article

The Total Food Effect: Exploring Placebo Analogies in Diet and Food Culture

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Food and medicine share an inseparable history with essential evolutionary underpinnings. In addition to nutritional, medicinal or toxic components, the tastes, colours, shapes, names and labels of foods elicit emotions, expectations, associations and conditioned responses rooted within both public consciousness and individual experience. This combination of chemical-driven bottom-up and meaning-driven top-down influences provides a fertile framework through which to explore metaphors of placebos and placebo-like effects. As reviewed, elements of placebo are widespread in food culture, appearing in numerous forms and with varying degrees of resemblance to those observed in medicine. We first adapt a model of placebo from the medical literature for application to the subject of food, diet and nutrition. Exploring the intricate interactions between drug or food, patient or consumer, and doctor or food source within different settings and contexts, we then demonstrate that the total effect of any food, meal or diet is seldom, if ever, strictly a function of nutritional composition or chemically-driven bottom-up effects. In closing, we summarize and integrate our observations relative to current understandings of placebo effects in medicine.

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Introduction

Central to human health and survival, food and medicine share an inseparable history with essential evolutionary foundations (Johns, 1999). In Chinese, Ayurvedic and Hippocratic-derived traditions, many indigenous healing practices and modern biomedicine alike, diet and nutrition are vital components of health maintenance and recovery from disease. Like medicines, foods contain biologically-active chemicals but also carry social and cultural meanings that contribute to their impact on our personal and collective health (Etkin, 1986). A distinction between food and medicine that emerged in the 19th and 20th centuries sets Western industrialized societies apart from most of world`s indigenous cultures of the past and present (Etkin & Johns 1998). Even in Westernized cultures, items such as vitamins, coffee, wine and `magic` mushrooms straddle the line while healthy eating movements and the health food industry are trying to erase it altogether.

In this light, the concept of placebo, generally defined in medical terms, may extend to our experiences of food and diet. Although the idea of a placebo hamburger may at first seem far-fetched (or like a dieter`s dream), a more nuanced approach reveals that food-related placebos and placebo effects abound—even if they, like their medical counterparts, appear in different forms and contexts.

A brief survey of food-related placebos and placebo effects

In clinical research, whether pharmacological or nutritional, placebos serve to control for the effects of time and participation in a study. While treatment with 'pure' placebos is likely less common in clinical nutrition than reports suggest of medical practice (Fässler, Meissner, Schneider, & Linde, 2010), nutritional interventions lacking evidence of efficacy from randomized controlled trials (RCTs) are widespread and may, in effect, constitute 'active' placebos. This is the case for many Complementary and Alternative Medicine (CAM) practices, collectively equated to 'mere' placebos following systematic reviews of RCT data ‡ (Bausell, 2007; Singh & Ernst, 2008). Similarly, some physicians prescribe vitamins in situations without demonstrated or expected clinical efficacy (Raz, et al., 2011; Tilburt, Emanuel, Kaptchuk, Curlin, & Miller, 2008).

A reliable paradigm for placebo research (Fillmore, Mulvihill, & Vogel-Sprott, 1994; Hammami, Al-Gaai, Alvi, & Hammami, 2010; Testa et al., 2006), drug-like foods such as caffeinated or alcoholic drinks and their inactive placebo counterparts offer everyday opportunities to experience placebo effects. For other examples, however, the analogy is more subtle. While food allergies and intolerances are immunologically and metabolically founded, personal experience, conditioning and expectancies undoubtedly influence

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‡ The authors agree that many CAM treatments work through placebo-like mechanisms but disagree that this detracts from therapeutic potential, as evidenced by recent clinical results (Haake et al., 2007; Cherkin et al. 2009).

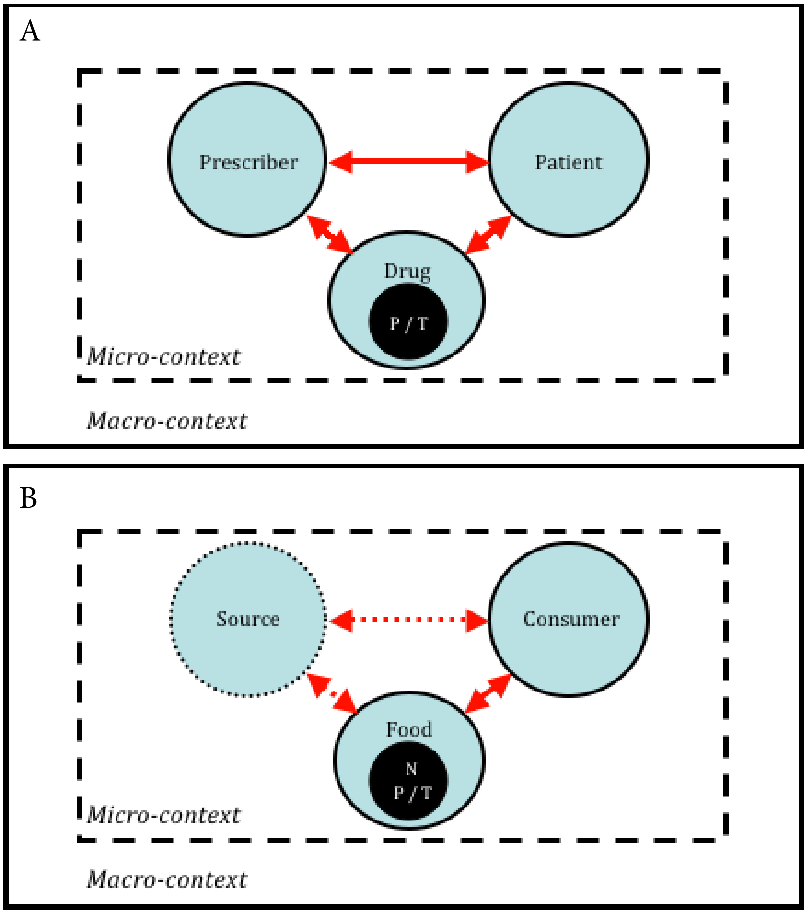

FIGURE 1. (A) **The Total Drug Effect model adapted from Helman (2007) and (B) the Total Food Effect model.** By removing the pharmacological (P), toxicological (T) and/or nutritional (N) components of a drug or food from the model, remaining effects on the patient or consumer can be interpreted as placebo-like and explained through interactions between the remaining elements. The dashed line indicates that the micro-context is distinct from, yet embedded within, the macro-context. The dotted line around the source signifies its potential ambiguity in, or absence from, the total food effect.

individual responses as well. Relatedly, food aversions and taboos, which can also provoke physiological responses when challenged, are founded in personal and cultural beliefs, sometimes with little or no basis in biology. Like taboo foods, comfort and ceremonial foods are defined by specific cultural and religious contexts. Although their chemical composition is often nutritionally or pharmacologically unfavourable, these foods offer a sense of comfort, contentment, tradition and connectedness that nonetheless contribute to mental health and well-being. In many cultures, foods may also be magical, sacred or curative, elevating their spiritual status and psychological impacts (Simoons, 1998)

In Westernized cultures of dieting and health foods, analogies of placebo are hard to avoid. From fad diets to hypnotic suggestions, countless people turn to alternative strategies for losing weight—at times with remarkable success. Conversely, product labels advertising "reduced fat", "low sodium", "organic" or "natural" often mislead consumers into false perceptions of a food's nutritional value, safety or environmental footprint. The expanding and largely unregulated health food* industry markets their products with reference to disease prevention and healthy aging, claims often based in scientific evidence but rarely supported by RCTs as required for pharmaceuticals. Emerging commercial interest in the marketing of functional foods with approved, evidence-based health claims draws attention back to placebos as controls in clinical research.

As illustrated by the examples listed above, whether closely or loosely related to medical placebos, foods are much more than the sum of their chemicals. As symbols, they create meaning that our minds and bodies interpret on a physiological level, influencing our food choices and health for better or for worse. Capturing the multidimensional nature of our relationships and interactions with food is not easily accomplished through a single lens but instead requires an interdisciplinary approach. But where to start?

ADOPTING A MODEL

Social scientists contribute important placebo-related insights on dietary habits, food choice and nutrition (Booth, 1994; Drewnowski & Rolls, 2005; Wansink, 2004). Although direct reference to placebo is rare, elements and terminology such as belief, expectancy, conditioning and context are clearly compatible with medical perspectives. As examined in this two-part special issue, several conceptualizations of placebo remain relevant outside of medicine (Kirmayer, 2011; Moerman, 2011; Orsini & Saurette, 2011). The concepts of 'context effects' (Di Blasi & Kleijnen, 2003) and 'belief effects' (Evans, 2003) also offer insight transferrable to food culture while, serving as a proxy for psychological and cognitive factors contributing to treatment responses in medicine, Moerman's meaning response is especially germane (Moerman, 2002).

As a promising model for exploring placebos in food culture, the "Total Drug Effect" (TDE) forwarded by Claridge (1970) and developed by Helman (2001, 2007) stands out in accommodating interacting contributions of multi-dimensional factors as well as variability in individual responses. According to Claridge (1970), the overall effect of a drug depends not only on its pharmacological properties but on the collective and interacting attributes of the drug, the patient, the physician and the physical setting. By adding the overarching social, cultural, economic

* Foods marketed with claims of improving or maintaining health. Regulated like other foods in the U.S., health foods are regulated separately and more strictly in Canada and many EU nations.

and political environment (macro-context) to the physical setting (micro-context) in which drug use takes place, Helman extends the model to all forms of drug use, from pharmaceutical and CAM to recreational and social (Helman, 2001, 2007). We discuss each component of the TDE (Figure 1A) in further detail in the next section but let us first briefly consider *who* consumes *what*, *when*, *where* and *why*.

For the sake of simplicity, we assume that everyone consumes food and medicine. In terms of what is consumed, the list is virtually endless. What constitutes a food or a medicine—and what an individual or society accepts as such—is largely culturally and socially defined though rooted in biological factors such as toxicity, digestibility and palatability (Moerman, 1996). Although people can consume food or medicine whenever and wherever desired, the time and place for eating and medicating are, again, generally prescribed by social and cultural norms. Unlike medicines, however, foods are consumed daily unless unavailable or avoided, from birth until death.

Both food and medicine maintain health and ultimately survival but the reasons people eat differ from those for medicating—at least at the surface. While a complete review of the physiological and psychological mechanisms underlying food choice and dietary habits is beyond the scope of this paper, the influences of homeostasis and reward contribute powerfully and inseparably (Lutter & Nestler, 2009; Volkow, Wang, & Baler, 2011; Zheng, Lenard, Shin, & Berthoud, 2009). People seek medication, food or water to relieve discomfort associated with disease, hunger or thirst. One noteworthy difference is that, whereas most healthy people have little desire to medicate, satiated people often remain motivated to eat. We not only eat to relieve hunger and obtain nutrients but for the sensory satisfaction, the provided comfort and the variety of social and cultural functions food serves. People also eat out of habit regardless of hunger, appetite or need.

Adapting the model

Despite the similarities and associations, the differences between food and medicine require that we redefine certain elements of the TDE model. The proposed Total Food Effect (TFE) nevertheless remains comparable in both structure and concept (Figure 1B). To bridge between models, we often refer to CAM, particularly natural health products as they fall somewhere in the middle of the food–medicine spectrum in terms of both chemistry and regulation.

Natural health products

Naturally occurring substances including vitamins, amino acids or essential fatty acids, probiotics and herbal remedies that are safe, used to restore or maintain health and available without a prescription. (http://www.hc-sc.gc.ca/dhp-mps/prodnatur/about-apropos/cons-eng.php)

Drug to Food

Medical treatments are more than their active or specific components. Treatment can be delivered in many forms (pill, injection, inhalation device, surgical or physical manipulation) that may have distinct colour, shape, size, taste, odour, physical sensation, name and marketing platform. The same is true for foods. Consider the endless variety of candy, each with its own colour, shape and brand name but all primarily from a single ingredient—sugar. Beyond diversity in form, the immediate sensory stimuli associated with eating, including aesthetic appeal, taste, aroma, texture and consistency, provide additional inputs to which the body and mind respond. This sensory richness is influenced by both culture and biology but founded primarily in chemical diversity.

Foods are far more chemically complex than pharmaceutical drugs. Most foods contain a chemical diversity unmatched by even the most complex drug regimen. An apple, for example, contains hundreds if not thousands of different molecules belonging to dozens of distinct chemical classes. Given frequent potential for drug–drug interactions when medications are combined, direct and indirect interactions among apple constituents are inevitable. The assortment of ingredients to make a dish, of dishes to make a meal and of meals to make a diet renders this complexity, together with related biochemical interactions, hard to imagine let alone assess experimentally. Moreover, whereas the specific, chemical-based effects of drugs are rooted in pharmacology and toxicology, such contributions are considered secondary to nutrient content when considering foods.

When lacking, in excess, or simply consumed, nutrients elicit specific responses that influence mood, behaviour and health. As such, we have added a nutritional component to the TFE (Figure 1B, "N"). Pharmacological effects are generally less pronounced with foods, in part because drugs are optimized for potency and in part because highly bioactive natural substances in foods often taste bitter or unpleasant (much like medicines) and may be eliminated or reduced through breeding, processing or cooking. A final distinction of note relates to consistency between products. Among other factors, food chemistry depends on genotype, growth and harvesting conditions, transport and storage, processing and cooking methods, etc. Two apples on the same tree are unlikely to have the same chemistry, much less two apples of different varieties grown in different climates. Conversely, pharmaceutical drugs are produced following strict protocols to ensure that each dose of a given treatment is chemically and visually identical. However, like medicines, even if all apples were identical, the total effect on health would nonetheless depend on the person eating.

Patient to Consumer

Most attributes of a treatment or food can be measured or at least observed directly. Even culturally-derived attributes like name and price usually relate to physical and chemical properties. The attributes of people are far more varied; in addition to physical and socioeconomic traits, people have personalities, experiences, beliefs, expectations and unconscious responses that, together with their individual chemistry and biology, change with time. As such, the transition from patient to consumer is fairly straightforward. Attributes relating to genetics and pre-existing health are similarly applicable to both models for obvious reasons. The role of others, such as personality and expectancies, may be more subtle or variable; shyness, tenacity and suggestibility will manifest themselves differently at the dinner table compared to the doctor's office. For instance, we expect foods to provide flavour, relieve hunger, perhaps lead to intoxication, indigestion, allergic reactions or weight change but, in general, to have no great influence on immediate health and physiology. In this regard, we expect far more of medicines—observable improvements in health or, alternatively, adverse effects.

Prescriber to Source

In Claridge's TDE model (1970), the prescriber, generally a medical practitioner, plays an integral role. Maintaining its central position in Helman's modified model, the prescriber can be a practitioner but also a drug dealer or peer providing access to or information about drug-like substances (Helman, 2001, 2007). In all cases, the component linking treatment to patient is a living person. Consequently, the attributes are human, as for patients and consumers. Affecting both genuine and perceived competence and therefore the TDE (Benedetti, 2010; Moerman, 2002), professional credentials, reputation, bed-side manner and personal appearance are particularly important. But what if no practitioner or prescriber is involved, for example taking ibuprofen to relieve pain based on common knowledge?

For CAM practices, the definition and role of prescriber is evident when seeing a homeopath, healer or other practitioner but begins to blur when self-prescribing herbal remedies or practicing meditation and yoga. The prescriber may resemble the peer in Helman's model—someone or something (like a commercial or website) endorsing or providing access to a given treatment—but may also be interpreted as any step in the physical or philosophical supply chain linking product or practice to consumer: from source of material (e.g. a plant) to producer, distributor and vendor or from source of knowledge (e.g. Hinduism) to philosopher, teacher and text. As a result, the notion of prescriber is better represented by the term source, which we have adopted for the TFE model.

Depending on the consumer and context, the source of a food, meal or diet could encompass the entire food production chain, from farm to table, or simply the final stages to which most industrialized consumers are predominantly exposed. If the latter scenario prevails, the role of individual people, from caregivers and grocers to restaurant staff and celebrity chefs, is once again apparent and salient. Alternatively, if any or all steps in the food supply chain are regarded as the source, the role of specific individuals diminish compared to that assigned to overarching corporations, technologies, policies or ideologies. For people of farming and hunter–gatherer communities, the source may be viewed as soil, sun and water, the fruit of one's labour or spiritual forces.

Information about food and diet in the form of recommendations, health claims, recipes, etc., provided personally or through popular culture and mass-media, can direct choice and impact health outcomes. Attempting to assign such attributes to the source inevitably merges with those of the food, the consumer, and the micro- or macro-context. As such, the source component of the model is illustrated with a dashed line (Figure 1B) to indicate its variable and potentially ambiguous contribution to the TFE.

Micro-context

Characterized by the physical and social setting in which eating or treating take place, the micro-context of most medical treatments involves a consultation in a healthcare-oriented environment with subsequent administration or use of the prescribed intervention on site, at home or wherever else symptomology and compliance dictate. With fewer constraints, people eat virtually anywhere and anytime desired. Little distinction is nonetheless required between the micro-context of the TDE and that of the TFE. Clearly, the type of establishment (or lack thereof, e.g. battlefield bunker, highway) and its related characteristics are central. Beyond structural and sensory elements, micro-context is further defined by geographical location, time of day,

Pure placebos

Interventions containing no active chemicals or components, such as sugar pills and saline injections.

Active placebos

Interventions containing active chemicals or components with no direct effect on the targeted problem, such as antibiotics for viral infections and vitamins for headaches.

time of year, and weather as well as the presence and interactions of other people, participating or not, and the social group(s) to which they belong. Together, these combined factors not only create a dynamic micro-context that is seldom replicated but contribute to psychological and physiological responses to medicine, food and placebos. Increasing evidence suggests that the structural and aesthetic design of healthcare facilities can impact health outcomes (Rubin, 1998) by influencing stress levels and rates of disease transmission among both patients and healthcare workers (Ulrich, 1992, 1997). How setting may affect food choice, eating behaviours and related responses to food, a topic we revisit in the following section, is similarly receiving increased attention.

Macro-context

The prevailing societal attitudes and values, the socio-economic and political climate, as well as the region's history, customs, geography and biological diversity are equally pertinent to the consumption of both medicine and food. Aborting a pregnancy and eating pork respectively present specific medical and nutritional consequences of the macro-context. Doing the former within a Catholic society or the latter within an Islamic one, however, may result in additional effects on social, psychological and physical health, regardless of personal attitudes and motivation. Language is a particularly important component of macro-context. Classification systems organize everyday life, including medicines and foods, into meaningful categories based in cultural beliefs and shaped by language (Bowker & Star, 1999; Foucault, 2002). Moreover, multiple independent classification systems may co-exist, each contributing different labels and meanings to the same thing. Eggs are not just part of the 'meat and alternatives' food group; they may be a breakfast food, an animal-based food, a taboo food, a nutrient-rich or high-cholesterol food, a yin (or cooling) food in Traditional Chinese medicine or a pungent, heating food in Ayurveda. Although classification systems are embedded within the macro-context, the pertinence of assigned labels varies from person to person and from place to place. Other factors, such as popular knowledge and stereotypes surrounding specific treatments, foods and the people associated with them, contribute to macro-context as well. When considering historic scenarios, the era is an essential consideration. For example, a barber's pole, once symbolic of the profession's dual role as surgeon, conveys a very different meaning today.

Placebo drugs to placebo foods

An obvious limitation of the proposed model is the lack of nutritionally inert foods—or pure placebos—in food and diet. That food-related placebos are almost always active placebos has practical and conceptual consequences for the TFE and placebo research in diet and nutrition. Placebo pharmaceuticals are straightforward; an inert substance is substituted for the pharmacologically active ingredients without significant impact on appearance or taste. Because pills are manufactured, the active can simply be omitted in place of the selected filler. Moreover, because pills are typically small and swallowed whole, the potential sensory and physiological effects of the filler are minimized. In contrast, placebo foods may designate either pharmacological (e.g. caffeine-free) or nutritional (e.g. fat-free) inertia. Whereas placebo versions of manufactured food can be easy to make, for instance not fortifying otherwise fortified foods, making placebos from whole foods is much more difficult.

In some cases, such as caffeine- and alcohol-free beverages, the extraction of drug-like non-nutrients is accomplished without greatly altering chemistry and sensory quality. The extraction of nutrients, conversely, is severely complicated by several factors. Most notably, nutrients make up the bulk of food; once removed, little is left save water (which many consider a nutrient). Exemplified by low-fat dairy products, specifically removing one type of macronutrient is more feasible but, interacting directly with sensory and homeostatic systems, its absence is easily recognized. For research purposes, particularly food challenges for allergy assessment, placebos are most often developed to mask the taste of both the "active" and placebo foods, which is simpler than simulating original sensory stimuli but limits the relevance to dietary preference and habit (Huijbers et al., 1994; Noe, Bartemucci, Mariani, & Cantari, 1998).

What is an appropriate filler for placebo foods? Lactose, a traditional pharmaceutical placebo, is neither nutritionally nor physiologically inert. Substituting any food component with lactose is thus the nutritional equivalent of substituting one active drug with another. Since foods are consumed in much larger quantity than drugs, finding fillers that mimic food qualities without altering digestive and metabolic processes is nearly impossible. Adding something indigestible, like most fat substitutes, likely affects sensory appeal but also interferes with nutrient digestion and absorption in the gastrointestinal system. Similarly, many sugar replacements are neither calorie-free nor biologically inactive. The lack of pure placebo foods confounds the study of non-nutrient effects since observed differences between placebo and experimental groups are not strictly attributable to top-down influences. On the other hand, so long as these limitations are acknowledged and controlled for, placebo foods—like placebo drugs—offer both a useful investigative tool and a potentially powerful health intervention.

Integrating the total food effect

How do interactions of the model's components influence individual food-related perceptions, behaviours and responses? Because the role of the practitioner translates inconsistently into the TFE model, we only briefly explore the source–consumer and source–food relationships before focusing on consumer–food interactions and the impact of micro- and macro-context.

The prescriber–patient and source–consumer relationships

When an identifiable person prescribes, suggests or prepares food (or a dietary plan) for the purpose of improving the consumer's health, interactions between the source and consumer influence the TFE as in medicine. The words, attitudes, reliability and behaviours of a practitioner can elicit neurological and physiological responses that impact patient trust and hope, perceptions of empathy, competence and—most importantly—recovery (Benedetti, 2010; Prévost, Zuckerman & Gold, 2011). For example, in a study on the effects of language in general practice consultations, 64% of patients recovered shortly after a 'positive' consultation consisting of a firm diagnosis and assurance of rapid recovery compared to only 39% among those receiving no diagnosis and uncertain prediction of recovery, regardless of symptoms, placebo prescription or sex (Thomas, 1987).

Indeed, language is a fundamental vehicle of suggestion (Shapiro, 2004), which in turn triggers both conscious and unconscious cognition leading to altered perception and behaviour (Raz, Moreno-Iniguez, Martin, & Zhu, 2007). Less subtle than suggestion, explicit information, for instance telling the patient what intervention they will receive and when it will be administered, elicits similarly mediated responses. Demonstrated repeatedly using open/hidden research paradigms, patients made aware of drug administration consistently respond better than uninformed patients, whether for treatment of pain, anxiety or Parkinson's disease (Colloca, Lopiano, Lanotte, & Benedetti, 2004). Without the involvement of placebos, these interactions can be more aptly attributed to "knowledge" or "attentional" effects.

Hawthorne effects

The modification of normal behaviour resulting from being monitored or participating in a study (rather than from experimental or environmental manipulations).

Relationships with dietitians and personal trainers represent obvious examples of source–consumer interactions but reported health benefits of home-cooked meals suggest that similar interactions exist with parents and care-givers. Eating at home or as a family, independent of factors like household income and education, is frequently identified as a positive contributor to diet quality, nutrient intake, and health, especially in children and adolescents (Briefel & Johnson, 2004; Patrick & Nicklas, 2005; Scaglioni, Salvioni, & Galimberti, 2008). Foods purchased and prepared by care-givers at home are not just nutritionally sound and dependable but imbued with the comfort and protection of family. Alternatively, unhealthy eating environments in the home can promote problematic eating behaviours in children (Scaglioni, et al., 2008).

If identified as commercial, the source's attributes and actions may impact consumer expectancies, choices and experiences but few have explored how such interactions influence health. One pertinent example is transparency on the part of food retailers regarding the nutritional value of their products, a legislated requirement in an increasing number of countries. Nutritional information may be listed on packaging, posters, pamphlets or menus but is often relegated to a company webpage. Whereas such information is infrequently accessed and unlikely retained unless available at the point of purchase (Bassett et al., 2008; Roberto, Schwartz, & Brownell, 2009), menus offer more promise in terms of calorie control. In a recent study (Roberto, Larsen, Agnew, Baik, & Brownell, 2010), diners presented with calorie-labelled menus ordered and consumed fewer calories than diners unaware of their caloric intake but increased their consumption to comparable levels when menus were redistributed after the meal. Only the diners presented with both calorie content and recommended daily intake consumed fewer calories throughout the study suggesting that listing calories on menus influences food choices and that nutritional recommendations alongside calorie labels more effectively controls consumption. Such knowledge-based or attentional effects may also involve other cognitive processes since the experimental milieu also allows for Hawthorne effects and mediation by social norms, pressures and appearances when eating in public.

The prescriber–drug and source–food relationships

Food selection based on knowledge or expectations of benefit is generally in the hands of consumers whereas, as illustrated by the preference for *double*-blinded clinical evidence in medicine, a prescriber's knowledge and expectation of therapy can modulate patient outcomes for better or worse (Gracely, Dubner, Deeter, & Wolskee, 1985). The relationship between practitioner and treatment is based on knowledge gained through prior experience as well as information gleaned from education and training, colleagues, sales representatives, seminars and the media. This relationship not only influences interactions with patients but guides practitioners in selecting from the 'menu' of appropriate treatment options once a diagnosis is reached. Comparable situations arise when consumer food choice is limited. For example, based on their expertise and knowledge, a chef will choose and prepare only the best available foods to serve customers. Similarly, a mother will choose and prepare only the best to serve her family—particularly if someone is unwell. When her son has the flu, a mother may serve him soup or some other comfort food that she knows provides energy and hydration but that she also expects will help him feel better based on her experience with other children and, perhaps most importantly, as a child herself.

When the source is a caregiver or anyone with a vested interest in providing the consumer with safe and nutritious meals, the impact of their relationship to foods on the TFE is often positive in terms of health and nutrition. This, however, is not always the case. Competing factors such as profit margins and consumer preference in the private sector (Glanz et al., 2007) or resource availability and food allergies in the public sector (Gregoire, 1994) must also be considered.

If the source stands to gain financially from the provision of food, the role of motivation requires some attention. Though a cynic may suggest otherwise, a physician's primary concern is patient health regardless of personal advantage. For practitioners whose income depends on non-pharmaceutical therapies in which they believe, the net impact of the prescriber–treatment relationship likely remains positive, particularly since patient improvement leads to repeat business and referrals. In contrast, for food producers and retailers, customer satisfaction and sales do not necessarily equate with positive nutritional value or health outcomes. Such considerations are usually secondary to palatability, convenience and economy, which collectively contribute to the flood of high-calorie, low-cost processed foods and the rising rates of obesity in America (Drewnowski & Darmon, 2005).

Source actions affect the attributes of food. Strategically designed by industry to meet strict regulatory guidelines and marketing goals, food labels selectively draw attention toward desired attributes and away from undesired ones. Though nutritional information is often included, many consumers ignore or don't understand it (Cowburn & Stockley, 2005). By manipulating the attributes of the food (label, price, colour), the source influences consumer beliefs and expectations. Sources directly impact food chemistry as well. Because doctors no longer prepare the drugs they prescribe, their only influence on drug chemistry is dosing. Cooks don't just select their ingredients but measure, mix and prepare them as they choose. Affecting the already diverse and variable chemistry of foods, a source's chosen practices of farming, processing, storage and/or cooking influence both nutrient content and food safety (Bhat, 2008).

The patient–drug and consumer–food relationships

Pharmacology and nutrition

Central to patient–drug interactions, the biochemical and subsequent physiological activities of pharmacotherapy provide the transition to consumer–food interactions. Whether consuming food or medicine, individual responses are rooted in biology. A drug, once delivered, must reach its specific target within the body in its active form at sufficient concentrations. This depends on—among other things—drug transport, metabolism and clearance processes that are largely predetermined by genetics. Age, weight, overall health and external factors (including diet) also alter pharmacokinetics and pharmacodynamics. Moreover, the presence of other drugs, foods or toxins metabolized in the liver can disrupt enzyme function to the same effect. Garlic and grapefruit, for instance, contain substances that increase drug levels by inhibiting metabolic enzymes and transport pumps (Diaconu, Cuciureanu, Vlase, & Cuciureanu, 2011; Gallicano, Foster, & Choudhri, 2003). Outside of pharmacology, active drugs and their metabolites can elicit allergic responses or gastrointestinal disturbances with considerable impact on the TDE.

The interactions between constituents of foods or natural health products generally follow the same principles and are subject to the same biological and environmental factors. As examples, genetics and epigenetics underlie the reduced capacity to metabolize alcohol and lactose in people of certain ethnic backgrounds (Edenberg, 2007; Swallow, 2003), a full stomach slows the absorption of alcohol along with the ensuing onset of cognitive impairment (Millar, Hammersley, & Finnigan, 1992) and vitamin C improves the uptake of iron from non-animal sources (Hallberg, Brune, & Rossander, 1986). Immune system-mediated allergies are likewise embedded in consumer biology. On the other hand, unlike drugs, nutrients are essential to everyday body and brain function so many are specifically monitored and regulated by the central nervous, endocrine and/or immune systems. Deficiency or excess of any nutrient is, in itself, a health concern only remedied by increasing or decreasing the availability of the particular nutrient. Offering a simple if not pure translation of Claridge's TDE into clinical nutrition, these situations warrant a closer look.

Tightly and efficiently regulated, macronutrients are stored or excreted when consumed in excess but long-term consequences include weight gain, metabolic diseases, kidney problems and cardiovascular disease (Hung, Sievenpiper, Marchie, Kendall, & Jenkins, 2003; Pecoits-Filho, 2007). Genetics play a role in the metabolism and storage of macronutrients, which together with age, physical activity and lifestyle not only influence our capacity to process and respond to foods but contribute to diet-related disease and death. In contrast, excesses of vitamins and minerals can lead to immediate and severe toxicity requiring immediate medical attention. Beyond overloading on iron, which has an established genetic component (Brissot et al., 2005), biological traits are largely irrelevant compared to diet, supplementation and exposure to environmental contaminants. In terms of nutrient deficiencies, the relevant consumer traits outside of diet are again seldom biological. Instead, economic, social, political, geographical and ideological factors, which are equally pertinent to situations of over-nutrition, are the primary contributors to nutrient deficiency (Tanumihardjo et al., 2007).

In all of these examples, nutrient content would dominate consumer–food interactions and the TFE, at least in terms of health effects; removing the nutrient component from the model renders the long-term prognosis for nutrient deficient individuals as poor regardless of any positive psychosocial benefits the food may offer. When energy-deprived, even if conditioned responses to the sight, smell and act of eating briefly reduce perceived hunger, such short-lived relief is of little benefit. The opposite argument generally holds for nutrient poisoning and over-nutrition—consumers would benefit from the removal of the nutrient in excess—except that, for the latter, the lack of energy dense carbohydrates and fats can also alter taste or texture and forego the addictively rewarding stimuli that contribute to chronic overeating (Smeets, Weijzen, de Graaf, & Viergever, 2011; Stubbs, 2001). Accordingly, any ensuing reduction in food intake is soon followed by renewed urges.

Flavour

Beyond nutrition and pharmacology, foods provide taste, odour, texture and colour as gustatory, olfactory, somatosensory, auditory, visual and trigeminal inputs that together determine individual flavour perception. Given the necessity of obtaining nutrients and avoiding poisons, our senses and responses evolved for these very purposes; we innately prefer sweet and salty, an indication of nutrient-rich foods, over sour and bitter (Birch, 1999). Several genes involved in taste perception have been identified, particularly with regard to bitter, sweet and umami sensitivity. Smoking and toxic exposure can also impact perception of chemical stimuli, as can personal health, particularly with regards to the respiratory and olfactory systems. Once perceived, subsequent responses and behaviours depend not only on the individual's sensitivity but on their prior experience with the specific food and its qualities as well as their personal dietary habits, preferences and traditions (Lindemann, 2001; Logue, 2004). Flavour perception is a fertile field of research with wide ranging implications for health, industry and basic science. Though rich in examples of placebo-like effects, a full discussion is beyond our scope. Instead, we briefly examine two examples, taste and colour, as interesting illustrations of combined biological and cultural influences on diet.

Of the known bitter taste receptor genes, TAS2R38 is the most studied. It is broadly tuned to perceive thiourea compounds commonly found in crucifers (cabbage family), green tea and soya. Recognized as a genetic trait long before TAS2R38 polymorphisms were identified, individual taste sensitivity to bitter tasting phenylthiocarbamide (PTC) and 6-n-propylthiouracil (PROP) distinguished individuals as super-tasters, medium tasters or non-tasters (Bartoshuk, Duffy, & Miller, 1994). Subsequent studies hypothesized that this variation affects individual food preferences, dietary behaviours and, through reduced consumption of vegetables, physical health. Although perceptions of bitter and sweet taste, the texture of fat and the astringency of alcohol associate well with PROP/PTC tasters status, studies fail to consistently report any relationship between TAS2R38 haplotype and dietary habits, anthropometric measurements or disease risk (Gorovic et al., 2011; Navarro-Allende, Khataan, & El-Sohemy, 2008; Ooi, Lee, Law, & Say, 2010; Timpson et al., 2005), suggesting that psychological and cultural factors outweigh genetically determined taste perception with regard to personal food choices (Gorovic, et al., 2011; Navarro-Allende, et al., 2008; Ooi, et al., 2010)..

Colour

All of the chemical traits discussed to this point involve genetic components and direct interactions between food or drug constituents and physiological processes or biochemical pathways. Moreover, such interactions require consumption and, with a few exceptions, represent bottom–up effects. In contrast, colour invokes expectations and elicits responses cued only through visual stimuli that are independent of the specific structure of colour-producing chemicals*. The well-established stimulant effect of red pills and the sedative effect of blue pills reflect the meaning ascribed to the respective colours. The observed culture- and context-dependent variation in meaning (Moerman, 2011) highlights the psychological underpinnings of the response as well as the role of macro-context. When associated with food, colours take on new meanings that shape consumer perceptions of flavour and quality through expectations and learned associations derived from previous experience. For example, when presented with liquids of various colours and asked what flavour they expected of each, the most popular response from British people was cherry for red and raspberry for blue while Taiwanese most frequently identified red as cranberry and blue as mint (Shankar, Levitan, & Spence, 2010). Colour also strongly influences flavour perception, green-coloured cherry-flavoured drinks are sometimes reported as tasting like lime, for instance (DuBose, 1980). Independent of sugar content, the addition of red colour to drinks increases perceived sweetness (Johnson, 1982), but not always (Strugnell, 1997), suggesting cultural influences are again involved. Similarly, the odour of coloured solutions is perceived as more intense than those of equally-scented clear solutions (Zellner, 1999).

In the sophisticated world of wine, red not only denotes distinct qualities but also beckons its own vernacular. In a study of 54 untrained wine-tasters, *everyone* described an artificially red-coloured white wine as a red wine based on its aromatic qualities (Morrot, Brochet, & Dubourdieu, 2001). Even wine experts are susceptible to "placebo" red wine; the aromas of a red-coloured white wine were more accurately judged when the wine was presented in opaque rather than clear glassware (Parr, Heatherbell, & White, 2002) and red-illumination of white-wine enhances perceived attributes of spiciness and astringency (Ross, Bohlscheid, & Weller, 2008).

* Because similarly coloured agents in foods and drugs are often chemically distinct, their biological activities (if present) likely work through distinct biochemical mechanisms.

Shape and format

Given that we are free to choose our own meals and that what we see affects taste and experience, the physical appearance of food heavily influences consumption. At the grocery store, we seek perfect-looking products. Beneficially, this serves as a safeguard against spoiled or unsanitary foods but, counterproductively, can also reflect the use of pesticides, waxes or preservatives rather than nutritional quality or flavour. At the table, we often want what looks good on the plates of other people. Conversely, if deemed unappetizing, certain foods can eradicate appetite on sight.

In medicine, different pharmaceuticals share several physical qualities; they are clean, evenly coloured, free of visual contamination and packaged in a labelled box or container. Also, because of the context of use, drugs are associated with medicine regardless of their mode of delivery. The psychological impacts of a pill or needle, however, differ. For example, placebo injections are more effective than pills for treating migraines (de Craen, Tijssen, de Gans, & Kleijnen, 2000). The effects of food format, for instance liquid versus solid foods, on appetite and satiety are unclear. Despite reports that liquids trigger satiation pathways less effectively than solids, leading to the recent admonition of sweetened beverages for their putative role in escalating rates of obesity, studies also report that liquid nutrients are equally or more satiating than solids (Almiron-Roig, Chen, & Drewnowski, 2003). This variability is not surprising since hunger, appetite and satiation result not simply from the activation of specific chemoreceptors in the gastrointestinal system but from the accumulation and integration of physiological, sensory and cognitive factors.

Food and nutrient format potentially affects consumer beliefs and decisions. Soy protein, for example, appears in countless shapes and textures. In nutritional terms, 'sugar' refers to mono- and disaccharides of different forms, sources and names but refers specifically to sucrose (table sugar) on food label ingredient lists. As a result, other forms are regularly added to foods: the more obvious brown, confectioner's, granulated, invert, maple, raw and white sugars as well as the less transparent processing variants (e.g. corn syrup, evaporated cane juice). Consumers inclined to read the list likely consider such ingredients, however interpreted, in making food choices.

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Number and quantity

How does quantity affect food consumption, dietary habits and the TFE? Looking first to medical research, four placebo pills are more effective than two for treating duodenal ulcers (de Craen et al., 1999). The meaning and expectancy associated with more pills is higher dose and greater response whether presented with real drugs or placebos. Because of difficulties in creating appropriate placebos for food psychology and nutrition research, comparable studies are lacking. Even if using liquid foods, the water necessary for dilution could influence intake as much as any nutrient or sensory quality. Nutritional supplements (which are typically not considered food) could provide some transitional insight but studies focusing on placebo effects in appropriate RCTs have not been reported. The potential for placebo-like effects related to the quantity of a nutrient are nonetheless plausible.

Although the immunosupportive effects of vitamin C are well substantiated, research has yet to conclusively show that, in foods or as supplements, it prevents or reduces the duration or severity of colds*, even at doses more than ten times the daily recommended value (Douglas, Hemila, Chalker, & Treacy, 2007). Still, despite the recent conclusion that, "routine mega-dose prophylaxis is not rationally justified for community use," (Douglas, et al., 2007) a great many people continue consuming vitamin C in large amounts expecting relief or protection from cold-like symptoms. The popular 'more is better' mentality of patients seeking drug therapy may thus apply for those seeking nutritional interventions but not as well to consumers seeking nourishment more broadly.

Analogous to pill number with relevance to food consumption, especially overeating, is serving size. Numerous studies, both laboratory and free-living, unfailingly demonstrate that increased serving size results in increased energy intake (Ello-Martin, Ledikwe, & Rolls, 2005; Fisher & Kral, 2008). This means that, regardless of what you ate for dinner, you eat more popcorn at the movies if you buy a large instead of a small. Here, cognitive attention and visual difficulty in judging portion size from larger containers are but two of the factors at play; the social environment and associated behavioural norms add another level of complexity. Increasing the number and variety of offered food items (e.g. popcorn, candies, nachos) similarly leads to higher energy intake (Cohen, 2008).

* Vitamin C supplementation for prophylaxis but not treatment may be justified in people exposed to severe physical activity and to cold environments (Douglas et al., 2007).

Price and labels

Like taste, colour and number, industry- and market-designated traits like price, brand name and packaging present both sensory and social cues that consumers associate with quality, value and, in the case of health foods and medicines, efficacy. The additional role of language and imagery, from product labels to magazines and the internet, in creating such learned, socially and culturally-contrived associations cannot be underestimated. The influence of direct-to-consumer advertising by the pharmaceutical industry on patient treatment preferences serves as case in point (Datti & Carter, 2006; Mintzes et al., 2003). In a classic demonstration of 'brand' effects in treating headache, patients received an unlabelled placebo, a branded placebo, an unlabelled analgesic or a branded analgesic. An hour after administration, analgesic pills were more effective than placebos but, for both treatments, branded pills outperformed unlabelled ones (Branthwaite & Cooper, 1981). Similarly, following electrical shocks to the wrist (an established protocol in pain research) prior to and after taking the pill, participants given 'regular-price' placebos reported greater pain relief than participants given 'reduced-price' placebos (Waber, Shiv, Carmon, & Ariely, 2008).

Interestingly, the study's motivation for exploring the therapeutic consequences of a drug's commercial traits stemmed from earlier research on the placebo effects of marketing on performance (puzzle-solving) following consumption of a food, an energy drink. By manipulating consumer expectations of quality without the use of placebos, the authors found that performance was affected not only by price but by previous brand exposure, self-reported expectancies and the provision and strength of materials supporting product efficacy (Shiv, 2005). More specifically, discounted price led to poorer performance, likely through unconscious processes since the effect was lost when attention was brought to popular price-quality beliefs. Notably, regular-priced drinks did not improve performance relative to the control group unless accompanied by strongly supportive statements, which also significantly improved self-reported alertness but not motivation, the former a major product claim—to "boost alertness"—and the latter lacking any direct association (Shiv, 2005).

Because consumers perceive lower-priced items—foods, drugs or other—as lesser in quality, they judge them as such (Gerstner, 1985; Roe, 1989). Furthermore, a drink labelled with a preferred brand can taste better and differentially activate the brain than the same unlabelled drink (Allison, 1964; McClure et al., 2004) and meat labelled as 75% lean tastes better than the same meat marked as containing 25% fat (Levin, 1988).

Personal experience

Previous experience with the sensory stimuli and specific effects of food or medical care lead to physiological and psychological responses mediated at both the unconscious and conscious level. Considered an underlying mechanism of medical placebo effects, classical conditioned (Pavlovian) responses are well-documented in the realm of diet, most notably conditioned taste aversions and, of course, salivating at the sight or smell of food (Klosterhalfen et al., 2000). Response expectancies form another core mechanism of placebo effects. With conscious exposure to any stimulus, in this case perceived food traits, personal experiences become integrated into memories, attitudes and expectations about that stimulus, influencing future experiences (Kirsch, 1999). While expectancy effects are acknowledged factors in both eating and healing, our experience with foods and flavours is broader and more deeply rooted than our experience with different medical treatments. This intimate, ongoing interaction between diet, mind and body—past, present and future—forms the foundation of personal food preferences and aversions ultimately manifesting as choices and habits that affect nutrition and health.

Classical conditioning

Initially described as Pavlonian conditioning or reinforcement, classical conditioning involves the unconscious pairing of a response naturally triggered by one stimulus to another, formerly neutral, stimulus. For example, as a result of Pavlov repeatedly ringing a bell prior to feeding his dog, the dog began to salivate at the sound of the bell alone.

Memory is imperfect. False memories, good and bad, can alter people's attitudes about food as well as their future decisions and actions (Bernstein & Loftus, 2009). Focusing on how memories influence behaviour, most of this psychological research has targeted foods like hard-boiled eggs, asparagus and dill pickles without concern for implications to personal health. One American study, however, demonstrated that people convinced they experienced a negative event involving a fattening food as a child avoided it in the future (Bernstein, Laney, Morris, & Loftus, 2005). Although memories manipulated through suggestion can potentially improve nutrition, the avoidance effect was only observed with regard to infrequently encountered high-fat foods (Bernstein, et al., 2005) suggesting that overall dietary habits are harder to break.

Second-hand knowledge

External information also influences beliefs and expectations leading to (perceived) consumer knowledge and enhanced awareness. Whether true or false, such information may be derived from an array of sources including spoken, written, and online evidence or accounts, observed experiences of family and friends or any common knowledge founded in the macro-context of use. This applies equally to food and medicine but with some deviation in emphasis. Information pertaining to health risks and benefits dominate practitioner and patient choices while packaging and second-hand knowledge of palatability, seldom a concern when choosing medicine, are often central to decisions about new foods. Similarly, patients using opiates probably do not care if the poppies were grown under organic conditions ten or ten thousand miles away and diners probably give no additional credence to restaurant recommendations from their doctors over friends.

The impacts of micro-context

Filled with staff, furniture, appliances and other sensory stimuli symbolic of food and cooking, kitchens and dining rooms are inherently associated with eating. Most restaurant owners pay meticulous attention to the floor plan, décor, lighting and music in order to create an environment appropriate for their clientele and the dining experience they wish to present. Though not for commercial purposes, many home owners invest in the design and décor of their dining rooms for similar reasons of culture, comfort and cleanliness.

The importance of setting in healthcare was documented by Florence Nightingale in the 19th century, noting that noise, light, ventilation and sanitation affected the health of English soldiers in her care (Nightingale, 1860). Today, mounting evidence confirms that characteristics of healthcare facility environments influence the health of both patients and staff (Rubin, 1998) leading to an emergent area of research into healthcare design (Ulrich, Berry, Quan, & Parish, 2010; Zborowsky & Kreitzer, 2008). Table 1 lists some relevant physical and social elements of micro-context that contribute to outcomes. If a hospital room with a window or single occupancy benefits patients more than a windowless or shared room (Table 1), how does this translate into eating environments and their effects on diet and nutrition?

Most relevant studies focus on external influences on food consumption. As noted above, the size of food portions can affect intake, as can the mere sight of food and its physical proximity (Wansink, 2004). Watching television or a movie increases food consumption. All of these effects involve cognitive processes such as attention and self-control, which are further modulated by other internal and external inputs. Common preference for 'a table by the window' suggests a similarly positive effect as a window in healing. Lighting also alters perceived tastes and calorie consumption (Wansink, 2004) with darkness confusing subjective satiety leading to greater food intake and inaccurate estimates of consumed calories (Scheibehenne, Todd, & Wansink, 2010). Alternatively, without vision, attention to other senses is heightened and enriches taste experiences, an effect promoted by trendy restaurants premised on fine-dining in complete darkness. Perhaps an analogue of medicine's high-tech, cutting-edge interventions associated with powerful placebo-like effects (Kaptchuk, Goldman, Stone, & Stason, 2000; Moerman, 2011), 'dark' restaurants may more appropriately owe their success to their modernity and the social and cultural esteem of the experience.

Although single-occupancy rooms may improve certain outcomes compared to shared facilities, this does not imply that social support and interaction is negative; the opposite is in fact true (Detillion, Craft, Glasper, Prendergast, & DeVries, 2004; DeVries, Craft, Glasper, Neigh, & Alexander, 2007). Rather, shared medical facilities may be undesirable for similar reasons as getting the table next to the washrooms. Whereas medicine is mostly private in Western cultures but social in others, as presented by Kirmayer (2011) in this issue, eating is almost universally a social activity with shared relations, experiences and cultures as a common point of reference. Still, the impact of social environment depends on individual preference and the context of eating. Eating socially or alone influences nutritional quality and energy consumption perhaps due to differing social pressures to arbitrate personal behaviour (Wansink, 2004).

The impacts of macro-context

As the source of culturally-dependent meanings ascribed to colour, format, number and price, the role of macro-context in the TFE and TDE is overarching. Other examples include the geographical, economic and cultural contributions to accessing, experiencing and interpreting foods and cuisines. Agricultural subsidies shape food markets by manipulating the availability and price of selected foods. Subsidized corn farming in the U.S. and the explosion of corn-based products in American diets is a clear illustration. Cultural norms dictate what types of food are acceptable and how they should be presented. Serving fish without the head may be more appealing to some consumers but also reduces the amount of available nutrients. Whereas the production and sale of genetically modified foods is well-established in North America, it is not tolerated in Europe. A highly nutritious and abundant food source, insects are considered taboo in some cultures but staples or delicacies in others. Whether we are conscious of it or not, macro-context often outweighs nutrition in our dietary habits and food cultures.

The typologies of food-related placebos and placebo effects

The variety of presented food- and medicine-related examples reveal that different interactions are central to different placebo-like effects. For example, unconsciously learned food aversions are typically based in conditioning whereas eating more from bigger bowls or less when ordering from calorie-labelled menus are cognitive effects. Both categories, like other possibilities (e.g. expectancy effects), can be divided and subdivided into more specific variants. Rarely, however, is only one mechanism at play. An alternative approach is to classify effects according to their founding relationships. The influence of price and marketing claims on puzzle solving after consuming an energy drink similarly implicates multiple relationships: consumer–food (conditioning and expectancies related to prior exposure), source–consumer (suggestion and attention related to externally provided information), as well as macro-context effects (mass media depictions and common perceptions of energy drinks).

Feature	Effect on patient health	Effect on staff health
Disruptive noise	↑ stress (Hilton, 1985) ↓ sleep (Richardson, Allsop, Coghill, & Turnock, 2007); ↓ preterm infant development (Brown, 2009)	↑ stress (Choiniere, 2010; Ryherd, Waye, & Ljungkvist, 2008); ↓ communication (Shapiro & Berland, 1972)
Controlled noise	↓ pulse amplitude & re-hospitalization of coronary care patients (Hagerman et al., 2005)	↑ speech intelligibility, ↓ pressure and strain (Blomkvist et al., 2005)
Lack of window	↑ disorientation; ↑ delusions (Keep, James, & Inman, 1980)	
Sunny rooms & views	↓ length of stay (Beauchemin & Hays, 1996) ↓ mortality after myocardial infarction (Beauchemin & Hays, 1998) ↓ use of analgesics (Ulrich, 1984)	↑ job satisfactions (Mroczek, Mikitarian, Vieira, & Rotarius, 2005) ↑ well-being (Leather, 1998)
Private vs. shared rooms	↓ infection (Shirani et al., 1986)	↓ stress (Chaudhury, Mahmood, & Valente, 2006)

Table 1. Examples of how micro-context traits impact the health of patients and healthcare staff.

Whereas analogies of placebos in food and nutrition expose the same core mechanisms of medical placebo effects, the exercise offers several novel variations on conventional types and relational structures. With clinically and self-prescribed dietary interventions or health foods, practitioners prescribe and patients purchase what they believe and expect will help. As such, those without proven benefit in RCTs can be construed as superplacebos (Ernst, 2001).

Superplacebos

Coined in reference to CAM, the term refers to interventions without specific benefit when examined objectively yet believed to be effective by both the patient and practitioner. Due to these shared beliefs and expectations, superplacebos can generate superplacebo effects (Ernst, 2001).

Food labels present a unique permutation of the placebo paradigm where, despite receiving accurate information, consumers often under- or overestimate their nutrient intake due to a limited understanding of food labels and nutritional recommendations. Artificial sweeteners and fat substitutes present another interesting variation. Sugar- and fat-free foods are designed to simulate calorie-rich foods in every way except their 'active' components, which in this case are associated with *negative* health outcomes (Hung, et al., 2003). Here, people *knowingly* consume these placebo foods expecting to reduce their risk of developing conditions such as diabetes, obesity and cardiovascular disease while enjoying the pleasures of indulgence. However, lacking the specific stimuli to activate the brain's reward circuitry, low-calorie alternatives often fail to provide the same sensory experience as the real thing. Perceived lactose intolerance offers yet another variation where consumers who falsely overestimate their inability to tolerate dairy not only react to lactose challenge but avoid dairy of all sorts, regardless of lactose content, with obvious dietary and nutritional implications (Casellas et al., 2010).

Placebo drugs are more effective in some circumstances than others (Benedetti, 2009). The evidence presented here similarly demonstrates that certain aspects of diet and nutrition are more or less responsive to placebo-like interactions. Placebo effects are insignificant with regards to nutrient deficiencies but often robust in trials on diet-related problems such as IBS and lactose intolerance (Casellas et al., 2010; Enck & Klosterhalfen, 2005; Kaptchuk, et al., 2010) as well as food-based intervention studies for the common cold (Carr, Einstein, Lai, Martin, & Starmer, 1981) and postmenopausal hot flushes (Nahas et al., 2007). Moreover, food-related placebo effects may be subjective or objective, as exemplified by flavour perception and caloric intake, and present short- or long-term consequences, as exemplified by enhanced cognitive performance and conditioned taste aversions, respectively.

In the medical literature, debate abounds regarding the definition, interpretation and use of the terms placebo and placebo effect. Because direct analogies of narrowly-defined placebos are scarce in diet, we adopt more inclusive definitions that serve well as an umbrella term since many such effects involve pleasing and desirable (placebo) or displeasing and undesirable (nocebo) responses to real or perceived stimuli.

Toward a common neurobiology?

Neurologically speaking, relieving (or suppressing) discomfort and getting rewarded share much in common. When someone wants to suppress hunger-related discomfort, he/she is actually seeking the reward of food, which in itself is a means of relieving hunger. Identified as the brain's motivation and reward centre, the mesolimbic dopaminergic system drives the seeking behaviours and rewards associated with eating, sex, gambling and euphoric or addictive drugs. Seeking relief from sickness is probably more like hunger and thirst than sex or gambling in that failure to act can be harmful to health and survival (Benedetti, 2010). Thanks to evidence derived almost exclusively from placebo research, we also know that expectations of treatment and improvement can activate the mesolimbic dopamine system of patients afflicted with pain, depression and Parkinson's disease (Benedetti, 2010; de la Fuente-Fernandez, Lidstone, & Stoessl, 2006; Zubieta & Stohler, 2009).

With expectancies appearing prominently in many diet-related placebo effects, dopamine likely plays a pivotal role here as well. However, given the integrated inputs mediating eating behaviour, other neurotransmitters and systems (e.g. endocrine, digestive, olfactory, etc.) are undoubtedly involved. Implicated in both placebo analgesia (Benedetti, 2006) and eating patterns (Davis et al., 2011), the opiate system is a promising candidate worthy of investigation.

Caveats and limitations

Beyond the previously addressed practical and conceptual limitations of nutritionally inert foods, our adapted model suffers from certain pre-existing limitations of the TDE approach as well as additional ambiguities and complications, particularly with regard to time and complexity.

Temporal constraints

Many human traits and corresponding interactions with food traits change with time. Accordingly, the TFE includes temporal considerations: consumer age, short-term and long-term effects of a single 'dose' and acute versus chronic consumption. Pharmaceutical (and placebo) research focuses primarily on the short-term effects of drugs (meaning or context) on a particular set of outcomes while long-term effects often remain unclear. The vast majority of the provided examples from food and diet similarly involve only acute effects. Although the long-term health impacts of individual nutrients can be ascertained by epidemiological approaches, at least correlatively, those of any specific food are much more difficult to assess at either the individual or population level.

Mentioned only briefly here, the influence of age on TFE deserves greater attention. In medical, nutrition and placebo research, paediatric, adult and geriatric individuals require separate consideration for reasons of biological, cognitive and socio-cultural development. Given that dietary preferences and habits form predominantly in early years, that marketing of food directly targets children, and that youth are, on average, more susceptible to suggestion, authority and placebo effects than adults (Kemeny et al., 2007; Lewis, Winner, & Wasiewski, 2005; Rheims, Cucherat, Arzimanoglou, & Ryvlin, 2008), the model warrants revisiting with a focus on childhood. Mindful of these limitations, we feel that the proposed model is sufficiently flexible for application to both short- and long-term effects of food and diet across the lifespan.

Quantity and complexity of interactions

In medicine, a patient normally consults with one or two practitioners who diagnose and treat then monitor response until treatment is discontinued. Even with multiple prescriptions, the TDE of each remains somewhat confined by the duration of exposure and symptoms and the limited treatment traits interacting within the clinical encounter. If eating multiple times a day in multiple settings, dozens if not hundreds of sources contribute different foods containing thousands of chemicals to our daily diet. Duration of exposure is rarely based on symptomatology but instead on availability, affordability, previous experience and culture, which collectively influence how frequently and copiously we consume different foods. As such, the number and complexity of interactions between stakeholder traits clouds the TFE of a single food, a particular meal or, most profoundly, an entire diet.

The ambiguity of the TFE's 'source' component can add more variables and the limitations of self-reported, recalled dietary and lifestyle habits constrain the validity of interpretations and conclusions. Nonetheless, compared to 1970 when Claridge introduced the TDE, progress in placebo research and our understanding of non-pharmacological factors in medicine, though still bourgeoning, has increased profoundly (Benedetti, 2009, 2010; Moerman, 2002). With evolving experimental paradigms, we can similarly dissect the TFE by judiciously manipulating selected variables while controlling for as many others as possible.

Closing Remarks

A wealth of research relevant to the TFE is scattered among different disciplines and sub-disciplines, each with their own interests and objectives. With the overarching emphasis of health on most research agendas worldwide, increasing prevalence and economic burden of diet-related diseases and greater acknowledgement of psychological, cultural and environmental factors in diet and health, converging evidence continues to emerge. Bringing some of this research together for the first time, the current paper identifies some of the known and unknown factors at play, giving body to the TFE framework. The publication of industry-generated, proprietary research regarding the effects of food appearance, flavour and marketing on consumer perceptions, preferences and consumption habits would provide a big step forward. Though unlikely, we can still hope.

Our relationships with food are complex, extending beyond nutrition, physiology, psychology or any other single perspective. Only through an interdisciplinary approach can we study and eventually understand the multi-layered interactions shaping the impacts of food on our personal and collective health. By extending the concept of placebos to diet and food culture, we not only gain new insights into mechanisms governing food-related behaviours and responses but also into clinical practice and research, diverse academic disciplines as well as industry and public health policy. Importantly, we can also identify new models and innovative avenues for studying placebo-related phenomena without some of the constraints imposed by medical research.

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