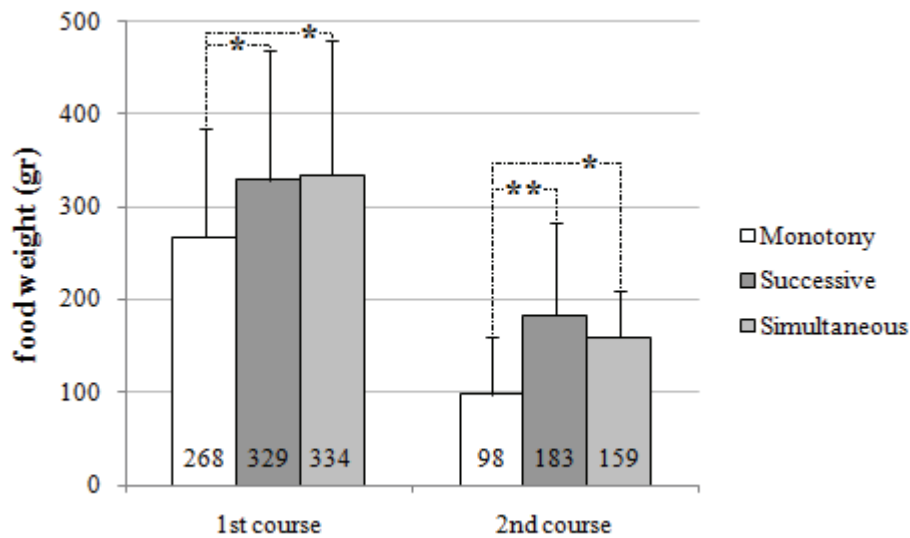
Figure 15. Consumed amounts (in gr) in the first (fries) and second course (brownies) of the three situations. (*) $p<0.05$; (**) $p<0.001$, values are mean ± SD

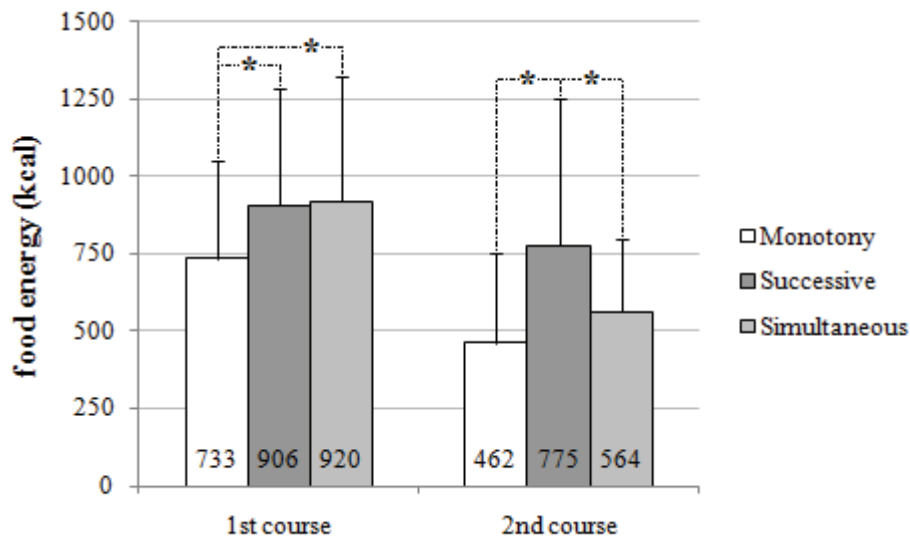Figure 16. Consumed energy (in kcal) in the first (fries) and second course (brownies) of the three situations. (*) $p<0.05$; (**) $p<0.001$, values are mean ± SD

- Objective 3: Concerning olfactory pleasure (OP), several findings can be reported:

1, Hedonic declines for the foods eaten were only partly specific in that they also affected foods not eaten in the course but which had similar hedonic profiles. Eating the 1st course (French fries with ketchup and mayonnaise) also resulted in a decline in OP for ham and fresh tomato. After the 2nd course (brownies with vanilla cream and whipped cream), OP also decreased for fresh banana.

2, Hedonic decreases for foods eaten in the 1st course tended to continue decreasing until after the 2nd course. This is notable as it points to an influence of postingestive events, probably from preabsorptive gastrointestinal feedback to the brain.

This is compatible with alimentary alliesthesia as the hedonic decreases were not entirely food-specific and also affected foods not eaten at all in both courses that nutritionally were very different (ham, banana). This is important because it shows that SSS and AA may be complementary in creating specific and general satiation given their mechanisms, sites of action and signaling pathways.

- Objective 4: Concerning the reasons for stopping intake (RSI) each course, the ranking of the three chosen predetermined reasons for stopping eating the 1st and the 2nd course was the same in all three sessions (see Table 9). As a general tendency, after the 1st course rather specific/hedonic reasons (got tired of food, mouth dryness, taste less pleasant) were rated high and frequently while after the 2nd course reasons reflecting installment of general satiation (no more hunger, stomach fullness) were ranked highest. Previous studies investigating reasons for stopping intake generally found fullness to be ranked higher than hedonic reasons, probably because they were focused more on general meal termination than on specific satiation. As this study distinguished between each course, it was shown that hedonic reasons are more important at the early stages of a meal while towards the end of a meal, when the stomach is filled with food from several courses, conscious perception of this fullness is the most important factor to stop eating a course or to finish the meal. This result, consistent with observations in the first study, has not previously been reported by studies looking into subjects' reasons for stopping intake.

Table 9. Most frequent reasons for stopping eating either course (Study 3).

1st course		2nd course	
"I got tired of the food"	25%	"no more hunger"	28%
"no more hunger"	17%	"stomach full"	20%
"mouth/tongue dryness"	15%	"I got tired of the food"	20%
"taste less tasty than initially"	15%	"mouth/tongue dryness"	12%
"stomach full"	12%	"tastes less tasty than initially"	12%

VII.4. Fourth study: Dishabituation

VII.4.1. Introduction

1. Presentation of the study

The third study demonstrated that successive presentation of condiments with food was successful in extending intake of a given food. However, there may be various reasons for this effect. In this final study, variety in the form of several levels of alternation was applied, to test if this sensory manipulation could lead to several levels of extra intake. If it was so, this might be attributable to disruption of habituation to a given flavor.

2. Objectives of the study

Functional neuroimaging and electrophysiological studies of E.T. Rolls *et al*. [574] and Diana Small [483] elucidated the neural mechanism behind SSS in showing that neurons stop responding for a food just eaten but still respond to foods with different flavors. Also Mc Sweeney [536] argued that SSS is consistent with habituation. The hypothesis of this study was that alternation of foods would increase intake since alternation of sensory food stimuli would dishabituate the subjects and the brain would consider that each new presentation represented a different food. If pleasantness of the flavor increased at each contact with a different flavor (even though eaten previously) might enhance food intake.

3. Choice of the protocol and methodology

Again, a standard western meal (1st course: meatballs and fries; 2nd course: vanilla cream and brownies) was simulated in the laboratory. In the baseline situation, subjects could eat each of these four food items without repeated alternation. The single repetition situation added one repetition of one food in each course, while in the multiple repetition situation, subjects had triple access to both food items in either course. While each alternation was a fixed amount that the subjects had to ingest, the last repetition in each course was always *ad libitum* (always French fries and brownies since intakes of meatballs and vanilla cream were imposed in the three situations). In this study, three subjects were tested simultaneously while eating together at the same table to avoid the clinical laboratory atmosphere by adding some conviviality.

Flavor pleasure was evaluated for the first and the last mouthful of each course. Olfactory pleasure and desire to eat (*i.e*., specific appetite) were evaluated again before, in-between and after the courses for ten food items eaten (meatballs, French fries; vanilla cream, Brownies) or not (salted biscuit, ham, tomato ketchup; fresh banana, strawberry jam, honey).

VII.4.2. Article

The following pages consist in the original PDF of the publication:

Alternation between foods within a meal. Influence on satiation and consumption in humans.
Brondel L, Lauraine G, Van Wymelbeke V, Romer M, Schaal B.
Appetite. 2009;53(2):203-9.

VII.4.3.Main results & Discussion

Concerning food intake of the two foods in the 1st course, an ANOVA did not show a significant main effect of session. Separate *t*-tests, however, delivered significant results only for fries in that more fries were eaten in the single repetition (+18%) and in the multiple repetition session (+13%) than in the no repetition one. In the 2nd course, more brownies were consumed during single repetition session (+16%) but less brownies (–20%) during the multiple repetition sessions than in the no repetition one. Intakes of meatballs and vanilla cream were no different in the three situations. Total cross-meal intake was 14% higher in the single repetition session than in the baseline condition. Interestingly, total intake in the multiple repetition session did not yield increased intake.

Flavor pleasure dropped during intake of each food in each course in all three situations and this drop was the deepest in the last repetition of each course (the one that was eaten *ad libitum*). Specific appetite (desire to eat a food) correlated with flavor pleasure. Olfactory pleasure for the ten food items smelled between courses followed a similar pattern to the one in the previous study:

1, OP for foods eaten (fries, meatballs, vanilla cream, brownies) dropped specifically during the respective course,

2, in addition, OP for all salty foods decreased during the 1st course and for all sweet foods during the 2nd course,

3, salty foods continued to decrease during the 2nd course (although sweet foods were eaten).

Also, the manipulation in this final study was successful in instigating participants to eat more, though it was less effective in doing so than the two preceding manipulations. Further, a high rate of repetition did not lead to additional intake in comparison to the baseline condition without alternation. This could be due to several reasons: on the one hand, repeated alternation between two foods and thus food flavors might have irritated participants, as this might have represented an unnatural way of eating, and cognitive, cultural, habitual or conditioned factors might have intervened. On the other hand, the reduction of intake (brownies) in the second part of the meal by repeated alternations of two flavors might have led to sensory over-satiation, and might have created disgust rather than a disruption of habituation, similar to TV-channel swapping (known as 'zapping', as mentioned in the discussion of the preceding study). This effect in food intake might be referred to as 'flavor zapping' or 'food zapping' and was supported by the lower desire to eat other foods after the multiple repetition-session than after the other two situations.

Also in this study, correlations confirmed a close relationship between the two components of reward, *i.e.*, between liking and wanting. As in the third study with prepared foods (but different from the first study with simple foods), olfactory pleasantness was only partly specific to the foods eaten, above all in the later stages of the meal. This underlines the importance of postingestive (and because of the early onset also preabsorptive) factors intervening in the hedonic control of food intake, compatible with the phenomenon of alimentary alliesthesia.

VIII. GENERAL CONCLUSIONS ON EXPERIMENTS

VIII.1.   Conclusions of Study 1

SSS was observed for simple unmodified foods and could be isolated from AA and CS in the short term. SSS for a simple food just eaten to satiation could be reversed by two manipulations: 1, by eating a different food, and 2, by seasoning a food just eaten. Restoration of food pleasantness was associated with additional food intake. This could explain how food variety can lead to over-consumption and as a consequence to over-weight.

VIII.2.   Conclusions of Study 2

In a large population with stable body weight, obese and normal weight persons displayed similar dynamics of SSS and similar consumption with simple foods. These findings were not influenced by gender and age.

This indicates that at a stable body weight, overweight and lean subjects have similar hedonic control of food intake with unprocessed foods without condiments added. This finding can bring new arguments to the debate on differences in SSS between lean and overweight persons and suggest an influence of the nature of food stimuli.

VIII.3.   Conclusions of Study 3

In humans, inducing successive and simultaneous food variety by adding condiments to foods as in a 'fast food' style meal, increased food pleasantness and intake in the short term. However, there was no difference in intake between successive and simultaneous presentation of variety. The increased consumption may come from disruption of sensory satiation for a given food by renewal of sensory stimulation. This disruption of sensory satiety by food variety could play a role in the obesity epidemic.

VIII.4.   Conclusions of Study 4

Moderate alternation between foods within a meal enhanced food intake in the short term, which can be explained by disruption of habituation. This could explain the increased intake with sensorily varied meals. Multiple alternations of foods at the end of the meal decreased intake, probably caused by sensory overstimulation or by cognitive factors involved in normal satiation.

IX. GENERAL DISCUSSION

The introductory chapters showed that the physiological control of human food intake enters the complex and multifactorial framework of regulation of the internal milieu of the primate organism. As such, the central element is the central nervous system which receives feedback from afferent pathways from various structures and systems:
- chemical senses (chemical receptors of gustation and olfaction),
- gastrointestinal tract (mechanoreceptors of the esophagus and stomach; chemoreceptors of the small intestine),
- blood (central detection of circulating nutrients, metabolites and hormones)

Among these, the chemical senses have a special place. On the one hand, they are the first to come into contact with foodstuffs and chemoreceptors have the power to give detailed information on nutrient composition of foods. On the other hand, based on memory, they enable recognition of previously eaten foods and enable food intake to operate with a high degree of specificity. These circumstances enable the brain to acquire and use sensory information for sensory regulation of food intake.

So far, three main distinct sensory mechanisms have been identified, each of which has its place in food intake control: sensory-specific satiety, alimentary alliesthesia and conditioned satiety.

Rolls's sensory-specific satiety[38] [364] is the most specific of the three phenomena and the only one that is capable of specifically limiting food intake in the short term (*i.e.*, before gastric fullness) because it is based on afferent information, which above all originates from the chemical senses. Rapid decreases in preference of eaten relative to uneaten foods can only be attributed to SSS.

Cabanac's alliesthesia [242] is less specific and takes longer to limit food intake as it is based on feedback from post-oral sites, most likely chemoreceptors in the small intestine. Furthermore, the concept of alliesthesia is of importance because it attributes a vital function to hedonics. *Via* pleasant and unpleasant sensations, the brain mediates necessities and warnings about harm or danger to the individual and thus motivates physiologically useful behavior.

Booth's conditioned satiety [108] is separate from the preceding phenomena in that it operates simultaneously with AA and SSS, but continues for hours after ingestion.

What all three mechanisms have in common is that they combine information from chemosensory receptors (olfactory, gustatory and intestinal) with information about variables describing the state and composition of the internal milieu (*i.e.*, the interstitial tissue fluid surrounding the cells of the organism) or gastro-intestinal mechanoreceptors to operate (Figure 17): CS couples sensory signals from the chemical senses with information about nutritional content from nutrients circulating in the blood plasma after intestinal absorption. AA interprets sensory signals from intestinal chemoreceptors or related pre-absorptive signals as a function of the state of the internal milieu. SSS predominantly requires olfacto-gustatory feedback during ingestion. However, at least feedback from esophageal or gastric mechanoreceptors is necessary for full installment of SSS.

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[38] first described by Le Magnen

Information source	CS	AA	SSS
Olfactory receptors	yes	no	yes
Gustatory receptors	yes	no	yes
Intestinal chemoreceptors	?	yes	no
Hypothalamic chemoreceptors	?	?	?

Figure 17. Localization of receptors conveying afferent signals in the three hedonic phenomena. Each phenomenon utilizes a distinct pattern of sensory information.

The first study presented in this thesis identified SSS as the predominant sensory phenomenon operating in the short term because only SSS can mediate flavor-specific satiation with inhabitual foods (exclusion of CS) and because AA has a later onset and nadir. This however does not exclude the action of AA during the postprandial phase of satiety or the action of CS, which relates post-absorptive effects of a food to its flavor and stores it in an unconscious part of memory. While olfactory SSS was highly specific to the foods eaten *ad libitum* in the 1st study with simple foods, it was only specific to spicy *versus* sweet foods in the 3rd study with prepared foods. This suggests that signals from post-gastric receptors (AA) are integrated with signals from olfacto-gustatory receptors (SSS). However, what is puzzling is that satiation was food-specific in the first study and not in the 3rd, which shared a very similar protocol. The only notable differences were the nature of the food stimuli used and energy intakes which may have caused the differential hedonic reactivity observed.

SSS is also the most salient explanation of the most important observation of the presented series of studies: manipulation of the sensory properties of foods by adding a condiment to a food just eaten to satiation was capable of 1, raising pleasure derived from the food just eaten to its pre-prandial level, and as a consequence 2, of instigating individuals to eat additional amounts of that same food. This finding suggests that satiation for a specific food was 'reduced' as subjects continued eating the same food which they just rejected when a little condiment was added. In neurological terms and according to the definition of sensory-specific satiety, it has to be said that SSS was not 'reduced'. Rather, two distinct sensory satiations were produced: one specific sensory satiation for the flavor of the food without condiment, and one for the resulting flavor of the combination of food with condiment. This should be considered whenever the term 'reduced SSS' (which may seem incorrect) is applied.

Therefore, modification of the flavor alone is sufficient to increase pleasure, probably by overriding habituation to a constant flavor through sensory variety, and consequently total food intake. Only few studies modified only the sensory qualities without affecting the nutritional properties. Rolls used distinctive pasta shapes [359] or chocolates that only differed in color but not in nutrient composition [359] and observed an increase in intake of 14% over three varied courses versus the preferred choice. In a third experiment with cream cheese sandwiches of the same composition, sensorily distinct non-caloric condiments (salty, sweet or spicy) were added (salt, non-nutritive lemon, saccharin or curry flavor)[359] to produce sensory variety (+15% caloric consumption). However, the three foods were offered successively and SSS was not investigated for each of the three flavors and it is not clear whether quantitative intake (in gr) was significantly increased. Yeomans added oregano and observed a 14% increase in the intake of pasta with tomato sauce (~350g plus 50g with additional ~95 kcal [651]) and termed it the 'appetizer effect' [151]. The reason for the relatively small additional intake may be the 'bland' baseline condition which was already spiced with tomato sauce.

In contrast, in the presented series of studies, the mean additional food intake was as high as 18% (study 4), 40% (study 3), and 84% (study 1). The cause of the large differences between study 4 and the other two may in part be to the distinct study protocol and as mentioned above to sensory overstimulation (study 4) and subsequent fatigue in the participants. The large difference between study 3 and study 1 might be due to the different caloric intakes in the 1st course (10 times more in

study 3 than in study 1). The differences in direct comparison are notable, as with less food intake (1.8 times less in quantity, 8 times less in energy) and with similar taste hedonics (initial flavor pleasure), similar levels of satiety were achieved. This suggests that simple foods, although generally lower in nutrient density, have a higher satiating power than processed foods. This is in line with a study that compared the satietogenic effect of several preparations of apples [620]. In fact, this principle is part of many slimming programs. Further, chemesthetic astringency (oral chemical irritation from compounds present in many fruit and vegetable species) may be a sensory factor that limits food intake [646,647]. Apparently, seasoning cucumber could suppress the oral sensation of astringency in the 1st study (experiment 3).

The reason for the human inclination to continue eating the same food when it is offered with distinct flavors and to spontaneously change to another food whenever variety is available may be rooted in the brain's distinction between foods based on sensory cues. Subjective and electrophysiological findings regarding SSS suggest that the brain stores sensory images of previously eaten foods. During intake, the image of the specific food eaten is hedonically devaluated by a brain mechanism related to SSS. This suggests that two similar foods with distinct sensory properties are represented differently in the CNS, *i.e.*, two foods that are sensorily distinct are represented as if they were different foods.

The inability of this CNS mechanism that mediates SSS to adapt to this situation may be related to the fact that during the vast majority of human development, man only had access to simple unmodified foods. Food preparation techniques that were acquired over the past millennia (mixing foods, seasoning, fire use for cooking, domestication of animal and plant species (inclusion of milk and cereals in the diet), pottery (cooking in water), grinding of cereal seeds (whole meal), salt usage, smoking (meat and fish), meal and sugar refinement, oil extraction) for the first time in human history enabled the production of sensorily distinct foods with similar nutritional properties. The modification of the sensory properties of foods in turn may influence the brain's sensory control of food intake by enhancing the palatability and increasing adipose tissue. For example, feeding highly palatable diets to rats induces an increase in brown adipose tissue necessary for survival during the winter months [648].

A distinct stimulation pattern of olfacto-gustatory receptors of simple versus prepared foods could in part explain why in the second study, obese subjects did not consume more than slim subjects and displayed similar hedonic dynamics when simple unseasoned and unprocessed foods were offered. It is known that mixtures of sweet and fat in foods (energy-dense sources of calories) are considered especially palatable by obese humans [649,650]. This introduces the evolution-related aspect of food intake. Humans have begun to ingest processed and transformed foods quite recently in evolutionary terms. In contrast, although the genetically closely-related great apes did not develop food preparation techniques, they have similar sensory perception and preference for cooked foods [645].

As a consequence, the sensory systems and the brain developed according to sensory cues present in that environment. This was sufficient, as during the pre-culinary era, sensorily different foods were indeed different foods with distinct nutritional properties. Therefore, if the sensory attributes of food are modified, the hedonic response of the brain is as if it would be confronted with a different food. However, today industrial food processing and food preparation enables the production of nutritionally very similar foods with very distinct tastes (*e.g.*, flavored yoghurts, pasta with different sauces).

It has been suggested that the mechanism of SSS evolved during an era when food selection according to nutritional needs was crucial for survival. Long before the era of food preparation, it might have been advantageous during human evolution as it ensured diversification of food intake through variety seeking in the prevailing nutritional environments in order to avoid nutrient deficiency [465,153,420]. Today, the immense sensory variety of processed foods available in supermarkets and the re-instigation of pleasure for food that had already been consumed to specific satiation may indeed facilitate over-consumption and be a factor in the growing obesity epidemic [546,144]. Conversely, this could explain the effectiveness of monotonous diets for weight

reduction in obese patients [407,465,652]. In the long term, manipulation of the sensory properties of foods may disrupt body weight balance and could also lead to nutrient deficiency if the same food is repeatedly eaten with different spices, flavors or sauces (*e.g.*, fruit-flavored yoghurts, rice or tubers with different sauces).

There is a centuries-old controversy about sensory pleasure. In Ancient Greece, there were two opposed concepts about hedonic sensations, and they still exist today in modern sensory science: hedonics 1, as pleasurable stimulation of the senses disturbing physiologic regulations, and 2, as a central element integrated in the regulation of physiologic processes. This controversy is most evident in discussions about the causes of the obesity pandemic.

However, functional brain imaging studies have revealed the existence of extensive hedonic circuitry integrated within the CNS and behavioral studies demonstrated that positive and negative hedonic sensations guide the individual in executing physiologically useful behavior. While Aristotle and Epicure already recognized an intrinsic function of pleasure in historic times, this has recently been put into question by Yeomans: *is palatability a response to nutritional need or need-free stimulation of appetite*? [581]. Or in other words, is sensory pleasure a sign of usefulness of food stimuli?

The results from the series of experiments presented in this thesis suggest that Cabanac's theory has validity, also concerning SSS – under certain circumstances.

It has been suggested that alliesthesia is a motor of useful behaviors in mammals which seek pleasure and avoid displeasure. Alliesthesia reflects the state of the internal milieu [241,243] and indicates need or usefulness, and guides behavior to accomplish physiological aims[39]. This led to the equations: pleasant = useful [233], and unpleasant = harmful. Thus, noxious stimuli perceived as unpleasant warn the individual of danger. According to Charles Darwin, organisms are adapted and receptive for stimuli of the *umwelt*[40] [669] in which they developed [653,654]. Accordingly, wild animals refuse to ingest burned substances [655]. In this way, the hedonic tone of the aroma [667,668] of a given food may reflect its usefulness.

Cabanac has demonstrated in a series of experiments that sensory pleasure and displeasure have the function of guiding an organism to optimize the composition of its internal milieu. However, as he stated in the book "*La quête du plaisir*" [320], there are situations when hedonics do not protect the organism, where 'pleasant = harmful' [320,334,336]: 1, hallucinogenic drug abuse, 2, food intoxications (mushrooms), 3, atherogenic diets, 4, deficient diets (*e.g.*, polished white rice and beriberi). However, these examples require manipulations (heating, pyrolysis, extraction) to be created or to develop the drug-specific properties (*e.g.* cannabis, coffee, tea). Psilocybe mushrooms do not require heat treatment to develop psychedelic properties but were reported to have an aversive taste which can be suppressed by sweetening [656]. Consumption of mushrooms usually causes nausea and violent vomiting [657], which can be considered as a secondary protective mechanism once the first protective mechanism preventing intake by an aversive taste has been overcome. Also, alliesthesic mechanisms can be deceived by artifice, by decoupling the sensory signal from its biologic significance (*e.g.* artificial non-caloric sweeteners). However, as stated by Cabanac ([320][41]), within a natural environment to which human physiology is adapted, the rule of pleasure as a sign of usefulness is quite valid ([317].

There are also situations where 'unpleasant = useful': pharmaceutical drugs (bitter taste) and pharmacopeia (*i.e.*, ingestion of bitter tasting plants with curative effects on certain diseases) [658,659,660,661,662,663,664,665].

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[39] *i.e., homeostasis – sensu largo*

[40] surrounding sensory environment

[41] see page 86: « […] dans l'environnement naturel de l'humanité la règle du plaisir signe d'utilité est bien valide. »

X.   SUGGESTIONS FOR FUTURE STUDIES

A large body of evidence is available on SSS in humans in the very short term (cross-meal). No studies have investigated the development of SSS in the short- to medium term (over a week to one month), and only one study over the long term (over three months [363]). The series of studies presented in this thesis was carried out in the short term in stable body weight populations. Medium- and long-term studies are necessary to confirm whether additional intake instigated by sensory variety in a single meal will increase body weight or whether the brain takes into account the additional calories consumed and will reduce food intake in subsequent meals. It would be very interesting to gather data about day-to-day preference changes of eaten and non eaten foods and to put these in relation to previous intakes.

Medium term studies on CS have shown at least some caloric compensation in subsequent meals. Little data is available on SSS over a longer period like a week or a month. Of course, the challenge will be to design protocols capable of isolating SSS from AA and above all from CS.

Studies on alliesthesia circumventing orosensory stimulation (and thus SSS) *via* gastric tubing only used prototypic solutions (sweet *versus* saline) and hence suggested that the specificity of AA is limited to these (besides food- *versus* non-food odors). Use of various semi-liquid foods could elucidate the question of whether gastrointestinal chemoreceptors or absorbed flavor molecules circulating in the plasma could be an additional route of feedback about the presence of incoming nutrients to the CNS. To our knowledge, only one study points to such a high specificity [55].

The second study found no differences in intake and hedonic reactivity between obese and normal weight subjects when simple foods were eaten. To our knowledge, only a single study [620] investigated the satiating power of different preparations of the same food and it found marked differences. Therefore, differences between simple and complex foods and meals in the installment of SSS, AA and CS during intake in normal weight subjects, in different obese subjects (stable, dynamic and massive obesity) and in unrestricted and restrained eaters remain to be evaluated.

Further knowledge should be acquired about the impact of flavor combinations, flavor intensity and chemesthetic astringency on palatability and satiety. Of further interest is the influence of individual differences in taste sensitivity and perception on dietary habits and weight control [413]. There have been no medium- or long-term studies on the impact of simple foods on body-weight regulation. The finding concerning similar hedonic control with simple foods suggests that the influence of the nature of food stimuli on meal termination warrants further investigation.

The present results in overweight persons suggest that the study of the impact of processed versus unprocessed foods on hedonics, SSS, satiety, body-weight and plasma profile on the long term could open a promising field of research. The positive effect on overweight may be an option in *ad libitum* weight-loss programs and warrant clinical application. Further research should be undertaken to study the impact on satiety and hedonic dynamics of various food preparations to predict intake.

Further investigation on the effect of food alternation in a meal is needed to understand how different alternations of foods influence intake. It would also be interesting to investigate what sensory properties of foods increase and diminish intake in different cultures.

Finally, physiological studies are needed to understand how peripheral sensory feedback is integrated into the framework of afferent information, how the brain handles sensory information to translate it into metabolic needs, and how the brain adapts the perception of pleasantness to signals from the internal milieu.

XI. REFERENCES

XI.1. Chapter Physiological Control

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XI.5. Chapter Sensory-specific satiety

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XII. ANNEX – ORIGINAL PUBLICATIONS

XII.1. Does modification of olfacto-gustatory stimulation diminish sensory-specific satiety in humans?

XII.2. Sensory-specific satiety with simple foods in humans: no influence of BMI?

XII.3. Variety enhances food intake in humans: role of sensory-specific satiety.

XII.4. Alternation between foods within a meal. Influence on satiation and consumption in humans.