Universitat Autònoma de Barcelona

Cognitive and hedonic responses to meal ingestion

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FERNANDO AZPIROZ VIDAUR Y DEBORAH PARETO ONGHENA

HACEN CONSTAR

Que la tesis doctoral titulada “Cognitive and hedonic responses to meal ingestion” presentada por TEODORA PRIBIĆ para optar al grado de Doctor se ha realizado bajo su dirección, y al considerarla concluida, autorizan su presentación para ser juzgada por el Tribunal correspondiente.

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Barcelona, Septiembre de 2017

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To my parents Radmila & Arsen

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It´s hard to follow your dreams.

It´s tragedy not to.

CONTENTS

INTRODUCTION

The biological response to a meal, considered as a whole, includes physiological changes, primarily the digestive process, and a sensory experience, involving homeostatic sensations (satiety, fullness) with hedonic dimension (gustation, satisfaction, mood). The responses to a meal include a series of events before, during and after ingestion.

1. THE DIGESTIVE RESPONSE TO FOOD INGESTION

The digestive process starts in mouth by chewing, the initial step of meal digestion. Food is, than, transferred through the finely regulated system of hollow viscera and modified first by digestion and then by absorption. Intraluminal nutrients contribute to the regulation of stomach and small bowel activity, however their effect on colonic activity is limited. Undigested rest products serve as nutritious ground for large community of colonic bacteria. Hence, the digestive system has a clear functional division: meal processing takes place primarily in the upper part, stomach and small intestine, while the colonic environment welcomes intestinal microbiota.[1]

The digestive system is controlled by a complex net of feedback mechanisms, by which the gut is able to sense and react to a variety of stimuli. Feedback control of gut function is operated via reflex pathways distributed within the enteric nervous system and the autonomic, both sympathetic and parasympathetic, nervous system. This organization allows the digestive system a high degree of versatility and adaptation to a wide range of situations.[2]

1.1 Effect of food on gastric and small bowel activity

During fasting, patterned activity of gastrointestinal tract removes the residues from the lumen and prepares the gut for the next meal ingestion.

Ingestion of a meal interrupts this cyclic activity and activates a series of reflexes that control the digestive process. Indeed, both motility and sensitivity of the gut are influenced by the presence of intraluminal content[3].

Traditionally the digestive process involves three phases: cephalic, gastric and post-absorptive. These three phases are not strictly sequential, but their effects overlap over time. Preparatory procedures of the gut occur prior to meal ingestion. These events referred to as cephalic phase in normal conditions also include an anticipatory reward sensation.[4] Meal ingestion activates salivation in oral cavity and peristaltic movements in esophagus. The arrival of the food into the stomach induces gastric accommodation, as well as secretion of juices rich in enzymes. Motility, secretion and absorption of the small bowel are influenced by the intraluminal nutrients adjusting the small bowel to the local requirements of the digestive process. Meal ingestion governs the change in the portion of gut proximal to the ileocecal junction, however the distal effect is limited to the gastrocolonic reflex.[3]

The meal exhibits its effect through different gut receptors and neuro-humoral pathways. This effect is rather complex due to the heterogeneous composition on the meals. Undoubtedly, all components of the meal have effect on the gastrointestinal tract, nevertheless, this effect seems to be most prominent for fats as they powerfully modulate motility, sensitivity and barrier function.[5] Different components of food manifest divergent responses with

possible antagonistic effects. Moreover, the same component might produce different effects when passing through different regions of the gut, i.e., stimulation of gastric secretion in the proximal small bowel and inhibition in the distal.[3]

1.2 Food and colonic microbiota

The human microbiota consists of large community of microorganisms predominantly located in the gut. Colon, providing the feeding substrate in form of meal residues, is the area most densely inhabited by this symbiotic organisms. The human organism and microbiota maintain a dynamic, mutually beneficial, relation; while the human organism feeds and hosts the microbiota, microbiota accomplishes a series of important functions for the host. However, these interactions remain poorly understood. Colonic microbiota, outnumbering the human cells more than 10 times, forms an ecosystem, of about 10^{14} microorganisms [6], which globally accounts for a gene catalogue of 3.3 million nonredundant genes, a figure 150 times larger than the human genome.[7] In this community, specific functions can be taken over from one type of microorganisms by another sharing the same genetic program for the metabolic pathways involved. The microbiome develops in the early life and then remains relatively stable. Humans share a common core of more prevalent species, and individuals cluster into three major groups with different ecological types

dominated by specific genera: Bacteroidetes-, Prevotella- and Ruminococcus-enterotypes.[8]

Microbiota is involved in series of important biological functions for the host [9-11], such as, a) development and functionality of innate and adaptive immune responses; b) development of the central nervous system and behaviour; c) modulation of metabolic activity, energy balance and growth; and d) regulation of the digestive system.

Meal residues entering the colon serve as substrates for bacterial metabolism and are thereby transformed. Some substrates undergo fermentative pathways releasing gas. Gas-related symptoms, either bloating or flatulence, are frequent complaints in patients with functional gut disorders. Shortly after ingestion of a meal colonic gas production increases and this effect lasts about 4-6 hours depending on the meal composition.[12] The volume of gas produced during 4 hours after meal increases from around 200 mL with a standard breakfast to about 600 mL with a flatulogenic meal. Furthermore, diet in a relatively short period of time modifies the composition of microbiota and influences gas production.

There is evidence which suggests the existence of bidirectional communication between the gut microbiota and the central nervous system which probably involves multiple and still incompletely understood pathways. The effects of microbiota on the central nervous system may have outcomes on the gut by modulation of motility and barrier function. There is evidence which

indicates that modulation of microbiota induces visceral hypersensitivity and visceral pain perception in rodents.[13.14]

2. SENSITIVITY OF THE DIGESTIVE TRACT

The gut as an extensively innervated organ has the ability to activate perception pathways and induce conscious sensations. The peripheral neurones of this viscerosensory system originate from paravertebral sympathetic ganglia, brainstem and peripheral afferent ganglia. Visceral afferent innervation derived from the posterior root ganglia involves regulation of blood flow, secretory functions and motility. Vagal nerve carries out dual function; via efferent signals regulates motor functions and via afferent fibres sensory.[15, 16] To some extent, the sensory system may be also involved in pleasant gut sensations, that may contribute to gastrointestinal comfort and well-being, but this aspect is yet to be explored.

2.1 Assessment of visceral sensitivity

In normal conditions sensations originated in gut are not recognized. In order to measure the visceral sensitivity different types of provocative tests have been used. Most commonly applied test is the distension of hollow viscera. Distension of gut in healthy subjects is associated with sensations such as fullness and abdominal pressure and demonstrates poor discrimination when it comes to the origin of the artificially induced stimuli. Interestingly, healthy subjects under such experimentally induced conditions exhibit gut originated

symptoms that are typically described by patients with functional gastrointestinal disorders.[17-20]

Distension of gut has faced several methodological challenges primarily dependant on the muscular tone of the gut walls. States of contraction or relaxation significantly impact the perception of the stimuli produced by fixed - pressure distensions or by fixed-volume distensions which created the need for a paradigm shift.[21] Introduction of tensostat or barostat, an air pump that applies fixed computer calculated levels of tension on gut walls offered a solution to these technical problems. Tensostat operates on the principle of Laplace´s law and applies fixed-tension distensions adapting to the states of contraction or relaxation of gut walls. It has been demonstrated that tension receptors rather than the intraluminal pressure are responsible for the gut perception in healthy subjects. Barostat is especially useful in evaluation of visceral perceptions in patients with functional gut disorders primarily because it offers standardization of distending stimuli.[22]

Even though somatic and visceral pain are two different entities some techniques such as electrical nerve stimulation and thermal stimulation can be used to evaluate both kind of responses.[23, 24] Electrical nerve stimulation provokes receptor independent response by signals emitted transmucosally through endoluminal tube.[25] Thermal stimulation by means of hot and cold in combination with mechanical and electrical stimulation may provide useful

information on visceral hypersensitivity.[26]

2.1.1 Measurement of gut responses to experimentally induced stimuli

There are three types of responses to gut stimulation induced in the laboratory that can be measured: conscious perception, evoked potentials at various levels of the afferent pathways, and reflex responses. The methodology for the first two has been developed in the area of somatic pain and later applied to viscerosensory testing.

Different paradigms have been used to assess the threshold level of the applied stimuli and to measure perceptual sensitivity. Conscious perception of the probe stimuli applied into the gut should be measured by means of rating scales instead of in the form of “yes-no” statement. Graduated scales may be either analog, numeric or descriptive. Furthermore, the application of questionnaires in such experiments allows obtention of the additional information regarding the type and location of the sensation.[25]

Sensory evoked potentials are another way of assessment of visceral sensitivity. Cortical evoked potentials represent electrical potentials generated by cortical neurons as a response to the stimuli originated from the gut. Central processing of gut stimuli can be recorded by means of cortical evoked potentials and magnetoencephalography. However, more advanced imaging techniques such as positron emission tomography (PET), single-photon

emission computer tomography (SPECT), and functional magnetic resonance imaging (fMRI) offer more precise information by providing images of the brain regions that change the level of their activation by visceral stimulation.[27, 28]

Reflex motor responses may be elicited by gut stimuli in the experimental conditions. Both pulse and sustained contractions are generated in the gut. Conventional manometry records phasic activity (pulse contraction) by measuring pressure changes within the gut. On the other hand, tonic contractions do not produce detectable changes in intraluminal pressure, and thus, the evaluation of sustained activity demands a different methodological approach. Barostat has the ability to record both gastrointestinal and intestino-intestinal reflexes as well as somatovisceral reflexes. Using the isobaric approach, changes in gut tone can be measured as changes in the volume of air within an intraluminal bag, maintained at a fixed pressure level by an electronic air pump.[29, 30] When the gut relaxes the barostat injects air into the intraluminal bag to prevent a pressure fall, and thus, a volume expansion reflects a relaxation. By contrast, when the gut contracts the barostat withdraws the air, representing a volume reduction the contraction of the gut wall.[19, 20]

Data from different studies demonstrate a rather heterogeneous nature of the perceptual and reflex responses to gut distension indicating that perception and reflex responses are dissociable entities probably mediated by different mechanisms.[19, 20] These findings imply that perception and reflex responses to

gastrointestinal stimuli may be independently altered in some conditions. Undeniably, more refined studies of reflex activity offer proves of involvement of both sensory and motor pathways. Altered reflex activity seems to be a common substrate in functional gastrointestinal disorders.

2.2 Modulation of gut sensation

The sensory signals from the gut can be modulated by different mechanisms on various levels of the gut-brain axis. Final perception depends on the interaction of these modulatory mechanisms.

The effective stimulus determines the perception in such way that the level of conscious sensation is related to the magnitude of the stimulus applied. However, a number of other factors such as the amount of receptors activated and spatial summation phenomena considerably influence visceral perception in humans. The extension of the particular area in intestine to which the stimulation is applied determines the intensity of perception. Furthermore, in the proximal portion of the small bowel the summation effects are similar independently of the location of fields stimulated.[31] These findings imply that the intestine may tolerate circumscribed activation of sensory terminals without perception and on the contrary stimulation of remote areas of the gut may induce symptoms.

Conscious perception is also influenced by synergistic effect of different

types of stimuli in the gut. Even at subthreshold levels, transmucosal electrical nerve stimulation amplifies the perception of concomitant gut distension.[25]

Intraluminal nutrients heighten gastrointestinal perception. This effect is more or less prominent depending on the type of nutrient and its concentration. In normal circumstances lipids have more remarkable effect in comparison to the carbohydrates.[32] The effects of nutrients on perception and alteration of gut motor activity are independent. Intraluminal lipids increase the sensitivity of the gut, however, this is not due to the changes in intestinal compliance. Nevertheless, sensations produced by lipids appear to be particularly related to mechanoreceptors.[33] Cholecistokinin has been shown to increase the mechanoreceptors response [34], and hence, it could be involved in these effects. Furthermore, in the presence of intestinal lipids, loxiglumide, a CCK-A receptor antagonist reduces perception of gastric distension.[35]

2.2.1 Somatovisceral interactions

A phenomenon known as counterirritation or stimulation analgesia represents a complex neural circuitry that modulates somatic pain and can be triggered by somatic stimulation. Spinal transmission is controlled by brain stem via descending inhibitory pathways as well as by higher levels of the somatic projection system.[36, 37] This control system is shared by the perception of somatic pain and visceral sensitivity and, therefore, allows the modulation of visceral perception by application of somatic stimuli. It has been shown that

transcutaneous electrical nerve stimulation applied on the hand reduces the discomfort produced by distension of hollow viscera.[38] Somatic stimuli may have the ability to attenuate the perception of uncomfortable, but not necessarily painful gut sensations. Impairment of these modulatory mechanisms responsible for the down-regulation could lead to visceral hypersensitivity.[37, 38]

2.2.2 Autonomic nervous system

Experimental evidence suggests that increased sympathetic activity enhances perception of gut stimuli, without affecting somatic perception [39] triggering visceral hypersensitivity of patients with functional gut disorders.[40] Interestingly, patients with the irritable bowel syndrome manifest visceral hypersensitivity by displaying increased sympathetic activity [41], but with normal or even increased tolerance to somatic stimuli.[18] Hence, sympathetic dysregulation of visceral sensitivity may have clinical relevance.

2.2.3 Cognitive processes

Cognitive processes regulate the sensitivity to intestinal stimuli in a selective manner. It has been shown that anticipatory knowledge increases perception to visceral stimuli from gut without the change in intestinal reflexes.[42] These findings may indicate the hypervigilant nature of the functional patients. Furthermore, it has been demonstrated that psychological mechanisms such as stress induced anxiety modify the perception of gut stimuli in healthy subjects.[43]

Several psychological treatments have proven to offer long-term maintained results in patients with irritable bowel syndrome. Cognitive behavioural therapy and hypnosis appear to be effective even in settings with fewer sessions or via phone contact.[44, 45]

2.3 Abnormal gut sensitivity as a cause of functional digestive symptoms

In normal conditions, the digestive response to a meal involves a cognitive-emotive component with a pleasant sensation of satiation, digestive well-being, even with positive influence on mood.[46] Patients with functional gastrointestinal disorders (FGID) exhibit abnormal gut function and increased sensitivity due to a mixed sensory-reflex dysfunction, so that physiological, normally unperceived, stimuli induce symptoms.[47, 48] Nutrients modulate the responses of the gut to various stimuli; and some of these modulatory mechanisms are abnormal in patients with FGIDs, which may explain the relationship between nutrients and functional GI symptoms. For instance, it has been consistently shown that FGID patients are much more sensitive to small intestinal lipid exposure than healthy controls.[49-52] These effects seem to be specific for fat, as isocaloric administration of other nutrients does not result in comparable symptomatic responses.[53-58] Capsaicin, an important ingredient in hot and spicy foods, induces sensations of burning and pain via stimulation of TRPV1 receptors on nociceptive C-fibres.[58] It has been shown that, acute ingestion of capsaicin induces more symptoms in patients with functional

dyspepsia than controls.[59] Repeated capsaicin exposure desensitizes C-fibres by temporarily depleting the nerve terminals of substance P so that the fibres become unresponsive to nociceptive stimuli.[60] In large, community-based studies coffee and alcohol do not appear as risk factors for functional dyspepsia.[61, 62]

Dyspeptic patients report the following foods to be associated with their symptoms: fried foods (52% of patients), pastry (33%), pickles (30%), spices (27%) and oranges (26%).[63] Other potentially offending foods include citrus fruit and fruit juices (30–46% of patients), spicy foods (32–54%), certain vegetables, including onions, cabbage and capsicum (24–56%), red meat (25–64%), coffee (32–72%), alcohol (57–80%), milk and dairy products (30–83%), carbohydrate-containing and wheat-containing foods, including pasta, breads, banana, beans and sweets (37–53%), as well as carbonated drinks (35–63%).[64-67] Despite the general acceptance that functional gut symptoms are induced, or exacerbated, by food ingestion, few studies have been performed to evaluate the role of specific foods.

Cognitive factors may contribute to functional digestive symptoms, because previous negative experiences might influence a patient's anticipation of symptoms. The role of anticipation has been shown in healthy subjects.[68] Study in patients with functional dyspepsia showed that information about the

fat content of a test meal increased the symptoms induced by a low-fat yoghurt when the patients were (mis)informed that the yoghurt was high in fat.[69]

Few studies have evaluated dietary habits in patients with FDG and the global outcome is not clear-cut.[64, 66, 70, 71] Furthermore, it is not clear whether the differences observed are the cause of symptoms, or whether the differences just reflect dietary modifications to prevent symptoms. One study reported a reduction in fat intake with a concomitant increase in percentage of carbohydrate intake in patients with functional dyspepsia.[64] By contrast, another study [71] reported higher fat intake and lower carbohydrate intake, in patients with FGD including both dyspepsia and IBS.

As discussed before, sensations originating in the gut depend on three factors: luminal content, gut function and sensitivity. Recent data indicate that microbiota might influence these three factors, and hence, may contribute to functional gut symptoms. Recent data suggests that microbiota in patients with functional gut disorders might exhibit some differences as compared to healthy subjects.[72, 73] Dysbiotic traits of microbiota, easily modified with flatulogenic diet, are present in patients complaining of flatulence. It was further found that a number of gut bacterial taxa correlate with anal gas evacuations and volume of gas evacuated.[12] However, these differences become blurred by the heterogeneity of functional gut disorders. It is conceivably that specific pathophysiological mechanisms in functional gut disorders are related to

variance in the composition of colonic microbiota. Given the heterogeneity of functional gut disorders, thorough physiological testing should be applied to select specific subgroups of patients that share a pathophysiological mechanism, and then analyze the composition of colonic microbiota. In these homogeneous subgroups classified by mechanistic criteria, the likelihood of detecting significant differences in microbiota composition might be higher.

3. CEPHALIC PHASE OF THE RESPONSE TO A MEAL

Before the meal, a series of factors related to the activity of the digestive system and the cephalic phase of digestion determine the pre-meal experience. Some characteristics of the meal, particularly smell and appearance, play a major role. The main factors determining the predisposition of the subject include appetite, cognitive factors and expectations. In the context of motivational aspects of food consumption the concept of “wanting”, as a response (desire of eating) to a particular food has been a focus of a recent research.

Two main sensations dominate the ingestive experience: the homeostatic hunger/satiation drive and the hedonic palatability construct.[74]

3.1 Palatability

Palatability is not a characteristic of the food, but the way it is perceived, specifically the hedonic gustatory component. Palatability depends on the organoleptic characteristics of the meal and the individual receptiveness: sensory response and interpretation. As the counterpart or complement of “meal wanting”, the concept of “meal liking” was developed. The gustatory experience of meal ingestion can be considered the component of meal liking that occurs during the ingestion process. Meal liking can be considered to

extend beyond the gustatory process and include the postprandial sensation of digestive well-being, although the original definition of the concept does not consider these correspondences.[75]

3.1.1 Sensing the organoleptic characteristics of food

Flavour can be defined as a “Complex combination of olfactory, gustatory and trigeminal sensations perceived during tasting. The flavour may be influenced by tactile, thermal, painful and/or kinaesthetic effects.” (Delwiche 2004.). Flavour, one of the most powerful human sensations, is an active multisensorial experience comprised of several exteroceptive and interoceptive senses.

Smell. Humans might be the only beings with two types of smell. Growing body of empirical evidence suggests the presence of orthonasal and retronasal system of odor perception. Through orthonasal system the odor molecules are inhaled via nostrils which results in the interaction with odor receptors. Retronasal system, on the other hand, detects the odors through posterior nares during the processes of chewing and swallowing of the food when we breathe out. After the odor molecules interact with the sensory epithelium the signals are being transported by two separate inputs to the brain where they are being processed in different areas.[76, 77]

Taste. Humans are sensitive to 5 basic tastes: sweet, salty, sour, bitter

and umami. Previously it was believed that each taste had a specific position of the taste buds on the tongue. Newer studies report that the taste buds for all tastes are evenly distributed on the tongue with the highest density in the area of the tip of the tongue.[78, 79] Nevertheless, the number of taste buds varies greatly among people. Around 25 % of persons have higher number of taste buds than the rest of the population. Due to this increase in the density of taste buds they are extremely sensitive to bitter taste and can be categorized as supertasters.[80]

Scientific evidence demonstrates strong interaction between olfactory and gustatory sensations in such way that gustatory cues enhance the perception of olfactory stimuli and vice versa even when presented subliminally.[81]

Touch. Oral cavity is one of the best innervated regions of the human body. This characteristic allows the perception and discrimination of fine stimuli by various receptors and nerve endings.

Texture of food refers to the qualities that can be perceived by the sense of touch; it is essentially how food feels in the mouth when it is eaten or in the hand when it is cut or touched. It is substantial for food preference and appreciation and represents the indication of the freshness of the food.[82]

Discrepant pairing of texture with food has influence not only on the

subjective perception of food but also on satiation and with that on energy consumption. However, studies have shown that this discordant texture - nutrient pairing has most of its effects of energy intake in the initial exposure and that the effect is lost with multiple exposures.[83]

A number of different factors influence texture. Some of them, such as culture, expectation, sensitivity of the mouth or saliva are subject dependant. Others like flavour, temperature, production and ingredients depend on the meal itself. Texture can be perceived by visual cues even before the process of eating starts.[84]

Temperature. Temperature modulation on different parts of the tongue can evoke the sensations of sweet, salty, sour or bitter without actually tasting them. This concept is known as a thermal taster. A simple experiment that can characterize one as a thermal taster consists of placing the ice cube on the lateral part of the tongue. In case of perception of any taste one can be considered a thermal taster. Interestingly, many supertasters are also thermal tasters.[85]

Sound. Since the perception of taste is a multi-sensory experience the sound as "the forgotten flavor sense" should be mentioned here as it has relevant influence on taste modulation. How important is the crispness of french fries for the experience of eating them? It is almost impossible to imagine french fries that do not produce the exciting noise when being eaten. Participants in a

study investigating the influence of crispness of french fries rated them as fresher when the sound they produced when eaten was louder and of higher frequency.[86] The sounds like crispy, crunchy or the sound of carbonation of a fizzy drink are the kind of sounds that make difference in our perception of food.[87]

Vision. Perhaps the most investigated visual aspect of the food is color. Studies have shown that the addition of yellow color to the sweet solution significantly reduced the participant's sensitivity to sweetness while adding green color increased it.[88] Red color, on the other hand, has no significant effect on sweetness threshold.[89] It is demonstrated that visual sense is superior and thus dominates other senses in such way that when fruit juices are colored differently the participants of the study identified wrongly the taste and their answers were more driven by colors than by the taste itself.[90] Color of a meal plays an important part in the expectations related to the dining experience, because we first eat with our eyes.

3.1.2 Taste preferences

All human senses are established at the very early stage. As early as the embryonic phase and at the beginning of the foetal phase. Nevertheless, their development rate differs, primarily depending on the maturation of the central nervous system. The appearance of the first taste buds at the end of embryonic phase (8th week of gestation) leads to the formation of the sense of taste. In

utero events and swallowing of the amniotic fluid are the first taste “lessons” and represent the initiation of the stimulation of the taste buds. Prenatal circumstances modulate the taste preferences meaning the beginning of the cultural exposure to taste stimuli long before tasting the actual food. Amniotic fluid is a unique blend of flavours and aromas reflecting maternal diet that enables diverse prenatal taste experiences. Furthermore, the formation of the taste preferences continues through the breastfeeding. Breast milk, similarly, to the amniotic fluid has a dynamic composition which continues to shape the acceptance of foods later on in life.[91, 92]

In the first weeks of life the taste sense is already the most important and most developed of all senses. The newborn shows a preference for sweet taste that is independent of the learning experience and aversion to greater extent to sour and to lesser extent to salty and bitter taste. Salt and bitter taste preferences are developed later at the age of small and school-child and are associated with a learning experience.[93]

The innate preference for sweetness can be explained by the fact that the sweet taste indicates a source of energy (carbohydrates). A bitter taste, on the other hand, represents a warning sign of toxic and sour of spoiled foods, while salty may be related to the presence of minerals in the food. The fifth basic taste umami might be associated with a source of proteins.[94]

Studies dealing with the preference of taste have a methodological

problem; mostly examining basic tastes isolated in the dimension of sweet, acid, salty and bitter taste, while not taking into an account that the sensory qualities of foods are multidimensional and in interaction with different flavouring agents, taste mediators and other factors like texture, colour, temperature, or smell. Additionally, the highest level of scientific evidence is provided by a randomized, double-blind, placebo controlled clinical trials. The application of placebo in food related studies is in some cases troublesome due to the difficulty to find the appropriate placebo. In dietary intervention studies, unlike in pharmacological clinical trials, it can often be challenging to elaborate the adequate sham test meal.[95]

3.1.3 Taste education

The formation of taste for food and the establishment of nutritional habits dependents on contact and experience with certain foods that will later on determine taste preferences. Training in the family as well as at the preschool and school on a daily basis develops habits of highly specialized feeding behaviours that will later in adulthood be regarded as normal behaviours in the diet. This actually represents sociocultural process of learning which includes creation of the taste preferences towards specific foods.

The comparison of the taste preferences between parents and their children, with a few exceptions, demonstrates similarities in the rejection of certain foods. This can partially be explained by the fact that the parents who do

not like certain food will also not buy it in which case the mere exposure effect is not achieved. The exception to this rule refers to the candies. There is a great overlap in what both parents and children prefer and less in what they do not. It has been shown that children have similar food preferences as their parents and, especially, their siblings.[96]

Children born in different cultures learn and accept a certain taste that is preferred in that culture by means of liking by tasting. The acceptance of some of the characteristic flavours, which are normally spontaneously rejected, e.g. coffee, is formed only under the social influence and by repeated exposures to these tastes. The need for social acceptance plays an important part in this process. All the models of behaviour in relation to food intake are subject to a process of learning that depends on the experience.[97]

3.2 The hunger/satiation axis

The normal homeostatic response to eating is a shift in the hunger/satiation axis as a mechanism that determines meal consumption. The pre-meal level of hunger influences the cephalic phase of digestion, the pre-meal experience and both the hedonic (gustatory) and homeostatic (satiation rate) components of the ingestive experience. Satiation has been measured under two paradigms: the level of satiation on a scale induced by a fixed meal or the amount “ad libitum” consumption.[98]

Appetite, hunger and satiation describe interoceptive sensations that govern the eating behaviour and should be able to explain what it is that triggers eating, maintains and ends it and what are the conditions that condition the choice of food/meal.

Hunger and appetite refer to such signals that as starting signals lead to the initiation of the food intake, and to satiation described as stop signal, which contributes to the completion of the food intake. However, in humans such experiences and signals do not fully control the behaviour of eating, because the man is able to eat even in the absence of hunger or appetite.[99, 100] Likewise, food intake can be completed even in the absence of satiation, as evidenced by hunger strikes, fasts and starvation in anorexic patients.[101, 102, 103]

Although, terms hunger and appetite are often used with the same meaning, these two experiences may differ significantly. Appetite is motivation for eating which is often directed at specific foods. Hunger is, on the other hand, the requirement to eat something, where that requirement is generally not directed towards a particular food.[104]

There are no concepts for satiation that highlight the quality of the satiation. Satiation is defined as "the physiological process of completion of the meal, which is caused by ingesting the food" and therefore prompts the termination of food intake. The result of the satiation process - satiety influences the period between two meals in which no food ingestion takes place. Signals

and processes that lead to the interruption of a meal or hinder the start of a new meal are often referred to as intra-meal satiety and inter-meal satiety.[105]

4. THE POSTPRANDIAL EXPERIENCE

The sensory response to a meal involves homeostatic sensations that have a hedonic dimension. The sensory experience is linked to the physiological response, and a distortion of the digestive process may impair postprandial satisfaction or even induce aversive sensations, i.e. digestive symptoms. Postprandial symptoms can be produced in the laboratory by experimental distortion of the digestive function in healthy subjects or may develop spontaneously in healthy subjects with functional gut disorders.[106]

The postprandial experience in normal conditions includes homeostatic sensations. After the meal the subjects experience a shift in the hunger/satiety axis towards a degree of satiety.[74] As an exception, “appetizers” have allegedly the function to increase hunger sensation and “open the appetite” in preparation to a forthcoming meal, but the evidence behind this effect is not clear. In English language a distinction is made between satiation, a homeostatic mechanism to terminate meal ingestion, and satiety, a postprandial mechanism to determine the inter-meal interval. Other languages lack such precision, with one term for both conditions.[107]

Postprandial satiety is frequently associated to sensation of abdominal fullness. Subjects could clearly distinguish between both sensations. It has been shown that the degree of fullness is lower than that of satiety (i.e., in general fullness sensation parallels satiety at a lower level.[46]

Homeostatic sensations have a hedonic dimension and are associated to changes in the sensation of digestive well-being and mood. An agreeable meal is followed by an increase in the sensation of digestive well-being (satisfaction) and mood.[74] The postprandial effect on mood is a constant feature in different experiments and has probably influenced business culture of closing deals over succulent meals. With agreeable meals the hedonic intensity parallels the homeostatic sensation up to a certain extent but this relation remains unclear, because even palatable meals may induce a negative hedonic sensation.

However, both homeostatic and hedonic sensations are mediated by different mechanisms and are dissociable, so that postprandial satiety/fullness may have a satisfactory or an aversive dimension depending on the conditions, including the type of meal, the digestive response and other conditioning factors such as the palatability of the meal.[108]

Homeostatic and hedonic sensations evolve along the postprandial period. Usually sensations are more intense immediately after the meal and gradually decay depending on the amount and type of meal ingested until satiety extinguishes and the sensation of hunger reappears as a homeostatic signal for the next food load. However, in some cases satiety increases during the early postprandial period, as if the satiation signal to stop ingestion were delayed, and this may lead to excessive fullness sensation a while after the meal.[46]

5. MECHANISMS AND MEDIATORS OF SENSATION

5.1 Relation between digestive and sensory responses to a meal

A proper digestive response to a meal seems key to a satisfactory postprandial experience, but the specific contribution of the different steps of the digestive process to sensations is not clear. Antral contractions have been associated with hunger pangs during fasting.[109]

Some data indicate that, disruption of the digestive response hampers the sensory experience. For instance, experimental increase of the tension of the gastric wall, by means of an intragastric bag connected to a tensostat, increases postprandial satiety and fullness and impairs digestive well-being. Experimental infusion of lipids directly in the duodenum via an intraluminal catheter during the postprandial period induces a similar effect of homeostatic sensations, increasing satiety and fullness, but does not affect the hedonic response.[110]

In patients with functional dyspepsia the stomach fails to relax in the process of meal accommodation with a stretch of the gastric wall by food ingestion and activation of tension receptors, and this is one of the mechanisms of their symptoms: early satiation, fullness and discomfort.[111, 112, 113]

By contrast, the role of gastric secretion in this context seems limited, because, potent antisecretory agents extensively used are not suspected to affect the postprandial experience, although this point has not been experimentally proven.

5.2 Circulating metabolites

Blood levels of many compounds change in relation to meal ingestion. These compounds may derive from the meal, such as glucose and lipids, or from the responses to the organism to the meal, such as hormones. Metabolites derived from the microbiota metabolism of meals residues may play an important, yet unknown, role. Interestingly studies indicate that some of these metabolites and hormones are related to specific homeostatic and hedonic sensations.[114, 115]

Meal ingestion prompts the hormonal response that interacts with the decision making circuitry and influences the quantity of the food intake. Leptin is a circulating hormone secreted by adipocytes that indicates the size of peripheral energy stores. It decreases food intake as energy stores increase by reduction of the hedonic response to palatable food among other mechanisms.[116, 117, 118] Ghrelin is a peptide hormone secreted which influences food initiation and termination. The concentration of ghrelin increases in the state of hunger and decreases with satiation.[119, 120, 121] However, its levels are influenced not only by the meal's nutritional content but also by the cognitive beliefs about how much was consumed. Nevertheless, it does not seem to increase the hedonic responses to food.[122]

The level of gastric relaxation and gastric emptying, as well as the distribution of other hormones such as cholecystokinin, peptide YY, insulin and

the stimulation of certain chemoreceptors in the stomach and upper small intestine likewise play an important part in hunger/satiety states.[123, 124]

By post resorptive processes are meant those satiation mechanisms that are caused by the reception of nutrients and several of their metabolites. These include the effects of glucose and various amino acids (e.g., tryptophan and tyrosine), that are protagonists in the central management of the postprandial experience after overcoming the obstacles of the blood-brain barrier.[125, 126]

5.3 Brain activity

Meal ingestion has been shown to induce changes in brain activity. The central nervous system plays a key role in homeostasis and control of food intake. Recent studies have detected changes in brain activity, specifically related to homeostatic and hedonic sensations.[127, 128, 129]

In humans changes in brain activity can be detected by different methods. Historically, neuroimaging was used to describe the structure of the brain. However, in recent years (since 1990s) the imaging techniques are emerging as a powerful tool for objectivization of not only neural structure, but also function providing substantial biomarkers for different conditions. Techniques like functional magnetic resonance imaging (fMRI), positron emission tomography (PET), multichannel electroencephalography (EEG), magnetoencephalography (MEG), near infrared spectroscopic imaging (NIRSI) and Single-photon emission computed tomography (SPECT) are providing

information by measuring localized neural activity or by recording of electrical currents or magnetic fields.[130, 131] A large amount of data obtained from neuroimaging studies approached through machine learning models offer relevant predictions on an individual scan basis and maximize the prediction accuracies based on big data.[132, 133]

fMRI is a technique used for measuring and mapping brain activity and it operates on the principle of the blood-oxygen-level dependent (BOLD) signal; an indirect measure of neural activity. Neurons use glucose as a primary source of energy for their function. When a particular part of the brain is activated (neuronal activation) the blood flow in that area is increased in order to bring more glucose but also more oxygen (phenomenon called hemodynamic BOLD response). This implies a replacement of blood depleted in oxygen with blood that is rich in oxygen. Oxygen in blood is transported by hemoglobin an iron-containing metalloprotein transporter situated within the red blood cells. Hemoglobin differs in the way it responds to magnetic waves. Deoxygenated and oxygenated hemoglobin have distinctive magnetic susceptibility and therefore demonstrate different magnetic properties which lead to generation of MR signal.[134, 135, 136]

fMRI, a widely used experimental tool, involves several different experimental designs. The first one to be used was block design where “off” and “on” periods take turns. During “on” periods subject is performing a particular

task (experimental condition) and during “off” periods baseline task (control condition).[137, 138, 139, 140] Another paradigm is resting-state fMRI; a method measuring brain activity when a subject is not performing any particular task and when the brain is at rest.[141]

Resting state networks (RSNs) localize the gray matter regions of the brain [142, 143] and cover a wide range of functional areas such as sensory and motor cortices, language and memory systems. Major brain networks identified using fMRI while the brain is at rest [144] include: a) visual areas - correspond to visual behaviour; b) default mode network (DMN) - the most studied brain network. It was proposed by the Gusnard and Raichle (2001) [145] as the baseline network and represents an interconnected and anatomically defined brain system that is active when brain is awake and at rest. It was shown that it is most commonly deactivated in task-based experiments; c) cerebellum - corresponds to action-execution and perception-pain paradigms; d) sensorimotor - responsible for action-execution and perception-somesthesis domains; e) auditory - accountable for auditory processing and language comprehension; f) executive control - involved in regions modulating cognitive control; g) frontoparietal - responsible for language/cognition as well as pain perception.

5.3.1 Brain regions involved in the control of food intake

Hypothalamus has significant role in maintenance of integral homeostasis through management of various vital functions among which are appetite and food intake regulation [146, 147] as well as survival responses.[148, 149] Series of studies conducted mostly on animals have concluded that some kind of the centre for satiation can be seen in the medial hypothalamus, more specifically in the paraventricular nucleus (PVN). If this centre is stimulated, either by electrical stimuli, or by neurotransmitter serotonin (5-Hydroxytryptamine, 5-HT), the amount of food intake is reduced by shortening the time of eating, and the speed of the food intake is also lower (intra-meal satiety).[150, 151]

The reverse effect is observed when it is interfered with PVN by the neurotransmitter noradrenaline (norepinephrine) via its effects on alpha-2 receptors: the level of food intake increases, extending the duration of the meal. These considerations are also supported by the fact that an increase in the flow of norepinephrine is observed in food deprivation. The increase of food intake is noted in case of targeted destruction of this brain region.[150]

The lateral hypothalamus, especially perifornical region represents, on the other hand, the centre for hunger. If this centre for hunger is interfered with the neurotransmitter dopamine, food intake is reduced, especially because of the delaying of the start of new food intake, while the duration of the meal does

not change. Therefore, it is considered that perifornical region participates in inter-meal satiety.[150] If this brain region is destroyed, the decrease in food intake is observed, the so-called hypothalamic anorexia.[152]

Furthermore, it can be determined that the food intake has a direct impact on central management of eating behaviour. A meal rich in carbohydrates leads to a significant secretion of insulin which increases the proportion of the amino acid tryptophan in the blood plasma in comparison with neutral amino acids. As a result, the influx of tryptophan in the brain is increased. Since tryptophan is precursor of the neurotransmitter serotonin, the serotonin synthesis is increased, which results in satiation with carbohydrates. According to this model, intake of carbohydrates would lead as a consequence to the specific carbohydrate satiation. Protein intake, on the other hand, reduces the supply of tryptophan to the brain, and leads to lesser synthesis of serotonin.[125, 153]

There are indications that the intake of carbohydrates and proteins increases the availability of amino acid tyrosine in the brain, wherein the effect of a protein-rich meal is greater than the effect of high-carbohydrate meal. Since tyrosine is metabolic precursor of the neurotransmitter dopamine and noradrenaline, analogue processes of control and feedback could as well take place.[154]

The latest discoveries of orexin and melanin hormone expressing neurons in the lateral hypothalamus offer further understanding of cognitive and

hedonic dimension on eating. Acting as metabolic sensors these anatomical projections act as a mediator between interoceptive stimuli and external environment in establishing homeostasis.[155, 156, 157, 158]

Brain regions involved in hedonic dimension of eating (insula, amygdala and orbitofrontal cortex) are activated during the fasting periods.[159] Similarly, the relay area between subcortical areas and cerebral cortex (thalamus) as well as the area corresponding to motivational aspects of food (caudate) respond to hypoglycemia by increase in activity.[160-162] These brain regions decreased the activity after the infusion of different macronutrients (fat, glucose and protein drinks) demonstrating slightly stronger response of amygdala to protein ingestion.[163]

Intragastric infusion of fatty acids induced the changes in the activity of lipid-activated brain matrix including brain stem, pons, hypothalamus as well as cerebellum and cortical motor areas.[164] The excessive hedonic drive is attributed to the ingestion of energy dense foods which through the brain reward circuitry generate pleasant emotional responses. Indeed, the altered function of orbitofrontal cortex, insula and operculum observed in obesity may imply higher sensitivity to food stimuli and determine the risk for increased food intake.[165] In spite of the inconsistency of the neuroimaging studies conducted in obese patients, most of them suggest that obese individuals in comparison to lean demonstrate higher anticipatory responses and increased activity in brain regions related to reward as well as possible impaired function of inhibitory

regions.[166] This discrepancy indicates that the mechanisms of food reward are rather heterogenous and require a broader approach that would take into an account other factors from both hedonic and cognitive sphere of perception as well as the biological aspects.

6. REGULATION OF FOOD INTAKE

Regulation of food intake is a complex psychological process. Biologically, meal consumption is regulated by homeostatic mechanisms operated by the hunger/satiation sensation. Satiation is specific of taste and so food variety influences meal consumption.[167] A specific aspect is the dessert mentality, getting space for a sweet dessert after salty meal. The concept of alliesthesia in regard to the homeostatic control of food ingestion has been proposed: the choice of food is driven by the needs of the individual. This is clear for water and liquid consumption, but may apply also to more specific foods.[168]

However, other mechanisms, particularly the hedonic drive, play an important role. In fact, hedonic eating frequently over rules the homeostatic control of food ingestion, and this seems to be a key mechanism in eating disorders and obesity.[169, 170]

In most individuals cognitive factors strongly influence the decision of meal choice and the amount consumed. However, in general, the ultimate factor that determines meal consumption is food availability (what is served on the plate or is the menu). Hence, acquisition of healthy habits and control of serving sizes are key factors in controlling food consumption both at the individual level and collectively. Indeed, excessive serving size has been proposed as an important factor in the epidemic overweight in some populations.[171, 172]

The ingestion rate is also determined by similar factors: homeostatic (pre-meal level of hunger), hedonic (meal palatability), cognitive (the idea of the amount to be consumed), habits and extrinsic factors (duration of lunch break, dinning company).

6.1 Mechanisms of satiation

There are a variety of mechanisms that contribute to the process of satiation that is induced by physical and chemical qualities of ingested food. Blundell proposed the model of satiety cascade which includes the relationship between satiety and satiation as well as different influencing mechanisms and mediating factors related to these processes. This model connects different mechanisms of satiation with the various stages of the process of satiety.[173]

Specific properties of the food such as appearance, taste and smell have notable effect on sensory processes. Positive labelling of different sensory qualities can lead to increased food intake based on the fact that the stop signals for food intake are reduced or delayed (the influence of food on the satiation). These processes are in conjunction with sensory specific satiety described as the phenomenon of ending the ingestion of food with certain sensory characteristics. If, nonetheless, other foods with different sensory qualities are offered the process of eating continues. Consequent application of this principle is a menu comprised of several dishes (appetizer, main course, dessert). It would be almost impossible to defeat the same amount of only one

meal because of sensory specific satiety. However, the change in the type of the taste creates the possibility and prerequisite that the offered amounts of food can be eaten as well as the different types of foods.[174, 175]

Cognitive processes describe the effects which are based on the opinions or representations of opposite foods. It was shown that for people who can restrain their food intake presumed (not actual) calorie content of the food to be eaten has a significant impact on the amount of food eaten.[176, 177]

Historically introduced models for the regulation of food intake known as glucostatic hypothesis, thermostatic hypothesis and lipostatic hypothesis can be classified in relation with post resorptive mechanisms.

Glucostatic hypothesis assumes that the diminished availability of glucose leads to starvation (interoception reciprocal of satiety), thereby stimulating food intake. The hypoglycemia is in normal physiological conditions the signal for hunger. This signal is perceived by glucose sensors which are located in the hypothalamus, a base of the brain and the liver. Meal ingestion causes the rise of glycemia back to normal levels and the food intake ends (post resorptive satiation).[178, 179]

Thermostatic hypothesis is based on the observation that a warm-blooded organisms consume more food when the temperature of the environment is lower. It is assumed that the heat regulation, measured by the interior temperature sensors, has impact on the food intake. Reduction of heat production would thus lead to the creation of hunger.[180]

Lipostatic hypothesis proposes the existence of lipid sensors, which can register metabolites of lipid metabolism. The reduction of fat depots in the absence of food or accumulation of fat in elevated food intake could be considered as signals of hunger and satiation respectively. This theory has undergone further fame upon the detection of obesity genes.[181]

Different processes and mechanisms of satiation cascade overlap in their central effects and thus lead to a combined process of satiation, which integrates different components due to the learning process.

6.2 Cognitive mechanisms

A significant component in the regulation of eating behaviour lays in the learning process. Food and energy intake commences anticipatory in greater level, if possible due to situational (and cognitive) factors and not when the intense sensation of hunger appears. Also, the intake of food often ends only after the appearance of an intense feeling of satiety. Appetite and satiety may be understood as a reaction in accordance with the scheme learned from classical conditioning.[182-184]

Model of satiation as a conditioned reaction is based on the fact that certain signals such as the sensory impressions or filling of the stomach are as conditioned stimuli associated with the unconditioned stimuli in form of nutritional effects of food. Nutritional consequences [185] as unconditioned stimuli

enhance the conditioned stimuli. The components of the food that was eaten reach through bloodstream the satiation centres in the brain and act as the unconditioned stimuli causing post resorptive satiation, wherein the strength of this unconditioned stimuli is related to energy level of the food that was eaten. On the other hand, the change in the level of absorption of certain nutrients in the gastrointestinal tract, which occurs shortly after food intake, can serve as an unconditioned stimulus.[184] A particular effect of carbohydrates, fast-oxidizing substances, such as alcohol, fats, and essential amino acids as unconditioned stimuli has been shown.

Almost all body signals or stimuli from the environment as well as social, cognitive or emotional circumstances can serve as conditioned stimuli. In particular, some of the properties of food such as taste, smell, appearance and texture should be considered apart and it can be presumed that the rapid satiation as a result of food intake is partly conditioned by taste stimuli and partly by signals of intragastric chemoreceptors.[186]

Such conditioned stimuli generally do not act isolated, but rather in a complex interaction with other stimuli and can be denoted as forms of appetite. Identical learning principles can be applied to a specific appetite, hence the constant preference for certain foods depends on the condition of the organism. Thus, appetite and satiation can be understood as a conditioned preferences or aversions, which depend on the nutritional status of the organism.[185, 187]

6.3 Set-point theory

The term set-point represents referential signal in the control circuit and a value to be attained with which the state of the system is compared. When deviations from these values occur appropriate procedures are activated in order to regulate and re-stabilize the entire system. In the set-point theory the condition of the system is evaluated via a size that can be measured (feed-back), and this value can be compared with a value to be attained.

Application of the set-point theory to the body weight indicates that the stability of the body weight in adults is predetermined and controlled by feed-back mechanisms. These mechanisms are by no means simple and do not rely on only one variable in order to attain the referential value. Many different biological and psychological factors contribute to the balance of the system. Characteristics of the meal such as its composition and organoleptic properties, hormonal parameters and factors involved in central control of food intake such as particular brain regions and neurotransmitters all act in conjunction and contribute to the maintenance of stability.[188, 189]

Theoretically such model representations are closely associated with the concept of homeostasis, which was introduced in 1932. by Cannon. Homeostasis is the state of the body (steady state), which is actively maintained by an appropriate physiological mechanisms and/or the appropriate behaviour. Compensating procedures achieve a high level of stability for the value that is regulated. However, stability does not mean that the regulated parameter

occupies only one specific value. In physiological conditions, depending on the particular circumstances or any malfunction, set-point values vary within certain areas of tolerance. Blood pressure, body temperature and blood electrolyte levels are only some of the examples of such regulated values.[190, 191]

However, set-point theory might not be fully applicable for the explanation of the astounding constant of body weight. According to this theory the daily intake of 100 kcal more than the number of calories necessary for the functioning of the body would cause a gain of 104 kg in 20 years. On the other hand, if a person eats less than what is needed, it could be calculated how long it would take to achieve a weight of 0 kg.

Although set-point theory looks attractive because it can somewhat explain the apparent stability of body weight in case of healthy eating habits, according to current scientific attitudes this kind of regulation is lost in case of unhealthy Western diets suggesting the implication of external factors which lead to failure of biological mechanisms in the regulation of body weight.[192]

6.4 The energy requirements

Energy represents a fuel that is among other functions required for metabolic and psychological processes, muscle activity, growth and synthesis of new tissues.[193, 194] The energy derived from food can be broken down into three components: 1. The energy which is necessary to maintain the primary

metabolic process in the standby mode - basal metabolic rate BMR, or resting metabolic rate RMR. It comprises of set of vital functions such as cell metabolism, maintenance of body temperature, brain function, heart activity, motility of gastrointestinal tract and accounts for up to 70% of daily energy needs, depending on age, gender, body size and composition [195]; 2. The energy that is required for metabolism of ingested food. People who consume mixed food can increase their energy expenditure by 10%; 3. The energy that is necessary for the activity and movement.[196] Additionally consumed energy, mainly in the form of fat, is saved. The Estimated Energy Requirements (EER) represent daily need for energy. Calculation of EER is based on the parameters like age, gender, weight, height and the level of physical activity. It represents the amount of energy expressed in kilocalories (kcal) needed to be consumed on a daily basis in conditions of equal level of physical activity in order to maintain the constant body weight.[197]

Studies dealing with the experimental formation of the excess of body weight in humans who volunteered to overeat in order to gain 20-25% of their body weight reported that some subjects were able to consume huge amounts of food, up to 10000 kcal a day, and not to gain weight with the expected speed. 4-6 months of overeating were necessary to achieve the desired weight. Achievement of stabile body weight required 27 additional kcal per kilogram of body weight and the achievement of weight gain 37 additional kcal. After returning to the "normal" diet, the weight of the subjects quickly returned to the

starting weight. Only 4 out of 15 subjects quickly gained weight as consequence of the intake of greater amounts of food. In the family history of 2 of these 4 subjects obesity or diabetes were recorded.[198-200]

6.5 Genetics and food consumption

Taste has repercussions on food choice and by that on food intake as well. Starting from the premise that the taste is not completely the same for everyone the importance of the genetic research in this field becomes prominent as the physiological features such as the density of taste buds and sensitivity of taste receptors among others are genetically dependant characteristics. Studies demonstrate that sensitivity for bitter taste may be associated to the body mass index, quantity of fat tissue in the body as well as risk factors for cardiovascular diseases. Sensitivity for sweetness, on the other hand, negatively correlated with body mass index.[201-204]

The brisk increase in obesity and associated conditions has urged the modern genetics research to find out why we eat what we eat. Some rare genetic disorders such as hyperphagia and some not so rare such as Prader Willi Syndrome have been described. In spite of the rareness of hyperphagia many less prominent variants exhibit their effects and contribute to the development of the obesity and associated comorbidities.[205]

The research conducted on twins, in which they consumed more calories

than their energy requirements concluded that twins behave similarly (gain weight) when given more calories. Large twin studies suggest that both genetic and environmental factors are implicated in their dietary behaviour.[206]

6.6 Energy storage

Apart from the quickly available glycogen storage [207], body is saving the excess of energy primarily in the form of triglycerides in adipocytes of adipose tissue. In longer energy deficits this energy becomes available by decomposition of body fat.[208]

The amount of fat tissue is determined by 2 factors: the size and weight of the individual fat cells and their number. Depending on these two factors, the overweight can be classified in a form of hypertrophic overweight (higher volume of the individual fat cells), hyperplastic form (greater number of fat cells), as well as a combined form.[209]

Studies in animals demonstrated that once enlarged fat cells cannot be reduced and for the long time it was believed that the situation in humans in the same. By reducing food intake the volume of adipocytes decreases, i.e. the weight of the individual fat cells, but their number remains the same.[210] There are indications that, depending on various factors, the organism regulates the average size of fat cells and maintains the stable population of adipocytes in adults. The number of adipocytes appears to be the main determinant for fat

mass in adults.[211] Recent studies show that after the reduction of body weight the number of fat cells decreases as well, however, not proportionally to the weight loss. This slow turnover of white adipose tissue (10% every year) may later lead to the accumulation of fat in the cells and failure of the dieting strategies.[212] After long-term changes in body fat (which last from 6 to 10 years) the number, but not the weight of fat cells is changed, while in the short-term changes (1-2 years) the weight changes, but not the number of fat cells. Sjöström assumed that the degradation of deposits initially reduces the weight of the individual fat cells, and then reduced weight of fat cells when it is significant and sustained over longer time, causes the breakdown of fat cells. It is unclear whether this degradation corresponds to the actual disappearance of fat cells or whether the fat cells are converted into postadipocyts.[213]

6.7 Regulation of macronutrients intake

The discussion about set-point theory revolves around the question whether and how are regulated the intake and energy expenditure in the body. The nutritional energy is available to the body in the form of macronutrients - carbohydrates, proteins, fats and alcohols. The question of whether the organism itself regulates energy intake and expenditure is intensively examined in recent years.

In spite of the worldwide epidemic of obesity there is still no general agreement on what is the optimal dietary pattern to prevent it.[214] There are a variety of epidemiological findings which suggest that higher fat intake corresponds to higher body weight and higher body mass index. These data are consistent with the fact that in recent decades in western industrial societies a percentage of fat in the diet increased and in parallel the proportion of overweight people. The relationship between fat and obesity is to some extent emphasized, while there is epidemiological evidence suggesting that the number of people with excessive body weight is reduced by increasing the intake of carbohydrates in diet. Such observations divert attention from fat to carbohydrates. Low-carbohydrate diets are more effective in a short-term weight loss, however it has not been demonstrated that this effect is maintained over longer periods of time.[215] It seems that the optimal amount of carbohydrates in diet that is inversely related to obesity is between 47% and 64% calories derived from carbohydrates.[214]

6.7.1 Metabolic destiny of macronutrients

Another impetus for studying the relationship of fat towards carbohydrates in the diet comes from a series of calorimetric studies. Indirect calorimetry as a gold standard in measuring the energy expenditure can determine not only the energy consumption, but can also examine the extent of oxidation of carbohydrates or fat, which means giving answer to which macronutrients are used for energy.[216]

Many studies observed that after administration of carbohydrates the oxidation of carbohydrates increases.[217, 218] This is partly inconsistent with the long-term conviction that the excess carbohydrate is converted into fat and stored in such a way. The conversion of carbohydrates into fat is a normal metabolic pathway in some animals, for example in rats. In humans, this de novo lipogenesis is possible, but under normal conditions it plays no role. Up to a limit of 500 g of carbohydrates they are, in humans, first oxidized and only the intake over 500 g leads to the de novo lipogenesis. In normal circumstances it is not easy to consume 500 g of carbohydrates, which corresponds to 2,050 kcal.[219]

While higher carbohydrate intake leads to enhanced carbohydrate oxidation, higher fat intake does not lead to increased fat oxidation. On the contrary, after the meal, the fat oxidation reduces and the first to burn are other macronutrients which results in the accumulation of fat in fatty tissue.[220]

When it comes to macronutrients there is a clear hierarchy in relation to their usage and storage. Alcohol due to its toxic effects on the body has no reservoirs for storage and is always the first to oxidate. Followed by carbohydrates for which there are little reserves of glycogen, and proteins, which are stored in the form of endogenous proteins. At the end of the hierarchy is the fat which is used to cover the remaining energy needs and whose excess is stored in fatty tissue.[221, 222]

6.7.2 Satiation by fats vs satiation by carbohydrates

A significant element in Flatts model about the importance of fats and carbohydrates is the assumption that carbohydrates control short-term food intake. If this assumption is correct, carbohydrates should have a much greater satiating effect than fat.[223] A series of studies indirectly confirmed this assumption.

Higher fat content in food is not equated with eating less. Fat exercises less satiating effect in comparison to meals rich in carbohydrates and proteins, therefore more nutritious energy is consumed at the high fat content intake. This phenomenon called passive overconsumption with fats is one of the key mechanisms leading to the obesity.[224, 225]

It is obvious that energy density (kcal per gram of food) plays an important role in different satiation effect. Normally, the energy density of food increases with higher fat content. Passive overconsumption with fat could not be determined when studying variable proportions of carbohydrates and fat, whereby the energy density was artificially kept constant.

6.8 The effect of preload

The preload paradigm is one of the most commonly used experimental tools for the study of short-term regulation of food intake. The effect of preload

should preferably be studied in a design which ensures the control condition, e.g. in a form of placebo and within subject repeated measures. Preload represents a defined portion of a meal with precisely characterized macronutrient composition. After a certain amount of time posterior to the ingestion of the preload the test meal is administrated either through accurately monitored test meal or ad libitum in which case the amount of the meal eaten is registered. The impact preload had on the consumption of the subsequent meal is then examined. Subjective determinants of digestive sensations are measured before and after the probe meal at predetermined time intervals.[226]

Data from several studies indicate that expectations about satiating and filling capacities of food influence decisions related to portion size, food intake and food choice [227, 228, 229], but also the perception of postprandial sensations. These expectations can be changed even by slight modifications of the sensory characteristics of a food and have further repercussions on the sensation of hunger and later energy intake [230, 231, 232]. Furthermore, it has been recently demonstrated that the presumed caloric content of the preload had effects on the decision of the energy value of the subsequent meal. Interestingly, one study demonstrated that expectations about food can override not only subjective gastrointestinal perceptions, but also hormonal responses implicated in food intake regulation. Consumption of what participants believed was the “indulgent” milkshake caused a steeper decrease in the levels of ghrelin in plasma as compared to “sensible” milkshake[121].

It was observed that the variation of the nutritional compositions and the taste of different preloads influences the following meal ingestion. After the high-fat preload subjects consumed more calories in comparison to the preloads rich in carbohydrates and proteins. Based on the taste evaluation in this experiment the mechanism of sensory specific satiety seemed superior to the sensory properties of the meals, while the composition of nutrients was less decisive.[233]

The concept of restrained eating was firstly introduced in the literature when it was observed that not only obese people differ in the level of set-point, but that such differences can, likewise, be found in individuals with normal body weight. People with statistically normal weight, but biologically underweight tend to overeat. However, due to cultural and social pressure they limit their food intake (restrain their eating), in order to achieve or maintain a desired weight. Restrained eaters eat more when this conscious restriction of food intake is highlighted by the experimental manipulation.[234]

In an experimental design that included three groups of subjects in which the first group received a milk-shake, the other two milkshakes, and the third has not received preload participants consumed ice cream as a test meal ad libitum. On the basis of a short questionnaire participants were furthermore divided into 2 groups: "severely restrained eaters" and "less restrained eaters". Results revealed that less restrained eaters behaved as expected: the more milkshake they drank, the less ice cream they ate. However, strictly restrained

eaters have behaved in a completely different manner: as soon as they drank milkshakes, they ate ice cream.[235]

By the consumption of milkshakes restrained eaters, were, possibly, experimentally forced to move their "allowed amounts" and to at least for a while abandon their measured food intake. Experimental manipulation relaxed cognitive control of eating behaviour and led to what is referred to as disinhibition which demonstrated that people with normal body weight, which usually eat less because they pay attention to their weight, under certain conditions tend to overeat.[236]

In a different set of studies all participants were given identical milkshake as preload, but only half of the subjects was informed that this was a high-calorie milkshake and the other half that it was a low-calorie milkshake. It was shown that restrained eaters ate a little more, if they were convinced that they have consumed a lot of calories, whereas unrestrained eaters ate a little less. It is obvious that this effect is not responsible for the actual food intake, but a subjective opinion, or attitude of subjects accordingly to how much they have already eaten: if restrained eaters think they ate too much, they do not maintain any more the control over food intake and eat more.[237]

6.9 Emotional overeating

In spite of the apparently self-explanatory name the nature of emotional eating still remains evasive. This phenomenon was initially referring to negative

emotions such as depression, anxiety [238] and stress induced loss of control over eating.[239] However, recent meta-analysis indicates that emotional eating can be likewise associated with positive mood and to even greater extent than negative mood.[240] In a series of experiments it was demonstrated that this aspect of influence on eating behaviour was wrongfully neglected as positive emotions increase the caloric intake as well.[241] Moreover, it has been proven that the term emotional eater may not fully describe the span of emotional states that influence food ingestion.[242] Emotional eating in terms of over- and under-eating is a habit adopted during childhood which may have impact on body weight regulation later in life.[243] Interestingly, it was reported that the eating behaviour is more powerfully driven by emotions rather than by healthy life-style which provides a valuable information for future public health strategies.[244]

7. EATING BEHAVIOUR

7.1 Genesis of eating habits

Eating behaviour is a rather complex type of behaviour. It is shaped since the early childhood through constant experiential training over the years with extremely high quota of repetition leading to habitualization. At the early age eating behaviour is primarily directed towards meeting the needs for optimal growth and physical and mental development. Initially, all necessary nutrients are obtained from one source i.e. milk which is later replaced by solid foods at which point commences the creation of eating habits. Parents serve as models for eating practices which results in transmission of behavioural patterns to their children. For this reason eating behaviour is considered extremely steady behaviour that cannot be changed in a short period of time.[245]

Children like adults eat more when presented with larger portion sizes. Their eating behaviour is not exclusively influenced by the type of food present in the household, but also by the amount of the food that is accessible.[246] Cognitive education attempts to direct children's feeding behaviour by means of rational presentation of the facts such as stories and pictures of caries in connection with the consumption of sweets. However, it has been demonstrated that children make healthier eating choices, such as vegetables consumption, when observing the example of their peers rather than the example of an adult indicating the presence of social modelling as early as at pre-school age.[247]

Feeding behaviour of children has adapted to address two, in developed countries historically present, major concerns for child´s health – shortage of food and infectious diseases. The intention to preserve child´s well-being has led to creation of feeding patterns that are being transferred though generations forming routine practices. These practices may be inappropriate for current circumstances and as well harmful due to the creation of blueprints for unhealthy eating habits while failing to address challenges of modern societies such as obesity.[248]

7.2 Management of eating behaviour

Eating behaviour is regulated by two competitive control mechanisms. Cultural norms reflecting eating habits of generations direct the eating behaviour to be motivated and accustomed and are opposed to the biological regulation related to instincts. Furthermore, eating behaviour has characteristics of an automatic form of behaviour which indicates that it occurs without cognitive direction. It has been demonstrated that people are often unaware of the amount of food eaten playing portion size control a major role in prevention of overeating.[249] Likewise, people often eat at meal time or if the food is available at short distance in spite the absence of hunger.[250]

Nevertheless, cognitive component of eating behaviour is subject to

external influences such as individual knowledge about nutrition, social norms and attitudes. In contrast to the patterns generated through the training processes not reflected on a conscious level, cognitive element represents the simplest way to influence the behaviour in diet of an adult. This, however, might not be the easiest way to influence it as it requires substantial amount of effort to put food intake under control and “simply” refuse the dessert. Another problem is the resistance to food temptation over longer periods of time as it depletes mental reserves and becomes unsustainable commonly leading to the weight regain.[251] As eating behaviour is an automatic behaviour people are, typically, unaware that they are not in control of it. Experiments have shown that when pointed out the automatic nature of their actions participants of the study refused to believe that those actions had no cognitive implications.[252] This may offer the explanation for eating of easily accessible energy dense foods.

By contrast, cognitive management can be placed at the service of such needs that are causing depleted caloric intake in desire of an attractive figure. This is very pronounced in some eating disorders such as bulimia and anorexia nervosa, providing an example of how a motive for the attractive figure causes a conscious degradation of nutrition in order to achieve the purposes for slimness defined by the society.

7.3 Concepts that influence decision-making

A series of factors have been described to influence eating behaviour such as taste demanding (sweet pleasure), sensation of hunger, economic conditions (special offer), cultural influences (croissant with coffee in the morning), traditional influences (characteristic dishes for Christmas), conditions of a habit (soup for lunch), emotional effect (chocolate in the stressful situation), social reasons (eating fondue), social status conditions (lobster as a classy food item). Choice is the consequence of the evaluation and judgement of multiple options. It is therefore a subjective decision susceptible to numerous factors. Decision making on a specific diet is actually a mixture of different motifs which are to greater or lesser extent associated with the biological sense of providing nutrients.[253, 254]

Consumers in developed countries are overwhelmed with the number of choices they are to make on a daily basis when deciding on food. Choosing between different brands, nutritional contents, organic versus conventional growth etc. is strongly predicted by person's personal attitude and believes.

The individual decision on the diet is a subjectively customized decision, based on the estimation of advantages and disadvantages, whereby, depending on the individual situation motifs can be differently evaluated. Many studies have shown that the nutritional knowledge plays an important role in food related decision making. People who are aware of dietary recommendations and understand the relation between nutrition and health and nutrition and

disease are more likely to make the right - healthy choices when it comes to food by using tools like for e.g. food labelling.[255] Furthermore, individual characteristics of a person such as dieting status, weight, and gender, bias food related decisions as influence people's perceptions of food.[256]

Any particular selection of food and thus the eating behaviour represents a multifunctional decision based on the optimization, which includes a wide variety of aspects that individuals personally assess. Therefore, some eating behaviour should not be characterized as inappropriate behaviour, but preferably as subjectively optimized behaviour that came out as a result of individual estimation.

The concept of inappropriate eating behaviour characterized by unhealthy choices is rather frequently used both by common people as well as by experts in the interpretations of the problems in relation with the eating behaviour. It classifies unhealthy eating habits as a "mistake" because they are not based on the norms of scientific knowledge regarding the optimization of health functions. However, this point of view gives no answer to the question why we eat what we eat in case of by passing cognitive control that adheres to rational standards.

The theoretical considerations of decision-making start from the fact that the decision about the diet depends on different motives. Each of these factors has a different significance for each person, e.g. the factor of the "disease" is of

less importance for healthy people, and it is difficult to significantly affect the decisions related to the diet. Eating behaviour largely depends on the situation. Thus, social context influences the way the meal is eaten. Modelling during dinning influences taste preferences. Adoption of eating patterns in social context is linked with the obesity through tendencies that promote overeating such as large portion size.[257] Changes of the situations provide opportunities for changing eating behaviour as both socio-psychological and environmental strategies seem to have an effect in changing behavioural eating patterns.[254]

WORKING HYPOTHESIS

As in any biological model the effect of a meal can be framed based on a stimulus-response model: specifically, our general hypothesis is that the postprandial experience depends on the characteristics of the meal (the stimulus) and the responsiveness of the subject (specimen tested) which can be modified by a series of conditioning factors. The effect of a specific factor can be tested keeping constant the rest. A large body of literature has focused on the characteristics of the subject that influence meal selection and consumption. However, their effect of the postprandial experience is not clear.

OBJECTIVES

The general objective of this work is to initiate the study of the mechanisms that determine the postprandial experience. Initially, surrogate markers of the subjective sensory experience will be searched in healthy subjects. For that purpose, we designed a specific paradigm to measure brain response through functional magnetic resonance and resting-state paradigm. Subsequently, proof-of-concept studies on two categories of conditioning mechanisms will be performed; specifically, we will investigate whether and to what extent the physical status (level of appetite) and the cognitive status (educational intervention) of the subject influence the postprandial experience.

Specific objectives

1. To investigate the reliability of brain imaging “in vivo”, by functional magnetic resonance and the resting-state paradigm, to the study of the subjective postprandial experience.
2. To determine the change in brain connectivity “in vivo”, measured by functional magnetic resonance and resting-state paradigm, induced by meal ingestion.
3. To establish the relation between postprandial perception and brain activity measured by functional magnetic resonance and resting-state paradigm, as potential surrogate markers of sensations.
4. To proof whether the physical status of the subject influences the postprandial experience; specifically, to determine the effect of preload conditioning of appetite on homeostatic and hedonic sensations.
5. To proof whether the cognitive status of the subject influences the postprandial experience; specifically to determine the effect of cognitive conditioning on homeostatic and hedonic sensations.

PUBLICATION 1

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ABSTRACT

Background: We recently reported interrelated digestive, cognitive, and hedonic Responses to a meal. The aim of this study was to identify brain networks related to the hedonic response to eating.

Methods: Thirty-eight healthy subjects (20-38 age range) were evaluated after a 5-hour fast and after ingestion of a test meal (juice and warm ham and cheese sandwich, 300 mL, 425 kcal). Perceptual and affective responses (satiety, abdominal fullness, digestive well-being, and positive mood), and resting scans of the brain using functional MRI (3T Trio, Siemens, Germany) were evaluated immediately before and after the test meal. A high-order group independent component analysis was performed to investigate ingestion-related changes in the intrinsic connectivity of brain networks, with a focus on thalamic and insular networks.

Key Results: Ingestion induced satiation (3.3±0.4 score increase; P<.001) and abdominal fullness (2.4±0.3 score increase; P<.001). These sensations included an affective dimension involving digestive well-being (2.8±0.3 score increase; P<.001) and positive mood (1.8±0.2 score increase; P<.001). In general, thalamo-cortical connectivity increased with meal ingestion while insular-cortical connectivity mainly decreased. Furthermore, larger meal-induced changes (increase/decrease) in specific thalamic connections were associated with smaller changes in satiety/fullness. In contrast, a larger meal-induced decrease in insular-anterior cingulate cortex connectivity was

associated with increased satiety, fullness, and digestive well-being.

Conclusions and Inferences: Perceptual and emotional responses to food intake are related to brain connectivity in defined functional networks. Brain imaging may provide objective biomarkers of subjective effects of meal ingestion.

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Brain networks associated with cognitive and hedonic responses to a meal

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Abstract

Background: We recently reported interrelated digestive, cognitive, and hedonic responses to a meal. The aim of this study was to identify brain networks related to the hedonic response to eating.

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Conclusions and Inferences: Perceptual and emotional responses to food intake are related to brain connectivity in defined functional networks. Brain imaging may provide objective biomarkers of subjective effects of meal ingestion.

KEYWORDS
brain imaging, hedonic response, meal ingestion, postprandial sensations

1 | INTRODUCTION

Meal ingestion has been well established to induce symptoms in some patient populations[1-3] and similar sensations can be induced experimentally using aversive stimuli in the laboratory.[4-7] However, the physiological mechanisms involved in the generation of various subjective postprandial sensations remain incompletely understood.[4,8-10] The subjective response to a meal involves a hedonic dimension in the form of pleasure, satisfaction, and wellness, which occurs when the characteristics of the meal (appearance, smell, taste, quantity) and the digestive response are appropriate.[11,12] By manipulating the experimental conditions, we have previously demonstrated

that the postprandial sensation (satiation, fullness) and the valence of this sensation (pleasure, digestive well-being vs unpleasant sensation, dissatisfaction) are dissociable,[12] ie depending on the conditions, equal degree of satiation/fullness may have a pleasant or unpleasant connotation. To further understand the central mechanisms underlying the experience of postprandial sensations, we used resting state MRI (rsMRI) to identify brain networks engaged by the ingestion of a pleasurable meal. We examined changes in intrinsic brain oscillations before and after a test meal which induced postprandial satiation/fullness associated with satisfaction in healthy male subjects. In rsMRI, information from the intrinsic fluctuations in regional blood oxygenation is used to identify brain networks without the need of an external stimulus and is thus well suited to the study of physiological states. We specifically focused on networks involving the thalamus and anterior insula which are involved in sensory processing and interoceptive awareness.[13,14]

By analyzing postprandial intrinsic connectivity changes within these networks in healthy males following the ingestion of a pleasant meal, we tested the following hypotheses: (i) meal ingestion is associated with changes in the intrinsic connectivity of thalamic and insular networks; (ii) subjective sensations with positive or negative valence are correlated with distinct thalamic and insular connectivity changes.

Key Points

- Meal ingestion induces cognitive and hedonic sensations, and our aim was to identify brain networks related to these sensations
- Perceptual and emotional responses to food intake are related to brain connectivity in defined functional networks
- Brain imaging may provide objective biomarkers of subjective effects of meal ingestion

2 | MATERIAL AND METHODS

2.1 | Participants

Thirty-eight healthy non-obese male subjects (median age 27.16 years; age range, 20-38 years, body mass index range, 19.6-30.7 kg/m^2), right-handed, and without history of gastrointestinal symptoms were recruited by public advertising to participate in the study. Absence of current digestive symptoms was verified using a standard abdominal symptom questionnaire (no symptom ≤2 on a 0-10 scale). Psychological and eating disorders were excluded using the following tests: Hospital Anxiety and Depression scale (HAD), Dutch Eating Behaviour Questionnaire (DEBQ—Emotional eating, External eating, Restrained eating), and Physical Anhedonia Scale (PAS). Handedness was determined using the Edinburgh test (laterality index).

The protocol for the study was approved by the Institutional Review Board of the University Hospital Vall d'Hebron and was registered with Clinical Trials.gov as part of the study NCT02592239. All participants gave written informed consent.

2.2 | Experimental design

The responses to a probe meal were studied in the afternoon after a 5-hour fast on two separate days (Figure 1). Participants were instructed to refrain from strenuous physical activity the day before and to have their usual breakfast after the overnight fast. On both days, a series of perception measurements (see below) were performed before and at different intervals after the probe meal. (i) On the first day, participants were studied in a quiet, isolated room sitting on a chair; perception was measured at 5-minute intervals immediately before and up to 30 minutes after ingestion of the probe meal. (ii) On the second day, brain imaging was performed (see below) immediately before (fasting scans) and after the ingestion of the probe meal (postprandial scan); the probe meal was ingested sitting in an isolated room adjacent to the brain imaging room. To examine the effect of time, two fasting resting scans were acquired before meal ingestion. Perception was measured at three time points: after the fasting scan and before and after the postprandial scan (20 minutes after the ingestion of the meal). For this pilot study no formal sample size calculations were performed.

2.3 | Probe meal

A probe meal that induced a consistent cognitive response (satiation) with a pleasurable hedonic dimension was developed by a systematic series of preliminary studies performed in healthy subjects. The probe meal consisted of a warm sandwich (58 g bread with 12 g butter, 38 g ham and 38 g cheese) and an orange juice [(200 mL) 300 mL total volume (total caloric content of 425 kcal; 47 g carbohydrates, 17 g lipids, 18 g proteins)]. The sandwich was cooked in a hot plate (Sandwich Maxi 20, Fagor, Olite, Spain) for 3 minutes and administered at standard temperature (allowed to cool down covered by a napkin for 3 minutes at room temperature). Subjects were instructed to eat at their rate of choice.

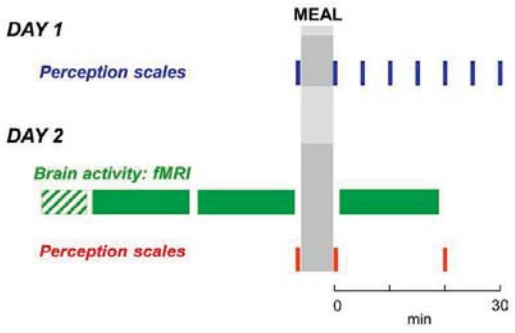

FIGURE 1 Experimental design. Perception in response to a probe meal was studied without (Day 1) and with brain imaging (Day 2: structural scan; functional scan)

2.4 | Assessment of subjective responses

Four 10-cm scales graded from −5 to +5 were used to measure: (i) palatability (very bad/disagreeable to very good/delicious), (ii) hunger/satiety-satiation, (iii) digestive well-being (unpleasant sensation/dissatisfaction to pleasant sensation/satisfaction), (iv) desire of eating a food of choice (impossible/eagerly); and (v) mood (negative/positive). Two additional 10-cm scales graded from 0 (not at all) to 10 (very much) were used to measure: (vi) abdominal bloating/fullness; and (vii) discomfort/pain. Subjects received standard instructions on how to complete the scales. The palatability scale was only scored once immediately after meal ingestion on the first study day. The other scales were completed both before and after meal ingestion on both study days. These scales have been previously used and were shown to be sensitive to detect the effect of dietary interventions under different conditions.[12,15]

2.5 | Brain imaging

2.5.1 | fMRI acquisition

One structural scan and two sequential resting (fast-1 and fast-2) scans (total duration, 40 minutes) were performed immediately before the probe meal and one resting scan (duration, 20 minutes) was performed immediately after finishing the meal (postprandial scan) (Figure 1). During the resting scans, subjects rested with eyes closed. Images were acquired on a 3.0 T whole-body MR scanner with a 12-channel phased-array head coil and a whole-body transmit coil (Trio, Siemens, Germany). The protocol parameters were chosen based on the ADNI initiative (http://www.adni-info.org/Scientists/ADNIStudyProcedures.html) and included: (i) fast dual echo T2-weighted transverse sequence (TR=3080 msec, TE_1=21 msec, TE_2=91 msec, voxel size=0.78 × 0.78 × 3.0 mm^3); (ii) transverse T2-FLAIR sequence (TR=9000 msec, TE=87 000 msec, TI=2500 msec, voxel size=0.49 × 0.49 × 3.0 mm^3); (iii) axial 3D T1-weighted gradient-echo (MPRAGE) sequence (TR=2200 msec, TE=3.26 msec, voxel size=1.0 × 1.0 × 1.0 mm^3); and (iv) resting-state BOLD sequence (TR=2000 msec, TE=28 msec, voxel size=3.4 × 3.4 × 4.0 mm^3).

2.5.2 | fMRI pre-processing

Resting scan images were preprocessed using SPM8 software (Welcome Department of Cognitive Neurology, London, UK). Data were slice-time and motion corrected, spatially normalized to the Montreal Neurological Institute standard template using their structural image, spatially smoothed with a 5 mm Gaussian kernel, and resampled to a voxel size=2 × 2 × 2 mm^3. The first two volumes were discarded to allow for stabilization of the magnetic field.

2.5.3 | Brain network connectivity

Group independent component analysis (ICA) was conducted to quantify resting scan network (RSN) connectivity pre- and post-meal ingestion. High-model-order ICA approaches of 70 components yield refined independent component networks (ICNs) which correspond to known anatomical and functional segmentations.[16-19] The pre- and post-meal ingestion scans from all subjects were simultaneously entered into the ICA which was implemented in GIFT v4.0a (http://icatb.sourceforge.net). Seventy independent components were extracted by independent component decomposition using the infomax algorithm.[20] Multiple runs (20 iterations) were performed using ICASSO to increase robustness of the results.[21] Individual subject maps were back-reconstructed and converted into z-score maps representing the degree of correlation between the voxel signal and the group-averaged time course of the network (ie intra-network functional connectivity). Higher z values indicate greater connectivity strength or influence of that voxel on the network.[22]

Components of interest were identified by spatial correlation with published ICN templates.[23] The anterior insula and the thalamus were selected as the primary networks of interest and cortical networks associated with sensorimotor, emotion-interoceptive, and emotion-cognitive functions were selected as secondary networks of interest. The thalamus was represented in two components, one comprising a more dorsal aspect, and one comprising a more ventral aspect, extending into the midbrain. In addition, the anterior insula was represented in two components, one comprising the left insula and one comprising the right insula.

2.6 | Statistical analysis

2.6.1 | Perception measurements

Mean values (±SE) of the parameters measured were calculated in each group of subjects. Normality of data distribution was evaluated by the Kolmogorov-Smirnov test. Comparisons of parametric, normally distributed data were made by Student's *t*-test, paired tests for intragroup comparisons and unpaired tests for intergroup comparisons; otherwise, the Wilcoxon signed rank test was used for paired data within groups, and the Mann-Whitney *U* test for unpaired data between groups. Correlations between parameters were evaluated by Pearson's test. Differences were considered significant at a *P* value <.05.

2.6.2 | Brain imaging and correlations with perception

The impact of meal ingestion on intra-network and inter-network functional connectivity was evaluated using the MANCOVAN toolbox in GIFT v4.0a. For the selected networks of interest, changes in intra-network connectivity were evaluated with a paired *t*-test (postprandial vs fast-2) using the subjects' reconstructed spatial maps. To evaluate changes in inter-network connectivity between the primary and secondary networks of interest, subject-specific ICN time courses were first detrended, despiked, and filtered using a fifth-order Butterworth low-pass filter with a high frequency cutoff of 0.15 Hz. Pairwise correlations between the preprocessed ICN time

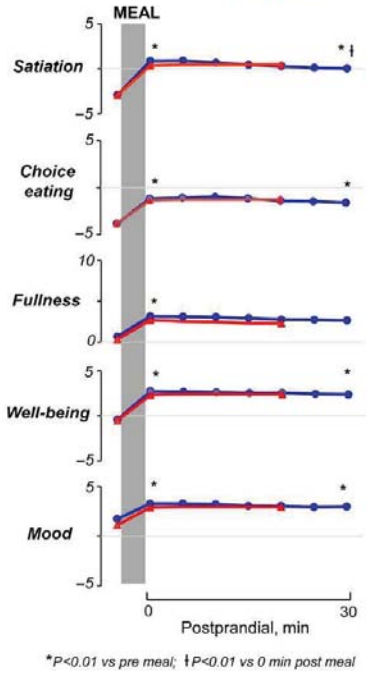

FIGURE 2 Cognitive and hedonic responses to probe meal in separate experiments with and without brain imaging. No statistically significant differences between study days were detected

courses were calculated and transformed to z-scores using Fisher's z-transformation for each scan. The transformed correlation coefficients were then entered into a paired t-test (postprandial vs fast-2 scores). A corrected $P<.05$ using a false discovery rate (FDR) was considered significant.[24] The relationship between changes in cognitive and hedonic perceptions and changes in inter-ICN connectivity was evaluated by Pearson correlation. A $P<.05$ was considered significant.

3 | RESULTS

3.1 | Perceptual/hedonic responses to the meal

On the first experimental day (without brain imaging) before the meal (baseline fasting period), subjects reported a sensation of hunger and a desire to eat which was accompanied by a positive mood (Figure 2). Hunger correlated with the desire of choice eating ($R=0.72$; $P<.01$), but not with digestive well-being or mood. Subjects did not report any baseline symptoms of bloating, fullness, pain, or discomfort. Participants ingested the test meal in 203±12 seconds (at the rate of their choice) and reported a palatability score ≥2 (3.8±0.1 score). Ingestion of the test meal induced satiation, mild fullness, reduced the desire of eating, induced a sensation of digestive well-being ($P<.01$; 0 minute postprandial vs fast for all), and slightly improved the positive mood state ($P<.01$; 0 minute postprandial vs fast), but did not induce discomfort/pain. These sensations developed immediately after ingestion and persisted over the 30-minute postprandial period: 30 minutes after ingestion all sensations were still significantly higher than before ingestion ($P<.01$ for all); satiation and fullness decreased slightly but significantly over the postprandial period as compared to immediately after the meal ($P<.01$ vs 0 minute postprandial); however, no significant changes were detected in digestive well-being, mood, or desire for eating a food of choice during the postprandial observation period ($P>.05$ vs 0 minute postprandial for the three) (Figure 2).

Sensations measured immediately before and after the test meal on the second experimental day (with brain imaging) were similar to those measured on the first study (Figure 2) and no statistically significant differences were detected.

3.2 | Brain network connectivity

No differences were found between the two baseline fasting scans (data not shown); thus, the second scan acquired immediately before ingestion was chosen to represent the pre-meal brain activity.

3.2.1 | Intra-ICN connectivity

A significant meal-induced reduction in connectivity within several component networks was observed, including the ventral thalamus ICN and sensorimotor cortical ICNs (left and right sensorimotor ICNs, bilateral secondary somatosensory ICN, bilateral SMA/paracentral lobule ICN) (Figure 3).

3.2.2 | Inter-ICN connectivity

Meal ingestion significantly changed the inter-network connectivity of the anterior insula with several other brain components, primarily resulting in decreases in functional connectivity (Figure 4). Significant meal-induced decreases were observed between the right insula ICN and ICNs representing: (i) bilateral anterior cingulate cortex/medial orbitofrontal cortex (ACC/mOFC), (ii) right temporoparietal junction (TPJ), and (iii) left dorsolateral prefrontal cortex (dlPFC). Significant meal-induced decreases were also observed between the left insula ICN and ICNs representing: (i) bilateral subgenual ACC, (ii) bilateral ACC/mOFC, (iii) left and right TPJ, (iv) right inferior frontal operculum, and (v) bilateral medial PFC. Significant meal-induced increases were observed between the left insula ICN and ICNs representing: (i) bilateral midcingulate cortex and (ii) dorsal thalamus.

Meal ingestion also significantly changed the inter-network connectivity of the thalamus with several other brain components, primarily resulting in increases in functional connectivity (Figure 4). Significant meal-induced increases were observed between the dorsal thalamus ICN and ICNs representing: (i) primary somatosensory (S1) cortex, (ii) secondary somatosensory (S2) cortex, (iii) subgenual ACC, (iv) superior temporal cortex, (v) left TPJ, and (vi) right inferior frontal operculum. Significant meal-induced increases were observed between the ventral thalamus ICN and ICNs representing: (i) S1 cortex, (ii) subgenual ACC, (iii) right and left TPJ, (iv) precuneus, (v) mPFC,

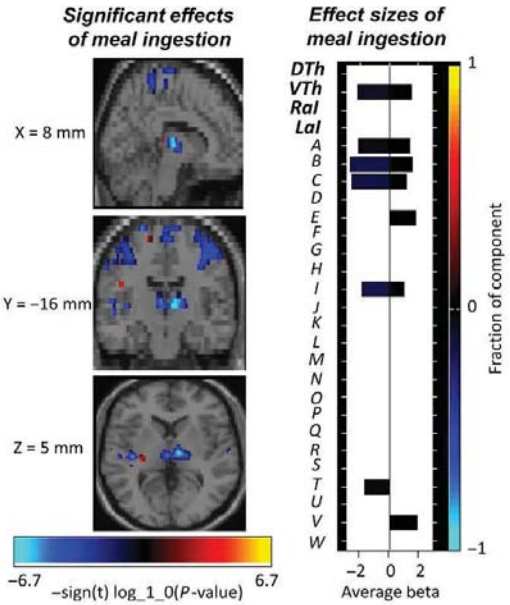

FIGURE 3 Composite image of the significant effects of meal ingestion on intra-network connectivity. The effect size for each component is shown to the right; primary networks of interest: dorsal thalamus (DTh), ventral thalamus (VTh), right anterior insula (Ral), left anterior insula (Lal); secondary networks of interest: bilateral secondary somatosensory cortex (A), right sensorimotor cortex (B), left sensorimotor cortex (C), bilateral subgenual anterior cingulate cortex (D), bilateral caudate (E), bilateral pallidum/putamen (F), bilateral hippocampus/parahippocampal gyrus/amygdala (G), bilateral anterior cingulate cortex/medial orbitofrontal cortex (H), bilateral paracentral lobule (I), bilateral primary somatosensory cortex (J), bilateral superior parietal (K), bilateral supramarginal (L), left temporoparietal junction (M), right superior/inferior parietal (N), bilateral ventrolateral prefrontal cortex (O), right left temporoparietal junction (P), bilateral medial cingulate cortex (Q), right inferior frontal operculum (R), bilateral precuneus (S), bilateral superior temporal (T), bilateral dorsal anterior cingulate cortex/medial cingulate cortex (U), bilateral medial prefrontal cortex (V), left dorsolateral prefrontal cortex (W)

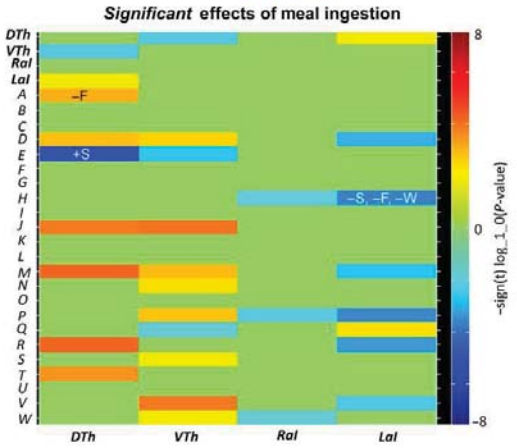

FIGURE 4 Effects of meal ingestion on inter-ICN connectivity. Heatmap depicting significant effects between the primary networks of interest (thalamus and anterior insula) and the secondary networks of interest. The thalamus and anterior insula ICNs displayed significant changes in connectivity with sensorimotor, emotion/cognitive, and interoceptive ICNs. Significant correlations, positive (+) and negative (−) correlation, between meal-induced connectivity changes and meal-induced perceptual changes are also indicated: △satiety (S), △fullness (F), △well-being (W). Considering the direction of meal-induced changes, a greater decrease in insula-ACC/mOFC connectivity is associated with a greater increase in satiety, fullness, and digestive well-being. In contrast, a greater meal-induced decrease in thalamus-caudate connectivity is associated with a smaller increase in satiety, and a greater meal-induced increase in thalamus-S2 connectivity is associated with a smaller increase in fullness. Primary networks of interest: dorsal thalamus (DTh), ventral thalamus (VTh), right anterior insula (Ral), left anterior insula (Lal); secondary networks of interest: bilateral secondary somatosensory cortex (A), right sensorimotor cortex (B), left sensorimotor cortex (C), bilateral subgenual anterior cingulate cortex (D), bilateral caudate (E), bilateral pallidum/putamen (F), bilateral hippocampus/parahippocampal gyrus/amygdala (G), bilateral anterior cingulate cortex/medial orbitofrontal cortex (H), bilateral paracentral lobule (I), bilateral primary somatosensory cortex (J), bilateral superior parietal (K), bilateral supramarginal (L), left temporoparietal junction (M), right superior/inferior parietal (N), bilateral ventrolateral prefrontal cortex (O), right left temporoparietal junction (P), bilateral medial cingulate cortex (Q), right inferior frontal operculum (R), bilateral precuneus (S), bilateral superior temporal (T), bilateral dorsal anterior cingulate cortex/medial cingulate cortex (U), bilateral medial prefrontal cortex (V), left dorsolateral prefrontal cortex (W)

(vi) dlPFC, and (vii) right superior/inferior parietal cortex. In addition, significant meal-induced decreases were observed: (i) between the dorsal thalamus ICN and ventral thalamus ICN, (ii) between the caudate ICN and dorsal/ventral thalamic ICNs, and (iii) between the ventral thalamus ICN and the MCC ICN.

3.3 | Relationship between perceptual and hedonic perceptions and changes in inter-network connectivity

All significant meal ingestion-related changes in inter-ICN connectivity were examined for relationships with changes in subjective perceptions and hedonic responses (post-meal-1 minus pre-meal; △Satiety, △Fullness, △Well-being, △Mood) (Figure 4). A significant negative correlation was found between meal ingestion-related changes in left anterior insula-ACC/mOFC connectivity and meal ingestion-related changes in satiety, fullness, and digestive well-being ratings. In addition, a significant negative correlation was found between meal ingestion-related changes in dorsal thalamus-S2 connectivity and △Fullness. Finally, a significant positive correlation was found between meal ingestion-related changes in dorsal thalamus-caudate connectivity and △Satiety. Considering the direction of meal-induced

changes as stated in the previous sections, these significant correlations reflect: A greater meal-induced decrease in insula-ACC/mOFC connectivity was associated with a greater increase in satiety, fullness, and digestive well-being. In contrast, a greater meal-induced decrease in thalamus-caudate connectivity was associated with a smaller increase in satiety and a greater meal-induced increase in thalamus-S2 connectivity was associated with a smaller increase in fullness.

4 | DISCUSSION

The main findings of the study were: (i) Meal ingestion changed the predominant baseline sensations and motivation from hunger and a desire to eat to one of satiation and mild fullness. These postprandial changes were associated with a feeling of digestive well-being. (ii) Subjective postprandial responses were associated with significant changes both in the connectivity within and between several component resting state networks of the brain. (iii) Functional network changes were correlated with changes in subjective responses to meal ingestion. To our knowledge, this is the first demonstration of distinct food-related changes in resting state networks in the brain following the ingestion of a palatable meal which are associated with food-related sensations and digestive well-being.

4.1 | Subjective responses to the meal

The ingestion of the test meal changed the sensation of hunger and motivation to eat into prolonged sensations of fullness and satiation, and a feeling of digestive wellness. These changes can be assumed to be mediated by the effects of endocrine and vagal afferent inputs to the hypothalamus and thalamic nuclei.[25] Postprandial hypothalamic and thalamic activity signals the insular cortex and associated regions of the extended central reward network, including the prefrontal/orbitofrontal cortex, anterior cingulate cortex, hippocampus and amygdala and basal ganglia.[26]

4.2 | Meal-related changes in intrinsic connectivity

Consistent with the known effects of meal-induced neuroendocrine signaling to the brain, we observed major, distinct changes in the brain's resting state activity and architecture.

4.2.1 | Thalamic connectivity

The thalamus is a relay station for a wide range of sensory information from the body. In particular, the ventral medial nucleus receives direct input from the vagal nucleus of the solitary tract, which conveys visceral and gustatory afferent activity, and projects to the anterior insula.[14,27,28] The thalamus and anterior insula then project to a wide range of cortical regions. Ingestion of the test meal was associated with extensive connectivity increases of both ventral and dorsal thalamic ICNs with sensory and affective brain regions, and with reduced connectivity between the two thalamic subregions and with the caudate nucleus, a brain region involved in reward and motivation. These changes may reflect increased transmission of visceral and gustatory signals from the thalamus to other brain regions, and a reduction in communication with the caudate nucleus, a major component of the brain's reward region.

4.2.2 | Insula connectivity

While the posterior aspects of the insular cortex represent the primary interoceptive cortex, anterior insula activity is associated with the awareness of sensations, including hunger and satiation, and this brain region is concerned with the integration of interoceptive, affective, attentional, and motivational signals.[13] Furthermore, through its connections with several other brain networks, the anterior insula is a key node in other overlapping brain networks involved in ingestive behavior and food-related sensations. These networks include the salience network, which in close association with the anterior cingulate cortex functions to identify and respond to salient, homeostatically relevant events among both internal and external stimuli,[28] and the extended reward network.[28,29]

Despite minor differences between left and right insula, meal-induced reductions in connectivity were observed between the bilateral insula and resting state networks representing bilateral anterior cingulate and medial orbitofrontal cortex (ACC/mOFC), right temporoparietal junction (TPJ), and medial and lateral prefrontal regions. The ACC and its subregions have close connections with anterior insula and their co-activation plays an important role in the generation of sensory and motivational aspects of emotional feelings.[14] The medial OFC is part of the prefrontal cortex and receives projections from thalamic subregions. It plays an important role in reward-related decision-making.[30] The TPJ is an association area which integrates information from both the external and the internal environment. It incorporates information from the thalamus and emotion-related brain regions, and from the visual, auditory, and somatosensory systems. When viewed together, the ingestion of the test meal was associated with extensive reductions in connectivity of the bilateral anterior insula with brain regions involved in sensory integration, salience assessment, and reward. This may reflect a reduction in communication within key regions of the salience network following meal ingestion.

4.3 | Correlation of functional network changes with subjective meal responses

Postprandial subjective sensations (satiety, fullness) and valenced feeling states (digestive well-being) depend on multiple factors. While the underlying neural circuitry responsible for these subjective responses is incompletely understood, we demonstrate significant correlations between these subjective responses and particular alterations in brain intrinsic connectivity. A greater meal-induced decrease in insula-ACC/mOFC connectivity was associated with a greater increase in satiety, fullness, and digestive well-being. Thus, a reduction in communication within key regions of the salience network following meal ingestion appears to be important for overall success of the meal in producing a homeostatically favorable state. In contrast, a greater meal-induced decrease in thalamus-caudate connectivity was associated with a smaller increase in

satiety, and a greater meal-induced increase in connectivity between the thalamus and the sensory cortex was associated with a smaller increase in fullness. Thus, changes in thalamic connectivity appear to be more related to a state of unfulfillment following meal ingestion.

4.4 | Limitations of study

We acknowledge several limitations of our study. Firstly, to prevent potential gender-related variability in the responses to food ingestion, only males were included in this proof-of-concept study. Furthermore, no formal sample size calculations were performed, and given the large number of variables analyzed, some effects may have been missed.

4.5 | Conclusions and clinical implications

Our findings demonstrate extensive meal induced changes in the connectivity of key brain networks and regions which are involved in the sensory, affective and motivational aspects of food intake. The general pattern suggests a reduction in connectivity within major sensory brain networks, and between key regions of the extended reward network. While the interpretation of all network changes will require additional research, our findings suggest that postprandial sensations of satiety and well-being are a reflection of specific connectivity changes within the extended reward network (including anterior insula, thalamus, medial orbital frontal cortex, and caudate nucleus) and in sensory brain networks. Future studies in patients with functional dyspepsia who experience greater satiation and primarily negative-valence postprandial sensations will be able to identify disease-related differences in these central network changes.

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CONFLICT OF INTEREST

No competing interests declared by all investigators.

AUTHOR CONTRIBUTIONS

Teodora Pribic, Lisa Kilpatrick and Barbara Ciccantelli contributed equally as co-first authors. EM and FA contributed equally as co-principal investigators in the design and interpretation of the study. TP was involved in study management, conduction of experiments and data analysis; LK was involved in analysis and interpretation of brain imaging studies and manuscript preparation; BC contributed to study management and conduction of experiments; CM contributed to study management and data analysis; AA was involved in study design and supervision of studies; AR was involved in analysis of brain imaging studies; DP contributed to study design, analysis of brain imaging studies and manuscript revision; EM contributed to study design, data interpretation, and manuscript preparation (brain imaging aspects); FA contributed to study design, data interpretation, and manuscript preparation (physiological aspects).

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PUBLICATION 2

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ABSTRACT

Background: We have previously shown that the postprandial experience includes cognitive sensations, such as satiety and fullness, with a hedonic dimension involving digestive well-being and mood. Preload conditioning has been shown to modulate appetite and food consumption under certain conditions, but its effects on the responses to meal ingestion are not clear. We hypothesized that appetite modulation by preload conditioning has differential effects on the cognitive and the emotive responses to meal ingestion.

Methods: The effects of preload conditioning (ingestion of a low-vs a high-calorie breakfast) on appetite and on the cognitive and emotive responses to a comfort probe meal ingested 2 hours later (ham and cheese sandwich with orange juice; 300 mL, 425 Kcal) was tested in healthy subjects (n=12) in a cross-over design. Sensations were measured at regular intervals 15 minutes before and 60 minutes after the probe meal.

Key Results: As compared to the low-calorie breakfast, the high-calorie breakfast reduced basal hunger sensation and influenced the responses to the subsequent probe meal: it increased satiety (4.3±0.2 score vs 2.7±0.2 score; P<.001) and fullness (5.4±0.5 score vs 3.1±0.5; P<.001), but reduced the expected postprandial experience of digestive well-being after a palatable meal (1.3±0.7 score vs 3.0±0.3; P=.045).

Conclusion and Inferences: Appetite modulation by preload conditioning has differential effects on the cognitive and emotive responses to a meal. Preload

conditioning of the postprandial experience may be applicable to dietary planning and prevention of postprandial symptoms.

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ORIGINAL ARTICLE

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Appetite influences the responses to meal ingestion

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Abstract

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Conclusion and Inferences: Appetite modulation by preload conditioning has differential effects on the cognitive and emotive responses to a meal. Preload conditioning of the postprandial experience may be applicable to dietary planning and prevention of postprandial symptoms.

KEYWORDS
meal ingestion, palatability, postprandial sensations, hedonic response, appetite, preload test

1 | INTRODUCTION

Meal ingestion induces a metered digestive response and conscious sensations.[1–3] We have previously shown that the postprandial experience includes cognitive sensations, such as satiety and fullness, and that these sensations have a hedonic dimension involving digestive well-being, ie, satisfaction, and mood.[1] When the conditions in terms of meal characteristics, subject preparation and digestive response, are appropriate the cognitive sensations have a pleasant dimension; however, in other conditions the same type of cognitive sensations, ie, the same degree of satiety/fullness, may have an aversive dimension. Hence, the cognitive and hedonic components of the postprandial

Abbreviations: LCB, low-calorie breakfast; HCB, high-calorie breakfast.

experience are dissociable. A recent study further showed that both components are associated to the activity in specific brain regions.[4]

The responses to meal ingestion are influenced by conditioning factors.[5] Preload conditioning, ie, a previous meal has been shown to modulate appetite and food consumption under certain conditions, but its effects on the responses to meal ingestion are not clear.[6–8] We hypothesized that appetite modulation by preload conditioning has differential effects on the cognitive and the emotive responses to meal ingestion, specifically increase in satiety/fullness and decrease in satisfaction. To test our hypothesis we designed a cross-over study in healthy subjects testing the effect of preload conditioning (ingestion of a low- vs a high-calorie breakfast) on appetite and on the cognitive and emotive responses to a probe meal ingested 2 hours later.

Key points

- The postprandial experience includes cognitive sensations, such as satiety and fullness, with a hedonic dimension involving digestive well-being and mood.
- Appetite modulation by preload conditioning influences the responses to a subsequent meal ingested 2 hour later.
- Preload conditioning has differential effects on the cognitive and emotive dimensions of the postprandial experience.

2 | MATERIAL AND METHODS

2.1 | Participants

Twelve healthy, weight-stable, non-obese men without history of gastrointestinal symptoms were recruited by public advertising to participate in the study. Exclusion criteria were chronic health conditions, prior obesity, use of medications (except sporadic use of NSAIDs and antihistaminics), history of anosmia and ageusia, current dieting or any pattern of selective eating such as vegetarianism, alcohol abuse, and use of recreational drugs. Absence of current digestive symptoms was verified using a standard abdominal symptom questionnaire (no symptom ≤2 on a 0-10 scale). Psychological and eating disorders were excluded using the following tests: Hospital Anxiety and Depression scale (HAD), Dutch Eating Behavior Questionnaire (DEBQ-Emotional eating, External eating, Restrained eating), and Physical anhedonia scale (PAS). Candidates were asked whether they liked the test meals to be tested (see below) and only those who did so were recruited.

Participants were instructed to refrain from strenuous physical activity the day before and from alcohol and smoking on the study day. The protocol for the study had been previously approved by the Institutional Review Board of the University Hospital Vall d'Hebron, and all participants gave written informed consent.

2.2 | Experimental design

The effect of a previous breakfast on the responses to a probe meal was studied in a crossover design. The effects of low-calorie vs a high-calorie test breakfasts were tested on different days and balanced order. Participants were instructed to eat a standard dinner the day before, to consume the test breakfast at home after overnight fast, and to report to the laboratory, where the probe meal was administered 2 hours after breakfast. Studies were conducted in a quiet, isolated room with participants sitting on a chair. Perception was measured at 5 minutes intervals 15 minutes before and 20 minutes after ingestion and at 10 minutes intervals up to 60 minutes after the probe meal. Based on previous data with the same probe meal,[9] sample size was estimated assuming a 15% difference in postprandial digestive well-being with 80% power and 5% significance threshold.

2.3 | Test breakfast

2.3.1 | Low-calorie breakfast (LCB)

Coffee with semi-skimmed milk and five biscuits (181 Kcal, 5 g lipids, 27 g carbohydrate, 7 g protein).

2.3.2 | High-calorie breakfast (HCB)

Coffee with semi-skimmed milk and two chocolate doughnuts (623 Kcal, 39 g lipids, 57 g carbohydrate, 11 g protein). To standardize the high-calorie breakfast, participants obtained the doughnuts directly in the research unit the day before the test.

2.4 | Probe meal

The probe meal consisted of a warm sandwich (58 g bread with 12 g butter, 38 g ham and 38 g cheese) and 200 mL orange juice (300 ml total volume, total caloric content of 425 Kcal; 17 g lipids, 47 g carbohydrates, 18 g proteins). The sandwich was cooked in a hot plate (Sandwich Maxi 20, Fagor, Olite, Spain) for 3 minutes and administered at standard temperature (allowed to cool down covered by a napkin for 3 minutes at room temperature). Subjects were instructed to eat at their rate of choice. The probe meal was selected by a series of preliminary studies in healthy subjects showing a consistent cognitive response (satiety) with a pleasurable hedonic dimension (pleasant sensation).[9]

2.5 | Perception measurements

Four 10 cm scales graded from −5 to +5 were used to measure: (i) palatability (very bad-disagreeable/very good-delicious), (ii) hunger/satiety (extremely hungry/completely satiated), (iii) digestive well-being (extremely unpleasant sensation/extremely pleasant sensation), and (iv) mood (negative/positive); two additional 10 cm scales

graded from 0 (not at all) to 10 (very much) were used to measure: (i) abdominal bloating-fullness, and (ii) discomfort-pain. Subjects received standard instructions on how to fill-out the scales.[1,10] The palatability scale was only scored once immediately after ingestion of the probe meal.

2.6 | Statistical analysis

Statistical analysis was performed using the SPSS 12.0 (SPSS Inc., Chicago, IL, USA) for Windows statistical package. In each subject, the values were averaged over 15 minutes periods (mean of 3 measurements) before and immediately after the probe meal. Mean or grand mean values (±SE) of the parameters measured were calculated in each group of subjects. Normality of data distribution was evaluated by the Kolmogorov–Smirnov test. Comparisons of parametric, normally distributed data were made by Student's *t* test, paired tests for intragroup comparisons and unpaired tests for intergroup comparisons; otherwise, the Wilcoxon signed rank test was used for paired data within groups, and the Mann–Whitney *U* test for unpaired data between groups. Differences were considered significant at a $P<.05$.

3 | RESULTS

3.1 | Demographics

Participants were 21-45 years age range with 19.7-24.8 Kg/m^2 body mass index range. All participants completed the studies and were included for analysis.

3.2 | Baseline conditions before the probe meal

After the low-calorie breakfast, subjects reported hunger, with no significant fullness and with sensation of digestive well-being. After the high-calorie breakfast, participants reported satiety instead of hunger and mild sensation of fullness ($P<.001$ vs LCB for both). Digestive well-being was somewhat, but not significantly higher than after the low-calorie breakfast ($P=.102$) and in both conditions participants reported a similar level of positive mood. Breakfast preload in either case did not involve any discomfort.

3.3 | Response to the probe meal

3.3.1 | Responses after the low-calorie breakfast

The test meal was ingested in 308±43s and all participants found the probe meal highly palatable (mean palatability score 4.3±0.1). Ingestion of the probe meal induced satiety ($P<.001$ vs baseline), fullness ($P<.001$ vs baseline), and improved both the sensation of digestive well-being ($P<.001$ vs baseline) and mood ($P=.008$ vs baseline) without abdominal discomfort (Figure 1). By the end of the postprandial observation period all sensations, but mood, had significantly decreased ($P\leq.036$ for all), although they were all still above pre-meal levels ($P\leq.027$ for all).

3.3.2 | Responses after the high-calorie breakfast

The test meal was ingested in 345±56s. Participants found the same probe meal somewhat less palatable after the HCB (mean palatability score 3.3±0.3; $P=.006$ vs LCB). Ingestion of the probe meal also induced satiation ($P<.001$ vs baseline) and fullness ($P<.001$ vs baseline). Absolute satiation and fullness scores were significantly higher than after the low-calorie breakfast ($P<.001$ for both); as compared to the

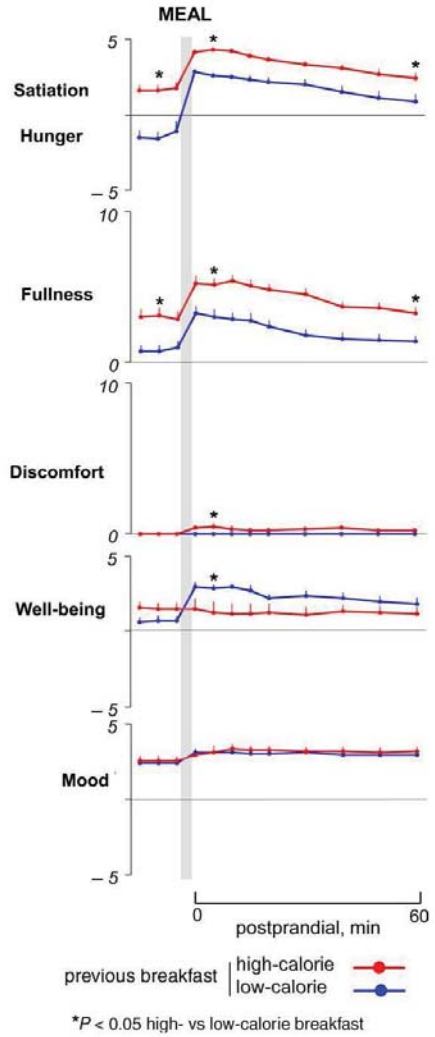

FIGURE 1 Effect of appetite on the responses to a meal. As compared to the low-calorie breakfast, the high-calorie breakfast reduced basal hunger sensation, and selectively influenced the responses to a meal ingested 2 hour later: it increased satiety and fullness, but reduced the expected postprandial experience of digestive well-being

LCB the change from pre-meal levels was similar for fullness and significantly smaller for satiation (P=.023). Interestingly, after the HCB the probe meal had no significant effect on digestive well-being and mood (P=.714 and P=.076 vs baseline, respectively); both the change in well-being, and the postprandial scores, were significantly smaller than after the LCB (P=.005 and P=.045 respectively). By the end of the postprandial observation period satiety and fullness had significantly decreased (P=.002 and P=.003 vs early postprandial, respectively); and all sensations, but mood, scored the same as before the probe meal (P>.082 for all). By the end of the postprandial observation period satiety and fullness were still higher than after the LCB (P≤.001 for both).

4 | DISCUSSION

Our study demonstrates that appetite modulation by preload conditioning has differential effects on the cognitive and emotive responses to a meal. Indeed, as compared to a low-calorie breakfast, a high-calorie breakfast, that reduced basal hunger sensation, influenced the responses to a subsequent meal: it increased satiety and fullness, but reduced postprandial satisfaction and the expected sensation of digestive well-being after a palatable comfort meal.

The relation between satiety/fullness and satisfaction after meal ingestion is complex. Cognitive sensations that fit into the same descriptors may have a different hedonic dimension. In a previous study we observed that increasing the caloric content of a meal with minimal change in meal volume and palatability (doubling the ham and cheese portions of a sandwich) increased postprandial satisfaction with limited effects on satiation.[9] In these experiments we did not perform a dose/response test, and hence, we cannot ascertain how the amount of meal influences the relation between cognitive and hedonic components of the postprandial experience. Conceivably, with small meals satisfaction parallels satiation, but at a certain level of satiation, satisfaction may decline; the factors that determine this yield point are not clear, and our study demonstrates the contribution of preload conditioning in this context.

Our study proves the concept of preload conditioning of the postprandial experience, and conceivably this effect depends on a series of interrelated factors in the conditioning paradigm. In the first place, the effect depends on the characteristics of the preload stimulus.[11–13] In our experimental design we included two breakfasts with different caloric content consumed under standard conditions (previous dinner and overnight fast), and their effect on baseline appetite, specifically on hunger scores two hours later, was distinctively and significantly different, hence, accomplishing the purpose of the preload test.

In previous studies, the effect of preload conditioning on appetite levels and subsequent food consumption was variable.[6,7,14] The relation between the preload amount and the intermeal interval (time lapse between conditioning and probe stimuli) are important, because the effect of the preload fades overtime.[15] Furthermore, food consumption is not only driven by hunger, and other independent factors, such as "wanting", education and personality traits, may have confounded the effect of the preload test in previous studies.[5,16] The impact of these factors was reduced in our design that evaluated the effects after consumption of a standard probe meal.

The probe meal also determines the effect of conditioning.[1,14,16] Indeed, previous studies showed that palatable meals with similar caloric content to the current probe meal but different composition (liquid nutrient preparations) induced satiation with a negative hedonic dimension; ie, a sense of dissatisfaction.[9,10]

The preload test influences appetite by homeostatic and cognitive/psychologic mechanisms, and these factors may be also involved in conditioning the postprandial experience.[5] Indeed, preload conditioning may influence visceral signaling, both gastric and intestinal, post-absorptive effects and the homeostatic responses to the probe meal.[17,18] The individual role of these factors is difficult to determine, because they are interrelated. In a previous study, we showed that experimentally induced fullness sensation by either gastric distension or intestinal nutrient infusion, conditioned the response to a meal and the effect depended on whether nutrient or inert meals were tested. Metabolomic studies showed that the cognitive and hedonic components are related with different blood metabolites.[1] Furthermore, studies with brain imaging indicate that both responses are linked to specific brain activities.[4,19–21] These differences may explain the differential effect of conditioning on the cognitive and hedonic responses to the probe meal.

The effects of preload conditioning, ie, increase in satiety/fullness and decrease in digestive well-being, are potentially relevant for dietary planning in clinical practice, but are still a fragment of information to be considered within a very complex context involving appetite, homeostatic signaling and eating behavior. Conditioning the postprandial experience could also play a role in the management of patients complaining of postprandial symptoms.[22] On the other hand, in the context of gastronomy, our data indicate that when considering the dining experience, the guest's previous meal may have to be taken into consideration.

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AUTHOR CONTRIBUTIONS

TP: study management, conduction of experiments, data analysis; AN: conduction of experiments; LH: conduction of experiments; CM: supervision of statistical analysis; AA: supervision of studies; FA: study design, data interpretation, and manuscript preparation.

CONFLICT OF INTEREST

No competing interests declared.

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ABSTRACT

Background: Ingestion of a meal induces homeostasis-related sensations (satiety/fullness) that have a hedonic dimension (satisfaction/mood). We have previously shown that a previous physiological intervention, a meal preload, influences the responses to a subsequent meal, specifically: it increases satiety/fullness and decreases satisfaction. We now wished to determine the differential effects of education on the homeostatic and hedonic postprandial experience.

Methods: Randomized, parallel study comparing the effect of real vs sham education on the responses to a probe meal. In two groups of healthy subjects (n = 14 each), homeostatic (satiety, fullness) and hedonic sensations (digestive well-being, mood) in response to a probe meal (250 mL soup, 25 g bread) were measured on 2 separate days before and after a single sensory-cognitive educational intervention (taste recognition test of supra-and sub-threshold tastands for real and sham education, respectively).

Key Results: Before education, in both groups the probe meal induced homeostatic sensations (satiety, fullness) with a positive hedonic dimension (increased digestive well-being and mood). In contrast to sham education, real education enhanced both homeostatic and hedonic responses to the probe meal ($P < .05$ vs sham education for all).

Conclusions and Inferences: Education modifies the subjects′ receptiveness and influences the responses to a meal, not only the hedonic postprandial experience, but also homeostatic sensations. Since homeostatic and hedonic responses are dissociable, education might be tailored to target different conditions.

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ORIGINAL ARTICLE

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Education of the postprandial experience by a sensory-cognitive intervention

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Abstract

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KEYWORDS
appetite, education, hedonic response, meal ingestion, postprandial sensations, taste recognition test

1 | INTRODUCTION

Ingestion of a meal activates the digestive system and induces a metered response to accomplish food digestion.[1-3] Meal ingestion also activates the central nervous system and induces conscious sensations, such as satiation and fullness, involved in the homeostatic control of eating behavior.[4] The response to a meal has also a hedonic dimension that influences digestive well-being and mood.[1,5,6] The responses to a meal depend on different factors including the characteristics of the meal and the individuals' responsiveness,[5-12] and these factors may affect differently homeostatic and hedonic sensations. For instance, we recently showed that a preload modifies

the individuals' predisposition to ingestion (reduces appetite) and thereby increases homeostatic sensations (satiety, fullness) and impairs the hedonic response (satisfaction, mood) to a subsequent meal.[6]

The potential to influence the individuals' responsiveness to meal ingestion may have practical relevance in promoting a healthy eating behavior, as well as in clinical conditions involving impaired, excessive or painful eating, eg, nutritional deficit, overweight or functional dyspepsia, respectively. Sensory-based food education programs have shown to increase willingness to try vegetables, berries and the preference for novel foods in children.[13,14] Based on these data we hypothesized that education increases the hedonic responses to a meal, and our aim was to determine the differential effects of education on the homeostatic and hedonic postprandial experience. To this aim, we designed a pilot, proof-of-concept study to compare in a parallel design the effect of real vs sham education on the responses to a probe meal. Since, cognitive interventions have been also shown to influence the responses to a meal,[8,15] we developed an educational procedure that combined a sensory training experience plus a cognitive intervention, to maximize its potential effects. As probe meal we used a soup with a rich, complex and unconventional flavor that was tested before and after a single educational intervention. The changes in the responses after real education were compared to those after sham education.

Key Points

- Ingestion of a meal induces homeostasis-related sensations (satiety/fullness) that have a hedonic dimension (satisfaction/mood).
- Education influences both homeostatic and hedonic responses to a meal.
- Since homeostatic and hedonic responses are dissociable, education might be tailored to target different conditions.

2 | MATERIALS AND METHODS

2.1 | Participants

Twenty-eight healthy, non-obese men, non-dieting and weight-stable without history of gastrointestinal symptoms were recruited by public advertising to participate in the study. Exclusion criteria were chronic health conditions, prior obesity, use of medications (except sporadic use of NSAIDs and antihistaminics), history of anosmia and ageusia, current dieting or any pattern of selective eating such as vegetarianism, alcohol abuse and use of recreational drugs. Absence of current digestive symptoms was verified using a standard abdominal symptom questionnaire (no symptom >2 on a 0-10 scale). Psychological and eating disorders were excluded using the following tests: Hospital Anxiety and Depression scale (HAD), Dutch Eating Behavior Questionnaire (DEBQ – Emotional eating, External eating, Restrained eating), and Physical anhedonia scale (PAS). Candidates were asked whether in principle they liked vegetable soup (the probe meal to be used; see below) and those who did not were not included.

The protocol for the study had been previously approved by the Institutional Review Board of the University Hospital Vall d'Hebron, and all participants gave written informed consent.

2.2 | Experimental design

This study was a randomized, single-center, parallel and single-blind study performed between November 2016 and January 2017. The study investigated the effect of a sensory-cognitive educational intervention on the postprandial experience by comparing the effect of real vs sham education on the responses to a probe meal. The study protocol was registered with the ClinicalTrials.gov (NCT02997917). All coauthors had access to the study data and reviewed and approved the final manuscript.

2.3 | General procedure

In each group the responses to the same probe meal were measured on two consecutive days before and after the educational intervention. The intervention was performed on the first study day 90 minute after the meal test. For both study days, participants were instructed to refrain from strenuous physical activity and to eat a standard dinner the day before (100 g chicken, 50 g rice, 50 g white bread and 1 apple; 503 Kcal, 7 g fat, 82 g carbohydrates, 30 g protein), to refrain from smoking on the study day, to consume only a standard breakfast at home after overnight fast (200 mL coffee with semi skimmed milk and sandwich with 50 g white bread, 30 g ham and 40 g cheese; 338 Kcal, 11 g fat, 38 g carbohydrate g, 24 g protein), and to report to the laboratory, where the probe meal was administered 3 hours after breakfast. Studies were conducted in a quiet, isolated room with participants sitting on a chair. Perception was measured at 5 minute intervals 10 minute before and 20 minute after ingestion, and at 10 minute intervals up to 60 minute after the probe meal. For this pilot study, no formal sample size calculation was performed.

2.4 | Randomization and masking

Participants were randomized by a computer generated randomization list. Participants did not know whether they were assigned to receive the real or the placebo education, and all underwent the same interventions.

2.5 | Probe meal

The probe meal consisted of 250 mL vegetable soup and 25 g white bread (Pan de molde blanco sin corteza, Hacendado, Valencia, Spain). As in previous studies,[1] the soup was administered at controlled

TABLE 1 Education procedure

Tastands	Detection threshold	
	Supra-threshold[a]	Sub-threshold[b]
Sweet: glucose, %[c]	10	0.5
Salty: NaCl, %[c]	0.9	0.05
Umami: monosodium glutamate, %[c]	1.5	0.02
Sour: citric acid, %[c]	0.5	0.025
Bitter: quinine, %[c]	0.01	0.00006
Carrot broth	Original	99.40% dilution
Leek broth	Original	99.85% dilution
Onion broth	Original	99.85% dilution

[a]Real education.
[b]Sham education.
[c]% = g/100 mL water.

temperature (55°C) and at a standard rate: 50 mL soup and 5 g bread were administered every minute (total ingestion time 5 minute). The main ingredients of the soup were onion, leek and carrot cooked at low temperature to enhance their flavor.

2.6 | Perception measurements

Four 10 cm scales graded from −5 to +5 were used to measure: (i) palatability (very bad-disagreeable/very good-delicious), (ii) hunger/satiety (extremely hungry/completely satiated), (iii) digestive well-being (extremely unpleasant sensation/extremely pleasant sensation) and (iv) mood (negative/positive); two additional 10 cm scales graded from 0 (not at all) to 10 (very much) were used to measure: (v) abdominal bloating-fullness, and (vi) discomfort-pain. Subjects received standard instructions on how to fill-out the scales.[1,5] The palatability scale was only scored immediately after ingestion of the probe meal.

2.7 | Educational intervention

The educational procedure consisted of a sensory training experience combined with a cognitive intervention, whose rationale was to enhance the participants' sensory discrimination and their taste awareness of the probe meal. Solutions of the five basic tastes (sweet, salty, umami, sour, and bitter) and broths of the 3 main components of the probe soup (carrot, onion and leek) were used. Solutions at supra- and sub-threshold concentrations for detection were prepared based on published data [16-18] by a series of preliminary studies in a group of healthy subjects, testing progressively increasing dilutions of the original preparations (Table 1). Solutions (10 mL of basic tastes and 20 mL of each component of the soup) were given every 10 minute with a mouth rinse after each test. Subjects were instructed that they were going to test a series of solutions and that after each test they had to score the sensation of sweet, salty, umami, sour and bitter on 0-10 scales (tasteless—very intense taste), and palatability on a −5 to +5 score scale (see above).

In the real education group, supra-threshold solutions of each tastand (Table 1) were given, and after each test the investigator described the characteristics of the solution tested. At the end of the tasting procedure, the investigator described the main ingredients of the soup (carrot, onion, leek) and its special preparation by prolonged cooking at a low temperature to preserve and potentiate the flavor of its components. In the sham education group, sub-threshold tastands (Table 1) were tasted and rated with no explanation provided.

2.8 | Statistical analysis

Statistical analysis was performed using the GraphPad Prism version 6.00 for Windows statistical package, (GraphPad Software, La Jolla, California www.graphpad.com). Mean (±SE) palatability scores and basal sensations (average of the 3 premeal measurements) were compared between study groups. Normality of data distribution was evaluated by the Kolmogorov–Smirnov test. Comparisons of parametric, normally distributed data were made by Student's *t*-test, paired tests for intragroup comparisons and unpaired tests for intergroup comparisons; otherwise, the Wilcoxon signed-rank test was used for paired data within groups, and the Mann–Whitney *U*-test for unpaired data between groups.

Temporal responses to meal ingestion on each study day were analyzed using one-way ANOVA for repeated measurements of the whole curve (10 minute pre and 60 minute postprandial period); when the ANOVA was significant, posthoc comparisons between time and points were performed applying the Bonferroni multiple comparison correction procedure. Previous studies with the same type of meal showed that the effects of the meal (and the differences between experimental conditions) were more prominent in the early postprandial period. For this reason, the effect of education (pre vs after and real vs sham) was evaluated using the first three time-points after the meal. In each group, comparisons between pre- and after education (day effect) were performed with a two-way repeated measure ANOVA (dependent variable: first three postprandial sensations scores normalized from basal; within-subjects factors: time and day). Comparisons between real and sham education (education effect) were performed with a two-way mixed ANOVA (dependent variable: change in normalized postprandial sensations from day 1 to day 2; within-subjects factor: time; between-subjects factor: education). ANOVA assumptions were checked and when sphericity was violated, Greenhouse–Geisser correction was applied.

3 | RESULTS

3.1 | Demographics and study compliance

No demographic differences were detected between the control group (20-37 years age range; 19.5-24.9 kg/m^2 BMI; 11.7 ± 1.1 stools per week; 3.5 ± 0.2 score on the Bristol stool form scale) and the education group (20-45 years age range; 21.5-24.7 kg/

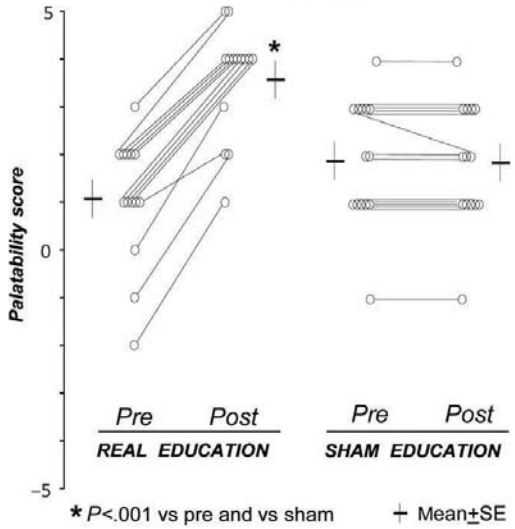

FIGURE 1 Effect of education on food liking. Real education increased the palatability of the probe meal (pre- vs post by paired Student's *t* test), whereas sham education had no effect. The effect of real education (post minus prescores) was significantly higher than that of sham education (by unpaired Student's *t* test). Individual data and mean ± SE shown

m^2 BMI; 12.5 ± 0.9 stools per week; 3.8 ± 0.1 score on the Bristol stool form scale). All participants completed the tests (n = 14 per group) and were included for analysis. In each test, participants followed the instructions and ingested the probe meal at the rate indicated.

3.2 | Control group: Within-group analyses

3.2.1 | First study day (pre-education)

Before the probe meal, participants reported significant hunger (negative hunger/satiety scores) without fullness, neutral digestive well-being and positive mood (Figure 2). Participants found the probe meal palatable (Figure 1). Meal ingestion induced satiety, some degree of fullness, and sensation of digestive well-being (main time effect $P \leq .001$ for all; see Table 2) (Figure 2). These sensations gradually decayed (Figure 2), but posthoc comparisons showed that all scores remained significantly higher than premeal scores (applying Bonferroni multiple comparisons correction) throughout the observation period, except for fullness, which fell to premeal levels 15 minute after meal ingestion.

3.2.2 | Sham education

All sub-threshold tastands were rated alike (Figure 3).

3.2.3 | Second study day (after sham education)

Baseline conditions before ingestion (mean premeal values day 1 vs day 2) and palatability of the soup were similar to day 1. The responses to the probe meal were all similar to day 1 without significant differences between both study days in any of the parameters tested (main time effect $P < .001$ for all; main day effect $P > .25$ for all) (Table 2 and Figures 1 and 2).

3.3 | Education group: Within-group analyses

3.3.1 | First study day (pre-education)

As in the sham education group, before the probe meal participants were hungry and on a positive mood (Figure 2), and found the soup palatable (Figure 1). Meal ingestion induced satiety, fullness, sensation of digestive well-being and enhanced mood scores (main time effect $P < .004$ for all; see Table 2) (Figure 2). Postprandial scores gradually decayed (Figure 2), but posthoc comparisons showed that all scores remained significantly higher than premeal scores (applying Bonferroni multiple comparisons correction) throughout the observation period except for fullness and mood, which fell to premeal levels 20 minute after meal ingestion.

3.3.2 | Real education

In the real education group, participants distinctively recognized the five basic tastands and a sweet-salty-umami pattern in the carrot, leak and onion broths (Figure 3).

3.3.3 | Second study day (after real education)

As compared to the first study day, before the meal, participants reported somewhat more hunger ($P = .006$) and lower digestive well-being ($P = .005$). The second study day, the palatability score (Figure 1) was higher than the first study day ($P < .001$).

The responses to the probe meal were more pronounced than during the first study day (main time effect $P < .001$ for all) with significant main day effect for satiety [$F(1,13) = 28.5$; $P = .001$] fullness [$F(1,13) = 8.1$; $P = .014$] and well-being [$F(1,13) = 30.8$; $P < .001$] with a trend for mood [$F(1,13) = 3.5$; $P = .085$] (Table 2).

3.4 | Effect of sham vs real education: Between-group analyses

3.4.1 | First study day (pre-education)

No consistent differences in baseline conditions, palatability of the soup and in the responses to the probe meal were detected between the education and the control group, except for somewhat less hunger before the meal ($P = .034$) (Figure 1 and 2).

TABLE 2 Statistical data

	Satiety	Fullness	Well-being	Mood
Temporal responses to meal[a]				
Before sham education (day 1)				
Time effect	F (3.0, 39.0) = 27.5 $P < .001$	F (2.6, 33.4) = 9.4 $P < .001$	F (2.2, 28.7) = 9.2 $P < .001$	F (1.9, 25.2) = 2.3 $P = .123$
After sham education (day 2)				
Time effect	F (3.2, 42.7) = 28.7 $P < .001$	F (2.6, 33.2) = 10.0 $P < .001$	F (3.8, 49.0) = 19.0 $P < .001$	F (2.1, 27.0) = 1.0 $P = .375$
Before real education (day 1)				
Time effect	F (2.1, 27.9) = 12.7 $P < .001$	F (2.8, 36.7) = 10.8 $P < .001$	F (3.2, 41.8) = 14.0 $P < .001$	F (3.2, 42.0) = 4.0 $P = .004$
After real education (day 2)				
Time effect	F (2.5, 32.7) = 47.2 $P < .001$	F (3.9, 51.3) = 40.0 $P < .001$	F (3.0, 29.3) = 41.2 $P < .001$	F (3.3, 42.8) = 6.9 $P < .001$
Pre- vs after education[b]				
Sham education (day1 vs day 2)				
Time effect	F (2, 26) = 1.41 $P = .263$	F (2, 26) = 2.91 $P = .072$	F (2, 26) = 3.14 $P = .060$	F (2, 26) = 0.134 $P = .875$
Day effect	F (1, 13) = 0.289 $P = .599$	F (1, 13) = 1.43 $P = .252$	F (1, 13) = 0.904 $P = .359$	F (1, 13) = 0.967 $P = .343$
Time[a] day interaction	F (2, 26) = 1.00 $P = .382$	F (2, 26) = 1.51 $P = .240$	F (2, 26) = 0.157 $P = .856$	F (2, 26) = 0.134 $P = .875$
Real education (day 1 vs day 2)				
Time effect	F (2, 26) = 1.05 $P = .366$	F (2, 26) = 1.44 $P = .256$	F (2, 26) = 0.426 $P = .657$	F (2, 26) = 0.684 $P = .513$
Day effect	F (1, 13) = 28.5 $P = .001$	F (1, 13) = 8.1 $P = .014$	F (1, 13) = 30.8 $P < .001$	F (1, 13) = 3.48 $P = .085$
Time[a] day interaction	F (2, 26) = 1.93 $P = .165$	F (2, 26) = 0.220 $P = .804$	F (2, 26) = 3.85 $P = .034$	F (2, 26) = 1.71 $P = .201$
Sham vs real education[c]				
Time effect	F (2, 52) = 2.51 $P = .092$	F (2, 52) = 0.676 $P = .513$	F (2, 52) = 1.99 $P = .147$	F (2, 52) = 0.597 $P = .554$
Education effect	F (1, 26) = 16.5 $P = .004$	F (1, 26) = 8.76 $P = .007$	F (1, 26) = 13.6 $P = .001$	F (1, 26) = 4.4 $P = .046$
Time[a] education interaction	F (2, 52) = 0.769 $P = .469$	F (2, 52) = 1.05 $P = .356$	F (2, 52) = 1.23 $P = .299$	F (2, 52) = 1.26 $P = .292$

[a]One-way ANOVA. Dependent variable: all pre- and postprandial values.
[b]Two-way repeated measures ANOVA. Dependent variable: three-first postprandial values normalized from basal.
[c]Two-way mixed ANOVA. Dependent variable: change in three-first postprandial values normalized from basal, from day 1 to day 2.

3.4.2 | Education

In the real education group, ratings of the five basic tastes were significantly different than the corresponding sub-threshold solutions in the sham education intervention ($P < .001$ for all). NaCl (salty) and citric acid (sour) solutions were also scored a mild umami taste ($P = .035$ and $P = .017$ vs sub-threshold tastands, respectively) and the bitter taste was found disagreeable (−3.7 ± 0.4 palatability score vs −0.2 ± 0.2 score with the sub-threshold tastand; $P < .001$). All 3 components of the soup (carrot, leak and onion broths) were found palatable (1.7 ± 0.4 score, 2.1 ± 0.3 score, and 2.9 ± 0.3 score, respectively; $P < .001$ vs respective sham solutions for all) and with a different sweet-salty-umami pattern than the sham solutions.

3.4.3 | Second study day (after real education)

Baseline sensations before the meal were similar as in the control group. The second study day after the education intervention, the palatability score (Figure 1) was higher than in the control group ($P = .001$).

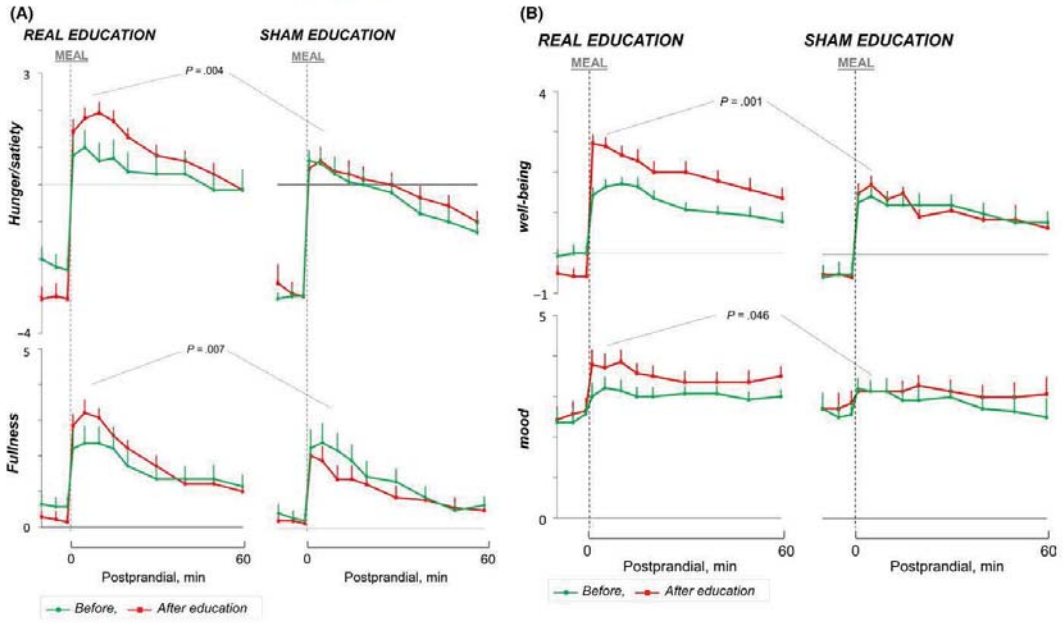

FIGURE 2 Effect of education on the homeostatic (A) and the hedonic responses (B) to a probe meal. Real education increased both the homeostatic responses and hedonic responses to the probe meal, whereas sham education had no effect. For clarity, only *P* values corresponding to education effect are shown: comparisons between real and sham education (education effect) were performed with a two-way mixed ANOVA using the change in postprandial sensations (first 3 time-points after the meal normalized from basal) from day 1 to day 2. All sensations measured on 10 point scales (fullness scored from 0 to 10, and hunger/satiety, well-being and mood from −5 to +5). Data are mean ± SE

The change produced by real education (increase in sensation scores from day 1 to day 2) was significantly different than that of sham education (no change) with significant main education effect for satiety [F (1,26) = 16.5; *P* = .004], fullness [F (1,26) = 8.8; *P* = .007], well-being [F (1,26) = 13.6; *P* = .001], and mood [F (1,26) = 4.4; *P* = .046] (Table 2).

4 | DISCUSSION

Our study demonstrates that education modifies the subjects' receptiveness and influences the responses to a meal, not only the hedonic postprandial experience, but also homeostatic sensations.

The probe meal used in our study induced a clear and consistent response, involving homeostatic sensations with a positive hedonic dimension, ie, pleasant satiety/fullness sensation. In contrast to sham education, real education had a series of significant effects: (i) participants were hungrier before the probe meal, (ii) rated the probe meal more palatable, (iii) experienced more postprandial satisfaction and (iv) reported higher satiety and fullness sensation. Different mechanism could mediate these effects of education on the responses to a meal (Figure 4).

In the first place, increased *hunger sensation* before the second probe meal could be related to the dinner's sensory expectation, ie, "anticipatory reward", induced by the educative intervention.[12,19] It has been shown that a milkshake presented as high-calorie, high-fat, indulgent product elicited a higher rise in ghrelin in anticipation to ingestion, a marker to hunger, than when the same shake was presented as low-calorie, low-fat, sensible product.[15]

Higher *palatability* of the probe meal, indicative of "meal liking", could be directly related to enhance sensory discrimination by the taste identification test in the education procedure.[12,19] Higher palatability could be also related to more hunger before the meal: in a previous study, appetite experimentally manipulated by a preload test, was directly related to higher palatability ratings of a subsequent probe meal.[6]

The increased *hedonic response* to the meal after education, an indication of "consummatory reward", could be related to several factors, among them appetite. Indeed, in the previous preload experiments, more hunger before ingestion was associated to more postprandial satisfaction.[6] This could be considered an extension of the concept of alliesthesia, postulating that the hedonic responses depend on the internal state.[10] Furthermore, increased palatability may have also played a role, because under equal conditions, postprandial well-being is directly related to meal palatability. It has been shown that postingestive signals influence perceived pleasantness. Our study demonstrates a component of perceived

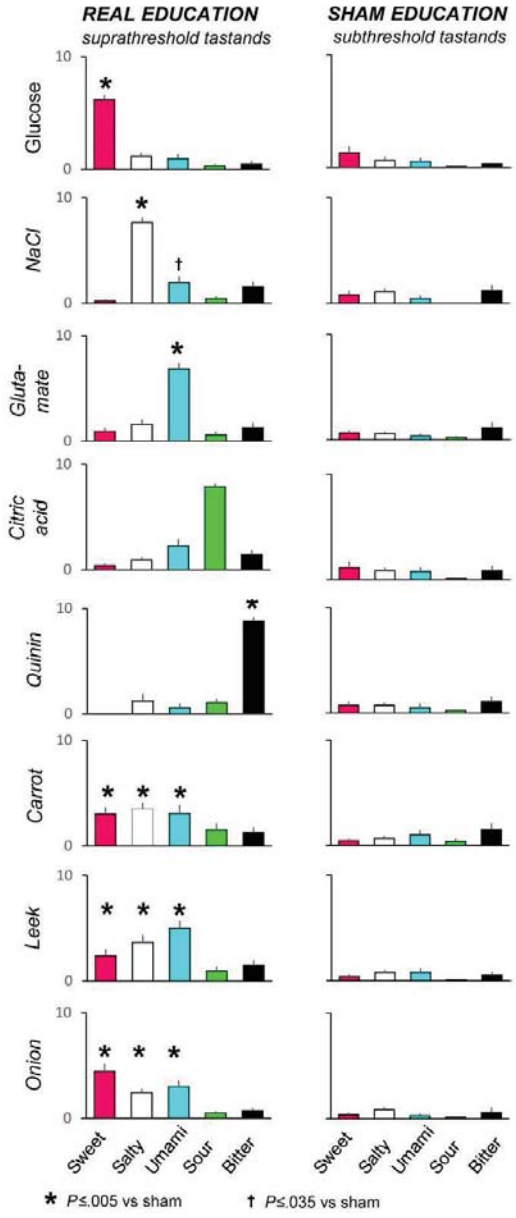

FIGURE 3 Responses to tastands. Supra-thresholds tastands in the real education intervention elicited distinctive gustatory responses, whereas sub-threshold tastands in the sham education intervention did not. Data are mean ± SE

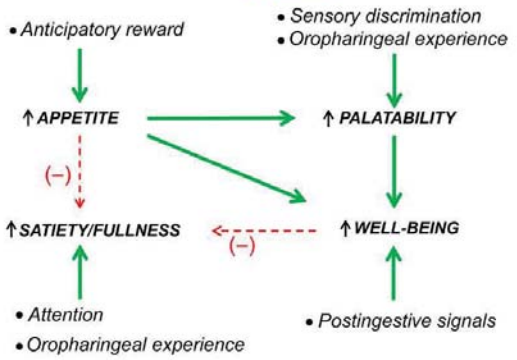

FIGURE 4 Effects of education on the responses to a meal: potential mechanisms. Education resulted in a significant increase in hunger (appetite), meal palatability, postprandial digestive well-being and satiety/fullness; arrows indicate potential influences either potentiation (green) or inhibition (red)

pleasantness that can be activated by a previous educational intervention. However, whether this component is independent of postingestive signals, is not clear, because it has been shown that the physiological responses to a meal (changes in ghrelin blood levels) can be modified by a cognitive intervention influencing mindset before ingestion.[15]

Interestingly, education also increased *postprandial satiety and fullness sensation*. The effects of education on homeostatic sensations seem not related to the hedonic responses, because the mechanisms that may increase hedonic sensations, ie, hunger and meal palatability, have been shown to reduce homeostatic sensations.[6,20] Hence, the influence of education on postprandial satiety/fullness observed might be mediated by independent mechanisms, such as mindset, attention and more intense oropharingeal experience. Previous studies modulating attention/distraction indicated that attention increases perception of intestinal stimuli,[21] as well as fullness sensation after a meal,[22] and conceivably, the degree of the dinner's attention to the probe meal was enhanced by education. On the other hand, it has been shown that slower eating rate prolongs oropharingeal signaling and increases satiation, reduces meal consumption and increases postprandial fullness.[23-26] In our study, both the eating rate as well as the amount of the probe meal consumed were fixed, but it could be speculated that sensory education enhanced the oropharingeal experience and stronger signaling increased satiety and fullness.[27-29]

Our proof-of-concept study demonstrates the potential effects of education on the responses to food ingestion. We designed the study with the educational intervention shortly after the first exposure to the probe meal, but the influence of the timing of the intervention with respect to the probe meals and the participant's digestive status, ie, fasting or fed state, is not known. Furthermore, education involved both a cognitive intervention and a sensory training experience; arguably, the latter may be stronger, but our study does not discriminate the contribution of each component. In our paradigm, education enhanced the rewarding value of the meal, increasing both satiation and satisfaction in parallel. This double homeostatic and hedonic effect could be applicable to promote healthy

eating behavior. However, since both dimensions are dissociable, education might be potentially tailored to produce differential effects. Indeed, education could focus on emotional aspects targeting the motivational value of reward clues, the reward seeking behavior and the valence of sensations.[9,19] Innocuous digestive sensations may become frightful through associative learning [30] and even palatable foods may become aversive as a consequence of a postingestional unpleasant experience.[31] Hence, education may imprint long-lasting conditioning effects with practical implications. By increasing satiety and decreasing satisfaction, education could discourage unhealthy eating behavior, making unhealthy foods more satiating and less rewarding. On the other hand, decreasing satiety/fullness and increasing the hedonic response could help in patients with impaired appetite and deficient caloric intake. It is tantalizing to conceive that education, by reducing homeostatic sensations and increasing the hedonic dimension, could improve meal tolerance in patients with functional gut disorders and reduce early satiation and aversive postprandial fullness sensation.[32,33]

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AUTHOR CONTRIBUTIONS

TP study management, conduction of experiments, data analysis; HV study design, probe meal, data interpretation; AN conduction of experiments; LH conduction of experiments; CM statistical analysis; AA supervision of studies; JR study design, probe meal, data interpretation; FA study design, data interpretation and manuscript preparation.

CONFLICT OF INTERESTS

No conflict of interests declared.

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DISCUSSION

Ingestion of a meal activates a series of receptors, initially linked to cranial nerves, during the cephalic phase, and subsequently, gastrointestinal receptors linked to myenteric and autonomic (predominantly vagal) afferents. Most of these afferents are linked to reflex pathways controlling the digestive response to the meal, but some afferents ascend up to the brain and mediate cognitive and hedonic responses.[3]

Our data show that meal ingestion influences brain activity, and that the responses of specific brain networks are related to homeostatic postprandial sensations and their hedonic dimension. Hence, changes in brain network activity, measured by functional magnetic resonance and resting-state paradigm, identify the brain substrates of cognitive/hedonic responses to a meal and may serve as biomarkers and objective surrogates of subjective perception.

In our study only one postprandial scan was acquired, so that our results are related to the early postprandial phase. The first-day experiment with sequential measurements of sensations showed specific time effects: while satiation and fullness partially reverted by 30 min, the effects of meal on digestive well-being and mood were more prolonged. Conceivably sequential scanning along the postprandial period may allow to study the dynamic relation of the cognitive to hedonic responses along the postprandial period.

The meal induced changes in intranetwork connectivity of sub-thalamic regions and resting state networks implicated in sensory, reward and motivation regions. These changes may indicate increased transmission of visceral and

gustatory signals from the thalamus to other brain regions as well as the implication of the brain's reward region in the perception of the postprandial experience. The changes observed in thalamic intrinsic connectivity appear to be related to the achieving of the homeostatically favorable state.[258] The ventral medial nucleus receives direct input from the vagal nucleus of the solitary tract, which conveys visceral and gustatory afferent activity, and projects to the anterior insula.[258, 259] Anterior insula is the overlapping region of the homeostatically-relevant and reward related brain networks which plays a role in the eating behavior and the awareness of food derived sensations.[260] Existing data suggest that anterior insula, as part of the primary taste cortex, contains taste neurons for encoding all five basic tastes.[261] Additionally, it appears to be a processing center for sensations from oral cavity such as temperature and texture of the food.[262] In our study the probe meal induced reduction in connectivity of the bilateral anterior insula which may reflect a reduction of communication within key regions of the salience network following meal ingestion.

We have identified objective changes in brain connectivity after meal ingestion under physiological conditions and intended to comprehend some of the mechanisms which influence the homeostatic and hedonic aspects of the postprandial experience. In clinical setting brain imaging studies may help to

elucidate the entire impact of meal-related complaints in patients with functional gastrointestinal symptoms.

Meal ingestion induces satiety and fullness and these homeostatic sensations have a hedonic dimension involving digestive well-being and mood.[45] The postprandial experience depends on the characteristics of the meal as well as on the features of the subject which can be impacted by a large variety of conditioning factors. The effect of a specific factor can be tested keeping constant the rest. These factors are not independent one of the other and any classification is rather artificial. In principle, in fasting, hungry subjects, consumption of an appetizing, pleasurable meal up to a level of satiation/fullness, i.e. hunger suppression, should have a positive hedonic dimension with pleasurable sensation of digestive well-being and satisfaction. Independent studies have demonstrated that the digestive well-being depends on a proper digestive response to the meal: experimental distortion of digestive function, for instance increasing intragastric pressure by a barostat, induced satiation with a negative sensation of digestive well-being.[45] Eventually, the characteristics of the meal and external conditioning factors influence the receptiveness and responsiveness of the subject.

Both the palatability and the composition of the meal play an independent role. Previous studies have shown that equally likable meals, i.e. with the same level of palatability, but different composition produced

distinctively different homeostatic and hedonic postprandial responses, in such a way that satiety/fullness may have a pleasant or an aversive dimension.[73] A recent study from our laboratory showed that as compared to a light meal, a meal high in fat content, but with otherwise identical characteristics, presentation and palatability induced more satiety and fullness, but less satisfaction (unpublished data).

Our studies have shown that the postprandial experience is not only conditioned by the characteristics of the meal, but also by the status of the eater. Different approaches can be undertaken to classify the factors not directly related to the meal that can influence the individual responsiveness and the postprandial experience. Subject related determinants such as homeostatic and innate factors as well as education act in cohesion to shape postprandial experience. The intrinsic innate factors seem to have the preconditioning effect. However, it is not known whether the part of the population which possesses the ability for finer taste distinction has as well different postprandial experience.[80, 200]

We demonstrated that a breakfast preload influenced the responses to a test meal eaten 2 hours later. The characteristics of the preload had a determining impact on the subsequent meal. The high-calorie breakfast reduced appetite and induced more satiety and fullness but lower postprandial satisfaction as compared to a light breakfast. Additionally, the later meal was

found less palatable. The high-calorie preload induced physiological (homeostatic) effects that influenced the postprandial response to the subsequent meal.

Our studies showed that education conditioned both homeostatic and hedonic responses to the meal ingestion. The mechanisms by which education influences the postprandial experience are not clear and several factors could contribute to the final effect. The impact that cognitive intervention had on the attention of the subjects may have influenced fullness sensation as well as the perception derived from the stimuli originated in digestive tract in general.[41, 263] The “anticipatory reward” produced by the educational intervention could be the reason for increased hunger sensation before the second test meal.[165] Additionally, slower meal ingestion rate prolongs oropharyngeal signalling and increases satiation and by that reduces the quantity of the ingested meal and increases postprandial fullness.[264-266]. Sensory training applied in our experimental design may have refined the oropharyngeal signalling and together with standardized meal ingestion contributed to the increased perception of satiety and fullness.[267]

Cognitive intervention and sensory training influenced meal liking and upgraded the sensory discrimination.[123, 165] Food liking is directly interconnected with the reward derived from the eating experience as it constitutes the anticipation of the hedonic event produced by orosensory stimulation.[268] Increased food liking and, therefore, increased anticipation leads to more

pronounced sensation of hunger prior to the consumption of a meal. These events in turn lead to increased appetite which may have reflection on the mechanisms of overeating causing the altered hedonic set-point.[68, 183]

Concurrent conditioning may also involve emotional or cognitive mechanisms, but their potential effect on the postprandial experience has not been formally investigated. Factors such as stress, attention and expectation remain incompletely understood. Environmental conditioning (fragrance, temperature, light, sound), meal presentation and company have impact on meal selection and eating behaviour, but their influence on the postprandial experience has not been investigated.

Some patients with functional gut disorders complain of meal-related symptoms under certain conditions.[5] The hedonic dimensions of the response to a meal in this context may play an important role in patients´ behaviour. Cognitive educational interventions may help change the expectations related to a particular meal and, thus, a subsequent energy intake by “re-educating” some aspects of eating behaviour. Our findings, obtained in the exploration of the postprandial experience, may be applicable to public health strategies and dietary planning in the management of obesity, eating and functional gastrointestinal disorders.

CONCLUSIONS

1. The functional magnetic resonance and resting state paradigm procedure is reliable for the evaluation of the postprandial experience; because postprandial sensations measured during the brain imaging procedure were similar as during physiological conditions.
2. Perceptual and emotional responses to food intake are related to brain connectivity in defined functional networks in conjunction with resting-state paradigm.
3. Functional magnetic resonance in conjunction with resting-state paradigm may provide objective biomarkers of subjective effects of meal ingestion.
4. Physiological conditioning by appetite modulation influences the postprandial experience with differential effects on the homeostatic and hedonic components.
5. Cognitive conditioning by education modifies the subjects´ receptiveness and influences the responses to a meal, not only the hedonic postprandial experience, but also homeostatic sensations.

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