Understanding sweet liking and disliking: re-evaluating sweet taste as a driver of overconsumption

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Declaration

The work in this thesis is presented in a 'papers-style' in which empirical chapters (Chapters 2-6) are written in a style that is appropriate for publication in peer- reviewed journals. Tables and figures are embedded in the main text. Empirical chapters are preceded by a synthetic overview and discussion of the field, the experiments undertaken, and future directions (Chapter 1). A composite bibliography is presented in APA style at the end of the thesis.

Portions of the thesis have also been published or submitted to the journals listed below:

Paper 1 reported in Chapter 2 is published in *Food Quality and Preference* as:

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Paper 2 reported in Chapter 3 is published in *Nutrients* as:

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Part of **Paper 3** (incorporating two studies) **reported in Chapter 4** has been submitted to *PNAS*

Paper 4 reported in Chapter 5 has been under-review in *Appetite*

Authors' contributions are noted in the relevant chapters. Overall, the thesis author was responsible for the main study design, execution (including data collection), analysis, and manuscript drafting across the presented studies. Co-authors provided commentary on study design and relevant manuscripts.

I hereby declare that this thesis has not been and will not be, submitted in whole or in part to another University for the award of any other degree.

Signature: Vasiliki Iatridi

Acknowledgements

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Chapter 4 (Paper 3): Effects of sweet liking on body composition depend on age and lifestyle: a challenge to the simple sweet-liker obesity hypothesis.

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UNDERSTANDING SWEET LIKING AND DISLIKING: RE-EVALUATING SWEET TASTE AS A DRIVER OF OVERCONSUMPTION

SUMMARY

Given the role of taste hedonics in directing ingestive behaviour, the abundance of highly palatable foods that characterises the modern food environment may contribute to the high prevalence of unhealthy eating habits and obesity globally. Sweetness has long been considered to elicit strong liking and, therefore, to drive overconsumption, possibly leading to weight gain. Despite these claims, Chapter 2 identified over 70 research papers reporting large variations in hedonic response to sweetness. Using sucrose solutions and hierarchical cluster analysis, Chapter 3 confirmed this variation, demonstrating three distinct sweet-liking patterns: a rise in liking with increasing sucrose concentration (sweet liker phenotype, SL), an inverted-U response pattern, and a decline in liking as concentration increased (sweet disliker phenotype, SD). Chapter 2 also identified inconsistencies, methodological weaknesses or limitations in adoption for large-scale studies in the previous methods used to quantify different sweet-liking patterns. To facilitate future research, Chapter 3established rapid and reliable swee-liking phenotype classification criteria. Chapter 4 confirmed the robustness of these criteria in a cross-country sample, and also explored the effect of phenotype on selected anthropometric, dietary, and behavioural characteristics: SLs had either lower fat mass or greater fat free mass than SDs and behavioural characteristics analogous to those of high interoceptive performers. A possible interaction between the obesogenic environment and most phenotype-specific effects was also suggested. In Chapter 5, SLs were found to perform better than SDs in objective cross-modal interoception tasks and to be more mindful and intuitive eaters. Chapter 6 tested the effect on affective responses to different tastants of an 8-day exposure to a diet high in simple sugars versus a control group. Contrary to liking for sucrose solutions, findings indicated a phenotype by condition interaction for hedonic responses to highly palatable foods and drinks with SDs experiencing the largest effect (increase).

Abbreviations

AISS - Arnett Inventory of Sensation Seeking

BIS - Barratt Impulsiveness Scale

BMI - Body Mass Index

BPQ - Body Perception Questionnaire

DEBQ - Dutch Eating Behaviour Questionnaire

EMAQ - Emotional Appetite Questionnaire

FFM - Fat Free Mass

gLMS - generalized Labelled Magnitude Scale

HCA - Hierarchical Cluster Analysis

IAcHDi - Interoception Accuracy from the Heartbeat Discrimination task

IAcHTr - Interoception Accuracy from the Heartbeat Tracking task

IAw - Interoceptive Awareness

IAwHDi - Interoceptive Awareness from the Heartbeat Discrimination task

IAwHTr - Interoceptive Awareness from the Heartbeat Tracking task

IC - Interoception

IS_HDi - Interoceptive Sensibility from the Heartbeat Discrimination task

IES - Intuitive Eating Scale

IS_HTr - Interoceptive Sensibility from the Heartbeat Tracking task

ITPE - Trait Prediction Error

IU - Inverted U

MEQ - Mindful Eating Questionnaire

NNSs - Non-Nutritive Sweeteners

OFC - Orbitofrontal Cortex

SD - Sweet Disliker

SEM - Standard Error of the Mean

SL - Sweet Liker

STT - Sweet Taste Test

SSBs - Sugar Sweetened Beverages

TFEQ - Three Factor Eating Questionnaire

VAS - Visual Analogue Scale

WLT - Water Load Test

WC - Waist Circumference

Chapter 1

Understanding sweet liking and disliking: re-evaluating sweet taste as a driver of overconsumption – Overview

1.1 Why investigate sweet liking and disliking in relation to food choice and intake?

1.1.1 Obesity: an alarming public health problem – the obesogenic environment

Termed a global epidemic, obesity and its associated health conditions including cardiovascular disease (Lu et al., 2014), type 2 diabetes (Ganz et al., 2014), and certain types of cancer (De Pergola & Silvestris, 2013) are a major concern worldwide. Global prevalence of obesity has nearly tripled over the past four decades and the problem shows no signs of abating (Bentham et al., 2017). In 2018, 67% of men and 60% of women in the UK had a Body Mass Index (BMI) higher than 25 kg/m^2; this included 26% of men and 29% of women who were obese (NHS, 2019). The same year, obesity accounted for more than 11 thousand hospital admissions, placing England's health care system under strain (NHS, 2019). Regarding anthropometric figures in the US, 73.7% of men and 66.9% of women are overweight or obese, with obesity rates being approximately 14 percentage points higher than the relevant rates in the UK (Flegal et al., 2016). Obesity has been estimated to contribute to over a quarter of the American annual health care spending (Biener et al., 2017).

The obesity crisis has a multi-factorial aetiological basis. It is fuelled by genetic, environmental, cultural, and interpersonal factors that variously affect energy intake and/or energy expenditure to govern energy homeostasis (Jebb, 1997). Given that, on an evolutionary time scale, the changes in the food environment and the manner food is obtained are relatively recent for our genome to adequately adapt, modern humans have to cope with a homeostatic system that is programmed for uncertain caloric availability and food scarcity (Carrera-Bastos et al., 2011). Activation of endogenous reward mechanisms originally evolved to increase intake of energy dense foods are no longer an asset (Olszewski et al., 2019). Therefore, the rapid upward trends in obesity prevalence most likely reflect changes in the environment (sleeping habits: Grandner,

2018; physical activity: Ng & Popkin, 2012; dietary intake: Popkin et al., 2012) coupled with the influence from epigenetics (van Dijk et al., 2015). Additionally, although genetic factors appear capable of explaining part of the individual susceptibility to obesity (Comuzzie & Allison, 1998), the pace at which obesity prevalence has grown at population level over the past few decades also points to environmental causes (Swinburn et al., 2011).

The concept of 'obesogenic environments' describes all the possible aspects of our environments which encourage weight gain in individuals or populations (Lake et al., 2011). Regarding food choice and intake, there has been a shift from diets high in complex carbohydrates and fibre, to what has been termed the 'Westernised Diet' with a high proportion of refined carbohydrates, simple sugars, and unhealthy fats, and a reduced consumption of fruits and vegetables (Popkin et al., 2012). It has been said that food and drinks that dominate this modern food environment are engineered to be highly palatable and thus encourage overconsumed (Sørensen et al., 2003).

However, even in the obesogenic world, we have not uniformly developed obesity: some individuals are less responsive to the external environment than others which enables their food intake to match their metabolic demands perfectly. Understanding why regulation mechanisms allow body weight to drift upward in so many others, calls for investigation. The present work would yield critical insights into the interpersonal variation in hedonic response to sweetness and how these individual differences may drive overconsumption.

1.1.2 Overconsumption as a cause for obesity development: what we know about the contribution of sugar intake

Obesity which is characterised by excessive fat deposition arises from an imbalance between energy intake and energy expenditure that is from repeated failure to obtain and consume foods that match ongoing metabolic demands (Spiegelman & Flier, 2001). Although approaching obesity aetiology from such a purely numerical viewpoint is a simplification of its multifaceted nature, it is accepted that when energy intake surpasses energy expenditure body weight increases (Jéquier & Tappy, 1999).

Over the past few decades, following a period when the outburst of mechanization was coupled with decreases in food energy supply and thus a rise in obesity rates was prevented, an energy balance flipping point was observed (Sassi et al., 2009). For example, a decline in occupation-related daily energy expenditure up to approximately 140 kcal has been reported (Church et al., 2011; Fogelholm et al., 1996). Since the mid-60s, hours spent on sedentary activities showed an annual increase of 1.3% and 1.4% in the UK and the US, respectively; engagement in leisure-time physical activities was, however, also increasing overtime (Ng & Popkin, 2012). As such, a review on the role of physical activity in body weight regulation concluded that the notion that obesity is a consequence of a consistent decline in energy expenditure is not sufficiently supported (Wiklund, 2016). Conversely, energy intake has been steadily increasing on a worldwide basis by approximately 450 kcal per capita per day during the same time-period (FAO, 2012). Further, in the current obesogenic environment, the abundant availability and relatively low costs of energy dense palatable foods (Drewnowski & Specter, 2004), their ubiquitous advertisement (Boyland & Whalen, 2015), and increased portion sizes (Nielsen & Popkin, 2003) are expected, among other factors, to disproportionally contribute to a positive energy balance and thus obesity development.

With the obesity epidemic being largely attributed to positive energy balance due to overeating, during the past several years much research has sought to disentangle the role of different macronutrients and food groups in eating beyond homeostatic needs. Reviewing dietary guidelines across the Globe and the health outcomes of different dietary patterns, a healthy reference diet was recently proposed: of notable relevance to this thesis a low quantity of sugars was highlighted (Willett et al., 2019). Indeed, one of the main dietary challenges in the developed world lies in the high consumption of foods and drinks rich in simple sugars (Popkin & Hawkes, 2016). For example, in the US population, over two thirds of purchased packaged foods and drinks contain caloric sweeteners (Popkin & Hawkes, 2016), while added sugars account on average for roughly 270 kcal or more than 13% of daily energy intake (USDA, 2015). A recent review summarising data from representative surveys across Europe estimated that added sugars contribute 7 to 11% of total energy intake in adults (Azaïs-Braesco et al., 2017). The latest data from the UK specifically, show that on average, free sugars

provide 11 to 13% of daily energy intake in adults (NDNS, 2018) which is more than double the relevant recommendations (SACN, 2015).

Yet, the role of simple sugars in the obesity epidemic remains controversial. As opposed to the view that the rise in the percent of the population being overweight or obese coincides with an increase in intake of simple sugars, during the last decade, the absolute (g/d) and relative (% energy) sugar intake has been either stable or decreased in the majority of developed countries (Wittekind & Walton, 2014). Instead, the observed growing prevalence of obesity parallels with a rise in the widespread use of non-nutritive sweeteners in food products (Qing Yang, 2010). According to the Food and Agriculture Organisation, between 1961 and 2009, simple sugars accounted for merely 5% of the increase in world total food energy supply (FAO, 2012). Nonetheless, cutting down on simple sugars has been postulated as an effective strategy to lower excessive energy intake that associates with the current obesity epidemic, as diets featuring large amounts of simple sugars appear to predict weight gain (Hu, 2013). However, some ambiguity still remains as to whether intake of simple sugars is directly associated with weight gain or whether changes in body weight are rather due to sugars' contribution to positive energy balance (Bray & Popkin, 2014; Kahn & Sievenpiper, 2014). Randomised control trials have shown that, overall, changes in body weight did not differ after isocaloric exchange of simple sugars with other macronutrients (Prinz, 2019). On the other hand, excessive intake of simple sugars has been related to dysregulation of (cardio)metabolic indices (e.g., glucose, lipids, blood pressure) in some part independent of the resultant changes in body weight (Stanhope et al., 2018).

From the dietary sources of simple sugars, sugar-sweetened beverages (SSBs) have proven more problematic. For instance, observed associations between intake of sugars and BMI in prospective cohort studies have primarily been limited to intake of SSBs (Malik et al., 2013; Te Morenga et al., 2013), whereas substitution of SSBs with water or low-calorie beverages appears to have some beneficial effects on body weight outcomes (Zheng et al., 2015). SSBs are not the focus of such attention unreasonably. First, in highly obesogenic environments such as in North America, sugar-sweetened beverages account for the greatest proportion of sugars consumption (Brisbois et al., 2014; Sánchez-Pimienta et al., 2016; USDA, 2015). In contrast, in European countries

sweet tasting foods (e.g., confectionery, chocolates, cakes and biscuits, sugar, and jam) have been reported as the leading source of added sugars in the diet followed by beverages (fruit juices excluded: Azaïs-Braesco et al., 2017). Secondly, since energy consumed from drinks may not provide equivocal satiety-promoting effects as energy from solid foods (Mattes, 2006), sugars from liquid sources are more likely to lead to excessive energy intake and consequent obesity development. A recent meta-analysis confirmed that decreased oral processing related to chewing is inversely associated with food intake (Krop et al., 2018). Finally, the potential implications of the relatively short orosensory exposure time (i.e. in-mouth sensory perception time) of liquid and soft foods to overeating even independent of eating rate (Lasschuijt et al., 2020) have been proposed (de Graaf, 2020) suggesting that the longer lasting stimulation of the oral gustatory nerve endings induced by taste substances released during chewing (breaking down of food structures) and mastication (enzymolysis of saliva) is likely to override the known inverse relationship between viscosity and perceived sweetness intensity (Liu et al., 2017). Therefore, it could be speculated that insufficient processing of the taste properties of liquid and soft food products may lead to inadequate pleasure and satiation signalling and in turn to failure of negative feedback loops to terminate eating as appropriate.

1.1.3 Taste hedonics as a driver of food choice and intake

Regulation of food intake occurs even before ingestion. Sensory cues including taste and cognitive processing of food (thoughts or discussion), are cephalic signals that trigger physiological response: salivation and secretion of gastric acid, orexigenic hormones (e.g., ghrelin), and insulin, all increase (Smeets et al., 2010). Therefore, food choice and intake are complexly shaped by physiological, genetic, environmental, and social variables (de Castro, 2010), as well as by psychological factors including various forms of learning (e.g., exposure, nutrient or flavour conditioning, etc.: Yeomans, 2012) and personality traits (Prescott, 2020). Given the links between the obesogenic environment and overconsumption, it is argued that sensory characteristics of foods and drinks greatly influence the decisions we make about what to eat and what not to eat (de Graaf, 2020). From the sensory determinants of food choice and intake, taste

hedonics is considered a key point of study for understanding the drivers of ingestive behaviour (Hayes, 2020). As illustrated in Figure 1.1, a product's explicit and implicit characteristics elicit sensations; generation of pleasure follows, which in turn determines use, i.e. orients consumption behaviour (Hayes, 2015). Of particular relevance to this thesis is the idea that individual differences at each step may partly mitigate the variation in susceptibility to the influences of the obesogenic in food intake and subsequent obesity development.
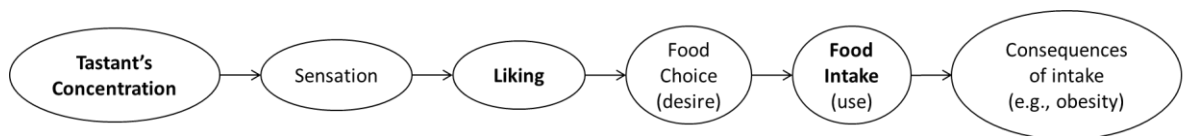
Fig. 1.1 A working model of taste is related to intake through pleasure (Apapted from: Hayes, 2015, 2020)

In more detail, when an individual consumes food, specialized taste receptor cells throughout the oral cavity capture the information about the molecules that constitute the stimulus and the associated signals are transmitted to the brain (Chaudhari & Roper, 2010). Information from the internal state of the body (i.e., homeostasis), taste properties (i.e., hedonics), and pressures from the environment are centrally integrated before the final ingestive decision is reached (Finlayson & Dalton, 2012). The degree to which ingestive behaviour is biased toward hedonic or homeostatic signals may shift depending on the current needs (e.g., energy depletion) and the type of food (e.g., palatable) (Rossi & Stuber, 2018). For example, bitter taste that may signify the presence of a toxin, at least initially, generates aversive responses (Ventura & Worobey, 2013), whereas in states of excessive loss of electrolytes, detection of saltiness is most likely to promote intake (Denton, 1982; Djin G. Liem, 2017).

In the obesogenic environment with abundant options, it is increasingly believed that decision making about eating is primarily driven by signals related to the hedonic value of the food stimuli (Drewnowski, 1995). Consistent with the externality theory stating that obese individuals are more sensitive to external than internal cues (Schachter, 1968), when hedonic eating becomes dominant over homeostatic needs, i.e. there is an imbalance in the control exerted by reward versus hypothalamic circuits,

obesity prevails (Egecioglu et al., 2011). There is evidence from both animal models and human studies to suggest that Westernised diets characterized by a high intake of refined sugars and saturated and trans fats negatively impact regions in the brain, which are known to be involved in the homeostatic regulation of food intake (Francis & Stevenson, 2013; Yeomans, 2017) such as the hippocampus (Stevenson & Francis, 2017). A vicious cycle begins, whereby dietary sugars and fats dysregulate homeostatic mechanisms including appetite signaling either directly (e.g. Stevenson et al., 2020) or indirectly though the observed impairment in cognitive functions such as learning and memory (e.g. Attuquayefio et al., 2017) and subsequently lead to intake beyond homeostasis (Francis & Stevenson, 2013; Yeomans, 2017). A recent neuroimaging study also showed that, for participants being overweight or obese, experience of sweetness resulted in increased activation in brain areas related to responsiveness to external stimuli; authors concluded that in the obesogenic environment, this may further contribute overconsumption which worsens weight gain (Sadler et al., 2020).

Keeping up with the same idea, it has been posited that the prioritisation of hedonic over homeostatic signals could also reflect an obesity-specific shift in the hedonic set point for the reward value of food stimuli (Egecioglu et al., 2011). More specifically, prolonged exposure to highly palatable foods and drinks may cause an overstimulation of the endogenous reward system which in turn weakens dopamine signaling (Kroemer & Small, 2016); dopamine release in response to energy intake has been reported to be inversely associated with BMI (Wang et al., 2014). Consequently, if obese, one may consume increased amounts of foods and drinks high in sugars and fats to compensate for the hypo-functioning brain sites that mediate rewards (Wang et al., 2002). Nevertheless, this reward deficit theory lacks agreement across scholars (Stice & Yokum, 2016), while the view that such a blunted reward sensitivity in obesity is due to the reduced availability or expression of dopaminergic receptors in the brain is also weakly supported (Benton & Young, 2016). In accord with the incentive sensitization model (Berridge et al., 2010), it has been posited that the primary mechanism that maintains overconsumption of highly palatable foods and drinks when these cues are encountered, is the conditioning produced after the initial hyper-firing of dopamine neurons (Stice & Yokum, 2016).

Taken together, taste modalities with properties that potentially elicit strong liking that is they are of high hedonic value (liking and hedonic value will henceforth be used interchangeably), may systematically steer our choices in a way that favours overconsumption. A comprehensive understanding of the hedonic response to such taste modalities would greatly contribute to addressing the vicious circle where overconsumption of energy dense highly palatable foods brings about undesirable changes in body weight, which further perpetuate overconsumption.

1.1.4 The special role of sweetness and sweetness hedonics in directing ingestive behaviour

Sensory scientists generally agree on five basic taste qualities: sweet, bitter, salty, sour, and umami taste (Chandrashekar et al., 2006), although the complete list of tastes may go beyond these basic five (e.g., fat taste: Keast & Costanzo, 2015; starch taste: Lapis et al., 2016). From the basic tastes, sweetness has long been the subject of intense interest. The reason stems from the high palatability of foods and drinks rich in sugars (Drewnowski, 1995), as well as the deterioration of dietary quality (Britten et al., 2000) and considerable adverse health consequences (type 2 diabetes: Lean & Te Morenga, 2016; obesity: Te Morenga et al., 2013, cardiovascular disease: 2014) resulting from excess intake of sugars. The narrative around sugar addiction is also an active area of scientific debate as some scholars have pointed to the similarities between over-indulgent eating of highly palatable foods and drug addiction (Alonso-Alonso et al., 2015; Olszewski et al., 2019). In the following subsections (1.1.4.2 and 1.1.4.3), the evolutionary and neurobiological basis of sweet liking will be discussed to provide some insights into the mechanisms mediating the impact of sweetness and sweetness hedonic in ingestive behaviour.

Evidence from the US (van Langeveld et al., 2017), Australia (Cox et al., 2018), and the Netherlands and Malaysia (Teo et al., 2018) shows that sweetness intensity of commercially available foods and drinks relates to their carbohydrate content. Considering the proposed link between sensations derived from a taste (food) stimulus and consumption (Figure 1), liking for strong sweetness may lead to high intake of sugars from one's diet. As the body's nutrient sensing system, taste may direct intake in other

ways, too. In the current affluent societies with the reduced risk for energy depletion, it has been argued that, as compared to liking, disliking is likely to be a more potent driver of food choice and intake (Hayes, 2020). Consistent with the contemporary models of appetite control implicating higher levels of cognitive functions (Higgs et al., 2017), the increased awareness of the health consequences of eating patterns characterised by high intake of simple sugars (Lustig et al., 2012) may also discourage intake and thus disrupt the link between liking and intake described above. Interestingly, Hare and colleagues have reported that focusing on the long term outcomes of eating unhealthy foods was associated with inhibition of reward-related activity in the brain (Hare et al., 2009).

1.1.4.1 Sensory processing of sweet taste

Sweet taste is elicited by a wide variety of chemical compounds (Briand & Salles, 2016) including mono- (e.g., glucose, fructose, galactose) and disaccharides (e.g., sucrose lactose, maltose), and non-nutritive sweeteners (e.g., sucralose, saccharin, aspartame, stevia). TAS1R2 and TAS1R3 taste receptor genes have been directly linked to sensory processing of sweet taste (Bachmanov et al., 2011). They code for the T1R2/T1R3 protein heterodimer, which provides the main receptor-ligand binding construct for sweet tasting molecules (Nelson et al., 2001); at least three binding sites have been have been identified in this heterodimeric receptor allowing for the synergy observed between some sweeteners (Briand & Salles, 2016). An alternative sweet taste receptor cell assembled by two T1R3 subunits has also been identified, but it is limited to detecting high concentration of sugars (Nelson et al., 2001). TAS1R2 and TAS1R3 taste receptor genes are also expressed in extra-oral tissues such as the gastrointestinal tract and pancreas, wherein it appears to regulate metabolic processes (Laffitte et al., 2014). Regarding the oral sweet taste receptor cells, they are organised in structures called taste buds, which are housed in different spatial distributions in the fungiform, foliate, and circumvallate papillae of the anterior, lateral, and central posterior tongue, respectively (Roper & Chaudhari, 2017).

Stimulation of the T1R2/T1R3 cells by sweet tastants releases neurotransmitters onto afferent fibers from the chorda tympani (cranial nerve VII) and glossopharyngeal (cranial nerve IX) nerves causing transmission of the sweetness sensation to the nucleus of tractus solitarius in the brainstem (Besnard et al., 2016; Chaudhari & Roper, 2010). From there, the taste signal projects to the primary gustatory cortex, i.e. the anterior insula and frontal operculum, which is implicated in the identification of the taste quality and evaluation of the taste intensity of the stimulus that initially generated the neural cascade (Besnard, 2016). Finally, the taste-induced input reaches the secondary gustatory cortex, i.e. the orbitofrontal cortex (OFC), which is responsible for determining the associated hedonic valence of the tastant and, therefore, the palatability of the associated food or drink upon integration of multisensory afferent information (Besnard, 2016). To do so, a cross talk between the OFC and the mesolimbic system about the hedonic experience ('liking') and incentive salience ('wanting') related to the taste is built (Berridge, 1996). In other words, the hedonic value of the tasted/ingested stimulus appears to be closely linked to the gustatory system, pointing to the possibility that sweetness drives a preferential consumption of highly palatable foods rich in sugars. To note, a pre-ingestive taste-induced cephalic reflex constituted by efferent signals from the tractus solitarius to the gut also occurs to ensure the body's preparation for food arrival such as secretion of hormones and enzymes related to digestion (Power & Schulkin, 2008).

1.1.4.2 Sweet liking and the need state (homeostasis)

Throughout most of our evolutionary history, we developed mechanisms that facilitated the intake of calorically dense foods to cope with food scarcity and insecurity. Hence, it is believed that taste systems were initially evolved to inform us about the nutritional value or toxicity of food stimuli aiming at promoting biological fitness (Drewnowski et al., 2012). A classic demonstration of this phenomenon is featured by sensory experiments in human and non-human neonates (Ventura & Worobey, 2013). For example, shortly after birth, sweetness and likely umami, as opposed to bitter and sour tastes, were seen to elicit stereotypical positive facial expressions and, to some extent, corresponding sucking responses (Desor et al., 1973; Maone et al., 1990;

Rosenstein & Oster, 1988; Steiner et al., 2001); both behaviours may resonate an inherent drive towards foods providing a safe and useful source of energy and rejection of those being potentially poisonous. In fact, not only we are born hard-wired to prefer sweetness (Ventura & Worobey, 2013), but such appetitive responses to sweetness might be evident even prior to birth: sweetening of the amniotic fluid through injecting saccharin into the amniotic sac increased foetuses' swallowing rate (de Snoo, 1937).

Complimentary to the argument that it might be in our innate nature to enjoy sweet foods, such typical sensory reactions have also been said to be a hallmark of periods of rapid development (Coldwell et al., 2009; Mennella et al., 2014). Available research examining age differences in sweet liking has documented that sweetness preferences are stronger in children and adolescents relative to their mothers (Mennella et al., 2012, 2014; Pepino & Mennella, 2005) or young adults (De Graaf & Zandstra, 1999; Desor et al., 1975; Desor & Beauchamp, 1987; Djin Gie Liem & De Graaf, 2004), whereas that difference may also occur independent of the of the caloric value of the sweet tastant (Bobowski & Mennella, 2017). That said, liking for potent sweetness, which may predispose one toward overconsumption, would not necessarily reflect a dysregulation of homeostatic control (for example due to influences of westernized diets discussed in 1.1.3), but it may constitute a physiological mechanism that contributes to the feedback loops generated as a response to the internal state of the body.

In that context, alliesthesia could serve as the foundation for the interplay between sweet liking and homeostasis. Alliesthesia, which has been proposed in a series of paradigms including taste, thermal and thirst sensations, is the phenomenon when the pleasure aroused by a sensed stimulus reflects the usefulness of that stimulus for the internal body (Cabanac, 1979) Indeed, protocols targeting the interior milieu either through pharmacologically induced hypoglycemia or through glucose loads have demonstrated a shift in sweet tastants' liking that follows a positive ('more pleasant') or negative ('less pleasant') alliesthesia pattern, respectively (Cabanac, 1979). Classic overfeeding studies of energy oversupply support that these systems may also protect against challenges in body weight in the opposite direction, i.e. defend weight gain (e.g., Bouchard et al., 1996).

1.1.4.3 Sweet liking and the hedonic brain

As food is essential to optimise survival and propagation, it is unsurprising that systems involved in homeostatic aspects of feeding also promote intake of rewarding stimuli or suppress appetite for stimuli being aversive (Rossi & Stuber, 2018). More specifically, the lateral hypothalamus is known for its role in regulating homeostatic feeding interacts, with the endogenous reward circuitries (Castro et al., 2015) mediating the incentive ('implicit wanting') and hedonic ('explicit liking') aspects of eating (Finlayson & Dalton, 2012). Dopamine projections to the mesolimbic system are thought to determine the motivation to eat, opioid-dependent hedonic hotspots in nucleus accumbens and ventral pallidum contribute to the formation of the affective pleasure of the taste stimulus, whereas amygdala and hippocampus are involved in the learned memory linked to the sensory experience (Berridge et al., 2010; Berridge & Kringelbach, 2013). In support of this crosstalk between 'liking' and 'wanting', availability of dopamine and opioid brain receptors has found to be highly correlated (Tuominen et al., 2015). Additionally, a direct interconnection between taste-responsive neurons and the lateral hypothalamus has also been demonstrated (Li et al., 2013), suggesting that signals relate to taste stimuli can also directly affect homeostasis. In that regard, sweet-liking could be considered as a typical example of the evidence about such an overlap between neurocircuits that facilitate homeostatic feeding ('metabolic' brain) and those linked to reward-guided ingestive behaviour ('hedonic brain').

Upon arrival of the sweetness- and/or sugar-specific afferent signal from the periphery (e.g., mouth, gut), dopaminergic pathways within the brain are activated causing an increased release of striatal dopamine that is known to mediate the rewarding effects of food ingestion (Wise, 2006). Dopamine release has been found to be proportional to the degree of pleasure elicited by food stimuli (Small et al., 2003), whereas dopamine deficits have been associated with weaker responses to food-conditioned behaviours, as well as decreased or poorly sustained efforts to gain food rewards (Salamone et al., 2003). Pepino and colleagues reported a reverse correlation between the binding potential of striatal dopamine receptors and liking for sucrose solutions in normal weight human participants (Pepino et al., 2016). Consistently, in animal models, manipulation of normal functioning of dopamine receptors has been

found to cause changes in the hedonic value of sucrose (Vigorito et al., 1994; Xenakis & Sclafani, 1982) and sugar cravings (Michaelides et al., 2017).

Operating in concert with dopaminergic neurons (Finlayson & Dalton, 2012), body's opioid system directs eating behaviour toward the acquisition and consumption of food (Yeomans & Gray, 2002). It has also been speculated that opioid-mediated palatability may have been evolved to facilitate maintenance of intake of energy-rich foods in response to their sensory properties, which in real-world diets is mostly indicative of their energy content, but yet beyond homeostatic needs (Kelley et al., 2005). Thus far, a wealth of animal research (behavioural and imaging studies) has illustrated the critical role of opioids in signaling the hedonic pleasure elicited from sweetness (see Olszewski et al., 2019; Olszewski & Levine, 2007 for reviews). In the human literature, a reduction in liking for sweetness (e.g. sucrose solutions or sweet tasting foods) after administration of opioid antagonists has been reported (Eikemo et al., 2016; Fantino et al., 1986; Yeomans & Gray, 1996). Other evidence has shown that both caloric sugars and non-nutritive sweeteners exert analgesic, i.e. opioid-like, action (Barr et al., 1999; Ramenghi, Griffith, et al., 1996; Ramenghi, Wood, et al., 1996). Of interest, effects were eliminated when sugars administered post-orally (Ramenghi et al., 1999) or oral exposure was inadequate (Lewkowski et al., 2003), suggesting that the crosstalk between sweetness-specific gustatory signals and the rewarding evaluation of food stimuli may occur independent of its post-ingestive metabolic effects.

Further highlighting the potency of the rewarding characteristics of sweet tasting stimuli, the neural circuitry activated upon sucrose ingestion appears to overlap with the circuitry activated by substances of abuse (Alonso-Alonso et al., 2015): that is activation of the dopamine and opioid systems by sweetness produces addictive-like behaviours (Olszewski et al., 2019), the so-called 'sweet addiction', and the parallels between sweet-liking and substance-related addictive behaviours are addressed in 1.5.

According to a separate internal positive feedback process termed 'appetition', which was put forward by Sclafani, distinct sensors in the gut discern the ingested caloric sugars and stimulate liking and intake for carbohydrate-rich foods by activating dopamine reward systems in the brain and possibly other neurochemical and/or hormonal systems (Sclafani, 2018; Shechter & Schwartz, 2018). Communication is likely

to occur via the gut-brain axis; vagal afferent neurons play the most important role (de Lartigue & Diepenbroek, 2016; Sclafani, 2018), although other populations of neurons such as those in brainstem have recently been implicated (Tan et al., 2020). In animal models, that post-oral stimulatory action of caloric sugars has been found to be independent of the congruent presence of sweet taste (e.g., sucrose vs. sucralose: Buchanan et al., 2020; glucose vs. sucralose: Han et al., 2016; glucose/sucrose vs. maltodextrin: Sclafani, 1987; glucose/non-metabolisable glucose analogue vs. saccharin: Zukerman et al., 2013). In fact, sugar related nutritional signals and sweetness appear to be encoded by separate brain networks to create sugar preference and motivate ingestion (Tellez et al., 2016). Looking at human studies, research has focused on the post-oral detection of sweet tasting molecules by the T1R2 and T1R3 receptors discovered in the gut, a process that produces both flavour-flavour and flavour-nutrient preference conditioning (Sclafani & Ackroff, 2012; Shechter & Schwartz, 2018). In contrast to the nutrient reinforcement encompassed in the classic appetition model, flavour-flavour learning that involves signalling from the gut to the brain may occur independent of the caloric content of the ingested stimulus (e.g., Brunstrom & Fletcher, 2008; Mobini et al., 2007). Nevertheless, congruent caloric sugars-sweetness conditions, i.e. flavour-nutrient models of preference development, enable establishment of more potent hedonic (e.g., Brunstrom & Mitchell, 2007; Yeomans et al., 2008) and metabolic (e.g., Veldhuizen et al., 2017) response.

Emerging evidence from bariatric patients further supports the contribution of post-oral detection of sugars to their rewarding properties. Recent work suggests that, due to the distinct alterations to the anatomy of the gastrointestinal tract, the two most common types of bariatric surgery (Angrisani et al., 2018), the Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG), have differential effects on sensory evaluation of taste stimuli (Nance et al., 2020; Shoar et al., 2019) and other aspects of eating behaviour (Brutman et al., 2019; Orellana et al., 2019). More specifically, while, after a SG, food reaches the duodenum as normal, i.e. the vagal nerve remains intact or is less damaged, the resultant gut remodelling after RYGB surgery, where the entire stomach and upper small bowel are bypassed, alters gut-brain signalling and causes alterations to the mesolimbic dopamine circuitry (Brutman et al., 2019; Orellana et al., 2019). As an

example, to substitute the reward once filled by food stimuli, human participants who have undergone RYGB, but not SG or similar restrictive bariatric surgeries, report increased alcohol intake (e.g., Gallo et al., 2015; King et al., 2012; Östlund et al., 2013). Regarding post-operative alterations in sweetness hedonics, in support of the role of vagal nerve and duodenum in appetition process, gastrointestinal rerouting characteristic of the RYGB surgery was found to abolish sweet appetite, while the suppressing effects overturned when brain dopaminergic sites were artificially activated (Han et al., 2016). In an fMRI study with human participants the decrease in activation of a reward-specific brain site in response to images of high caloric food was greater in those undergone RYGB relative to controls but not between those receiving a SG and the control group (Faulconbridge et al., 2016). However, comparison of the sensory-specific effects of RYGB versus SG has shown the same decrease in either lab-based (e.g., Nance et al., 2017) or survey-reported (e.g., Hubert et al., 2019) sweet-liking; development of sweet liking is clearly more multifaceted.

Collectively, besides the classic reinforcing properties exerted by sweet taste detected in the oral cavity and its effects on dopamine- and opioid-dependent brain circuits, this evidence reveals an additional post-ingestive gut-to-brain sugar- and sweetness-sensing pathway, which supports the notion of highly appetitive effects of both nutritive sugars and sweetness. Such a powerful hedonic drive towards sweetness can hence be proposed as a significant contributor towards overconsumption and subsequent excess weight gain.

1.2 Sweet liking and disliking: classification methods to identify the distinct hedonic responses to sweetness – Introduction to Papers 1, 2, and 3

By signifying nutritious and safe food sources (Drewnowski et al., 2012) and activating reward circuits in the brain (Wiss et al., 2018) sweetness is thought by many to evoke mostly pleasant sensations, meaning that it is in human nature to be attracted to sweetness. However, in the modern world, when we do not face the risk of food scarcity and uncertainty, variations in the preferred level of sweetness are expected. Conditioned learning (e.g. routine consumption of naturally bitter food products such as coffee or tea) and cognitive evaluation of the consequences of particular food choices

could further allow dislikes to emerge (Hayes, 2020). At the same time, this food abundance and specifically the availability of highly palatable foods and drinks rich in simple sugars and unhealthy fats may exert the opposite effect on hedonic decisions, that is to offset possible dislikes and enhance likes (Sørensen et al., 2003). Dysregulation of the homeostatic system by the obesogenic environment (Yeomans, 2017), along with the self-reinforcing properties of sweetness (liking vs. wanting: Berridge et al., 2010; appetition: Sclafani, 2018) appear to further support the view of a universality of the 'sweet tooth'.

However, while research from a motivational standpoint has focussed on the universality of sweet liking, research founded in sensory science challenged this assumption (Iatridi et al., 2019). In the next section the evidence that there are clear and measurable individual differences in the expression of sweet liking which by their very existence challenge the simple idea that sweet liking is universal.

1.2.1 Sweet liking and disliking: classification methods to identify the distinct hedonic responses to sweetness – Summary of Paper 1

As a direct challenge to theories based about a universally positive hedonic response to sweetness across species and from infanthood, in an early foundational study, Pangborn documented three distinct liking patterns for simple sucrose solutions: a sweet liker (SL) phenotype showing a rise in liking with increasing sucrose concentration, an inverted-U (IU) response pattern, and a sweet disliker (SD) phenotype characterized by a decline in liking with increasing concentration (Pangborn, 1970). As liking is a driver of food choice and intake (Figure 1.1) and food choice and intake contribute to the regulation of energy balance (Spiegelman & Flier, 2001), it was deemed important to investigate whether distinct responses to sweetness measured in the laboratory while using simple taste (sucrose) solutions are widely evident in the sensory literature. Paper 1, also aimed to critically appraise the methods which have been used to identify those potential distinct sweet liking patterns.

Literature search for eligible studies published in the past 50 years (1970 to 2017) confirmed that sweet liking is not universal but varies across individuals across different intensities. The review also exposed a complex issue: different classification methods to identify these distinct patterns (i.e., sweet-liking phenotypes) using different sensory protocols (e.g., number and concentration range of sucrose solution, rating scales, participants' motivational state) have been developed and, although all had some degree of utility, not a single one stands without methodological challenges. First, when classification into different groups was based on visual interpretation of hedonic response curves (Method 1a) the likelihood of subjective or unblinded decision could not be eliminated. Use of agglomerative hierarchical cluster analysis (HCA) to statistically interpret these curves (Method 1b), despite overcoming the previous challenge, entailed a particularly resourceful and complicated testing and analysis protocol, hence less appropriate for a wider application by large epidemiological studies. Finally, methods that assigned participants into a particular phenotype based on either what sucrose concentration was rated highest for liking (Method 2) or preferred the most after multiple paired comparisons (Method 4), or on whether average hedonic score for all the presented stimuli was higher or lower than a particular cut-off liking value (Method 3) suffered from both arbitrariness associated with the classification criteria and/or strength of the taste stimuli and an increased risk of misclassification, primarily due to the forced dichotomous discrimination approach.

Regarding the true number of distinct sweet-liking phenotypes, overall, three main distinguishable patterns were identified. If liking ratings were plotted against sucrose concentrations, these patterns would be visually described as a positive slope (SL phenotype: strong liking for potent sweetness), an inverted-U (IU phenotype: maximal liking for moderate sweetness), and a negative slope (SD phenotype: strong aversive response to potent sweetness). However, most scholars adopted a simpler grouping: they dichotomously discriminated between SLs and SDs whilst labelling potential IU-like hedonic responses as a SD-like response or even collapsing IUs with SDs under the same group. On the basis of this simplified approach and independent of the classification method, participants across all studies reviewed here were roughly split between the SL and SD phenotype. Due to characteristics inherent to the classification

criteria adopted by each method and some discrepancies in mean age and BMI between studies using each method differences in the prevalence of each phenotype per method were revealed: studies using method 2 and those using method 3 possibly overestimated the true number of SDs and SLs, respectively.

In summary, the systematic review presented as Paper 1 in this thesis confirmed that sweet liking is not universally expressed in humans, and all methods found evidence that the proportion of people express a clear dislike for more intense sweet tastes cannot discounted.

As an adoption of a common method to identify sweet-liking phenotypes would possibly resolve inconsistencies in the literature regarding the food choice and intake (1.3.1) and weight status (1.3.2) of the different hedonic response patterns to sweetness, lacking a sweet-liking phenotype classification method which is distinctly superior to the others called for action. Adopting recommendations derived from this review paper with regards to cohort size (minimum of 100 participants per cohort) and number and concertation range of taste stimuli (4-5 to 8-9 different concentrations excluding water up to 1.0 to 1.1 M sucrose), the key issue of developing a robust method for identifying different sweet-liking phenotypes was addressed in Papers 2 and 3.

1.2.2 Sweet liking and disliking: classification methods to identify the distinct hedonic responses to sweetness – Summary of Paper 2 and Paper 3

Studies reviewed in Paper 1 varied, amongst others, in the methods used to identify the distinct sweet-liking phenotypes, the range of sucrose solutions served to evaluate liking (which is important for allowing within-subject and between-subject differences to emerge, but preventing adaptation or fatigue: Asao et al., 2015; Lawless & Heymann, 2010), and the testing conditions in relation to participants' motivational state, i.e. pre-test levels of hunger or satiety (which may mask/shift true responses as alliesthesia suggests and a meta-analysis of neuroimaging studies recently confirmed: Cabanac, 1979; Chen & Zeffiro, 2020). Thus, using a classification method that eliminates subjectivity and controls for parameters of the taste test was deemed essential to identify the true number of distinct sweet-liking phenotypes. As papers dealing with the

effects of distinct sweet liking patters on diet and weight status can be helpful in understanding the different susceptibility to the effects of the obesogenic environment, the secondary aim of Paper 2 was the development of a rapid, easy to use, and reliable sweet-liking phenotype classification criteria for future studies; Paper 3 checked the reproducibility of these criteria. As both Paper 2 and 3 dealt with the same main hypotheses, they are presented as a series of complementary studies.

Healthy participants 18-34 years old were recruited from the University of Sussex (N = 148; 29% men) and the Penn State University (N = 126; 32% men) to taste and rate 7 suprathreshold sucrose concentrations (0.03125, 0.0625, 0.125, 0.25, 0.5, 0.67, and 1.0 M) and water blank solution prepared based on mineral water. 10 mL aliquots of each stimulus were presented at room temperature in a randomised order using a sip and spit protocol. The taste test was replicated in two separate blocks for a total of 16 tastings. Computerised visual analogue scales (VAS) anchored 'Dislike extremely' (-50) and 'Like extremely' (+50) and the generalised labelled magnitude scales (gLMS) ranging from 'No sensation' to 'Strongest imagined sensation of any kind' were used to assess sweet taste liking and intensity, respectively; scale-specific standardised training was provided. Participants were advised to refrain from eating and drinking flavoured beverages for the two hours prior to the taste test. Pre- and post-test levels of hunger, satiety, and thirst were also recorded.

To identify the true number of distinct sweet liking patterns in this cross-country sample, Method 1b, i.e. the statistical interpretation of individual hedonic response curves using agglomerative HCA, was selected. According to insights gained from Paper 1, Method 1b is the most promising of the sweet-liking phenotype classification methods that are currently used as it both enhances statistical robustness and eliminates subjectivity and arbitrariness in the phenotyping process. To test reproducibility of the findings in regards to what is the true number of the main sweet liking patterns in young adults, HCA was carried out separately for each cohort (Rani & Rohil, 2013). Analyses revealed three distinct phenotypes which shared very similar hedonic response patterns between the two cohorts: some individuals showed a monotonically increasing liking for sweetness as concentration was raised (SL phenotype: 31.5% and 23.1% in the UK and the US cohort, respectively); in others liking

increased to a maximum (0.25 and 0.5 M sucrose in the UK and the US cohort, respectively) and then decreased (IU phenotype 50.0% and 51.2% in the UK and the US cohort, respectively); and in a third group liking for sweetness decreased monotonically as a function of concentration (SD phenotype: 18.5% and 25.6% in the UK and the US cohort, respectively). Pre- and post-test levels of hunger and thirst did not predict liking neither differed between phenotypes.

Acknowledging that development of a merely robust protocol that lacks an easy application profile might be ineffective in addressing the emerging need for a universally adopted sweet-liking phenotype classification method, the dyads of sucrose concentration and liking scores with the highest sensitivity and specificity in predicting the three sweet liking patterns identified by the HCA were determined. Sensitivity and specificity analysis was conducted separately for each cohort. It was concluded that individuals who rate liking for the 1 M sucrose higher than +15 on the -50 to +50 VAS can reliably be classified into the SL group, while those rating the same level of sweetness as -15 or lower could reliably be considered as SDs; all responses in-between fall into the inverted U group. To note, the 1 M sucrose solution was also associated with one of the higher reproducibility when the agreement in liking ratings between the two repetitions of each sweet stimulus was tested.

In summary, the initial experimental work in this thesis provided an evidence-based and robust methodology which if widely adopted will ensure greater reliability in the identification of different sweet-liking phenotypes across populations and laboratories, making it easier in future to generalise findings with confidence.

1.3 Sweet liking and disliking as a driver of overconsumption

1.3.1 The role of sweet liking and disliking in food choice and intake – Introduction to Paper 3

The purpose of ingestive behaviour is to supply enough energy and the necessary nutrients for the body's physiological processes to continue at an adequate level. In support of the view that information about nutrients is a critical part of food choice and intake, substantial research has shown that we are born to like tastes that signal energy

and beneficial nutrients (Desor et al., 1973; Steiner et al., 2001). However, gustatory stimuli differ in taste quality and intensity and therefore they are sought out based on individual needs and preferences. As sugars elicit potent sweetness which is known for its potent rewarding properties, and at the same time delivers energy, both their hedonic and physiologic features influence food choice and intake. As comprehensively reviewed in Paper 1, the pattern of liking across concentration of sugars in tastants however varies. Therefore, investigating whether variability in hedonic response to sweetness may have downstream implications for what we like and chose to eat or what foods we reject due to the unpleasant sensation they evoke may contribute to the hypotheses abound concerning the origins of the overeating and consequent obesity development.

In a review of sugar consumption from nationally representative dietary surveys across the world (Newens & Walton, 2016), intake of total sugars was estimated to be the highest among children (20 to 38% and 15.4 to 29.6% of total energy intake in toddlers and schoolchildren/adolescents, respectively) and decrease over the lifespan (13.5 to 24.6% of total energy intake in adults). Such a consumption trend parallels with the well-documented age-specific decline in sweet liking from childhood to adulthood (Venditti et al., 2020) suggesting that the higher the liking for sweetness the higher the intake of sweet tasting foods and drinks. However, as reviewed by Tan and Tucker (2019), research directly testing the effect of sweet liking on sugar intake has had mixed findings. The sensory protocols used in these studies (psychophysical assessment of liking, type and sweetness intensity of tastant) varied considerably as did the dietary assessment methods (FFQs, food diaries, 24h recalls) partially explaining the observed inconsistencies in the data.

While studies of sufficient sample sizes which distinguished between SLs and SDs revealed significant relationships between diet and gustatory hedonics, mixed results are reported by those who did not determine sweet-liking phenotypes. In Garneau et al. (N = 418), SLs consumed more energy from SSBs as measured by a food frequency questionnaire compared to SDs (Garneau et al., 2018); equivocal results were reported by Holt and colleagues (N = 132) regarding total intake of refined sugars (Holt et al., 2000). Another study (N = 196) reported higher energy intake from beverages in SLs

relative to SDs based upon analysis of two 24h recalls (Turner-McGrievy et al., 2013). Methven and colleagues who used a food frequency questionnaire (Methven et al., 2016) and Sartor and colleagues who assessed dietary intake through food diaries (Sartor et al., 2011), failed to observe significant effects of sweet-liking phenotype on diet; they tested 36 and 12 participants, respectively. Among studies that did not determine sweet-liking phenotypes, analysis of 24h recalls (Leong et al., 2018) and food diaries (Drewnowski et al., 1999; Jayasinghe et al., 2017; Mattes & Mela, 1986) revealed either positive associations between liking for strong sweetness or most preferred sweetness level and higher intake of simple carbohydrates (Jayasinghe et al., 2017) or energy intake from sweet tasting food (Mattes & Mela, 1986) or no correlations (Drewnowski et al., 1999; Leong et al., 2018; Mattes, 1985). Elsewhere, there was also no relationship found between hedonic scores for sweet solutions and intake of either added sugars (Stevenson et al., 2016) or sweet tasting food (Rivers, 2015) assessed through FFQs.

The research discussed above indicated no clear pattern for a relationship between sweetness hedonics and dietary intake. Thus, there is still need to ascertain the effect of sweet-liking phenotypes on real life sugar intake; using precise dietary assessment methods and analysing distinct sweet-liking phenotypes separately would possibly strengthen findings.

1.3.1.1 The role of sweet liking and disliking in food choice and intake – Summary of Paper 3

The sensation of taste intimately relates to preference for certain foods (Drewnowski et al., 2012). According to knowledge from Papers 1, 2, and 3 regarding the variability in liking for different level of sweetness, it is tempting to hypothesize that the proposed classification into the three distinct sweet-liking phenotypes might be accompanied by distinct levels of sugar intake in the diet: individuals classified into the SL phenotype consuming more sugars in contrast to SDs. A number of studies that have investigated the relationship between sweet liking and sugar intake or type or amount of sweet foods and drinks consumed (habitual use or real life intake) has reported contradicting results (1.3.1). Tan and Tucker (2019), who recently reviewed the subject

area, concluded that failure to identify sweet-liking phenotypes could influence findings. For example, if a specific phenotype is overrepresented in a study sample but not identified, results could be skewed (Tan & Tucker, 2019). Besides classifying participants into groups of distinct sweet liking patterns, based upon the limitations of each dietary assessment methodology (Gibson, 2005), it appears that the use of more precise dietary intake tools (e.g., 24h recalls or food diaries) could further facilitate our understanding of the relationships between liking ratings for sweetness and dietary intake.

While taking part in the studies described in Papers 2 and 3, participants provided information about their diet and meal patterns. Dietary data were collected using semi-quantitative food frequency questionnaires (FFQs) which were focused on habitual use of beverages of any kind. In the UK cohort, a more precise measure of food intake was also recorded through obtaining 24 h dietary recalls (three recalls of nonconsecutive days, two referring to weekdays and one to a weekend day, spanning up to a two-week period).

Confirming previous work linking sweet liking and drugs (specifically alcohol) abuse (Kampov-Polevoy et al., 1999), as well sweet liking and habitual intake of sweet tasting beverages (Garneau et al., 2018), the by-country analysis showed that SLs reported greater use of spirits, i.e. the beverage with the highest alcohol content but also the alcoholic beverage most often reported to be consumed alongside sweetened soda drinks (e.g., cocktails, bottled flavoured alcoholic beverages, etc.), compared to IUs and SDs (UK cohort). Likewise, SLs had the lowest frequency consumption of beer and ciders (US cohort), i.e., the least 'strong' alcoholic beverage and the one that is potentially the most bitter; no other effect of phenotype on habitual use of beverages was observed. Regarding real life sugar intake, neither the amount of total carbohydrates nor sugars expressed as percentage of total energy intake differed between the three distinct sweet-liking phenotypes; the proportion of energy from carbohydrates consumed in the form of sugars was also equivocal. Finally, consistent with the bitter taste associated with food products naturally high in fibers such as vegetables (Drewnowski & Gomez-Carneros, 2000) and unprocessed grains (Bakke & Vickers, 2007), participants classified into the SD phenotype consumed significantly more fibers than SLs and IUs did.

In summary, it would seem from the present evidence that although strong liking for potent sweetness might not directly drive intake upwards, SLs appear to be predisposed toward adopting more westernized dietary patterns and seeking for intense rewards which is possible to undermine an effective balance between homeostatic needs and hedonic hunger in the long term.

1.3.2 The role of sweet liking and disliking in body composition – Introduction to Paper 3

From the foregoing, it is evident, that through the complex interplay between nutritive and hedonic signals, sweet taste with its potent reinforcing properties would be a significant influence on consumption. In 1958, Pangborn and Simone, who tested the hypothesis that increased liking for sweet foods (fruits in syrup and ice cream with varying sugar content) differs across body sizes, summarised the prevailing view about sweet liking and obesity: "In the mind of the layman, sugar and sweets are 'fattening' and most overweight individuals display a 'sweet tooth'." (Pangborn & Simone, 1958); they found no evidence supporting this hypothesis.

The continued study of the sweet liking-obesity relationship has shown complexity. Studies that determined sweet-liking phenotypes have reported either no effect of phenotype on weight status (Asao et al., 2015; Drewnowski et al., 1997; Garneau et al., 2018; Goodman et al., 2018; Methven et al., 2016; Turner-McGrievy et al., 2013; Weafer et al., 2017; Yeomans et al., 2007; Yeomans & Prescott, 2016) or, contrary to the idea that sweet-liking drives obesity, a lower BMI in those classified as SLs (Grinker, 1977; Grinker & Hirsch, 1972; Johnson et al., 1979; Malcolm et al., 1980; Thai et al., 2011; Thompson et al., 1976). Discrepancies in sensory protocols and/or classification methods used regarding the identification of the distinct patterns of sweet liking is likely to mediate the inconsistency in these findings. For example, in Methven et al. (2016) and Asao et al. (2015), due to the small sample sizes HCA failed to identify the typical SD pattern. In Garneau et al. (2018), while phenotyping results were in line with the emerging consensus on the true number of distinct sweet-liking phenotypes, participants were asked to assess relatively low sucrose concentrations (0 to 0.4 M) which most possibly alleviated aversive responses for the sweeter stimuli and in turn led

to misclassifications; the low proportion of SDs (8.4%) confirms this speculation. The likelihood for phenotypic misclassification was also increased in most of the remaining cohorts (Drewnowski et al., 1997; Goodman et al., 2018; Turner-McGrievy et al., 2013; Weafer et al., 2017) which also failed to find significant effects of phenotype on BMI but used the 'highest preference using ratings' classification method (dichotomous classification based on sucrose concentration associated with the highest liking rating). As explained in Paper 1, the 'highest preference using ratings' method does not distinguish between individuals with a moderate sweet-liking and those with strong aversive response to potent sweetness. In contrast, all studies observing lower BMI values in the SL group visually discriminated between the distinct sweet-liking phenotypes (Grinker, 1977; Grinker & Hirsch, 1972; Johnson et al., 1979; Malcolm et al., 1980; Thai et al., 2011; Thompson et al., 1976). Notwithstanding the subjectivity issues related to this approach, the inclusion in these experimental studies of a wider range of BMIs at enrollment and sweetness levels during the sensory tests may have allowed differences to arise.

Using sweet stimuli of varying sweetness (sweet-fat mixtures or fruit juices) other than simple aqueous taste solutions in lab settings, a few studies have also highlighted an inverse relationship between sweet liking and BMI: that is lean individuals liked sweet taste more than those with overweight or obesity (Drewnowski et al., 1985); positive relationships have also been seen (Rodin et al., 1976). In agreement with the original conclusion of Pangborn and Simone (Pangborn & Simone, 1958), other evidence indicate no link (Drewnowski et al., 1991; Rodin, 1975; Witherly et al., 1980). Examining cohorts that allow for causality to be inferred, a longitudinal study in France (N = 24,776) showed that heightened hedonic response for sweet tasting foods assessed through a lab-validated online questionnaire did not predict BMI changes in the 5 year follow-up (Lampuré et al., 2016). Conversely, both Salbe and colleagues who used lab-based sensory testing with milk-sugar blends but tested a small sample (N = 75) of Pima Indians (Salbe et al., 2004) and Matsushita and colleagues (N = 29,103) who included a single taste question ('Do you like sweet taste?') in the baseline sweet liking assessment (Matsushita et al., 2009) reported a positive association between sweet-liking and

future weight gain; for the latter study results were significant only for women (Matsushita et al., 2009).

1.3.2.1 The role of sweet liking and disliking in body composition – Summary of Paper 3

Results from previous studies examining the link between sweet liking and BMI are illustrative of the challenges raised by the inconsistencies in sweet liking measures and/or classification methods used for the identification of distinct sweet-liking phenotypes. Further, BMI, which has been markedly the most commonly reported measure of weight status in the relevant literature, does not distinguish between body fat and mass due to other tissues, nor the distribution of fat (Blundell et al., 2014). As the current state of published data about the adverse health effects of sugars' overconsumption involve metabolic disorders whereby adiposity and central obesity are the main forces that shape clinical outcomes (Lean & Te Morenga, 2016; Te Morenga et al., 2014), use of BMI might only provide an approximation of real adiposity. Therefore, it may be suggested that BMI should not be considered alone, but in conjunction with body composition and abdominal fat measures. Hence, the variation in the literature with regards to the influence of hedonic response to sweetness on body size was further explored in Paper 3.

Most participants described in Papers 2 and 3 (N = 141 and N = 109 in the UK and the US cohorts, respectively) revisited the laboratory for a separate early morning session for anthropometry. Following a research-based body composition preparation protocol (Kyle et al., 2004) and standardized assessment procedures (WHO, 1995, 2011) body height and weight, body fat and fat free mass using bioelectrical impedance, and waist and hips circumferences were taken. As strong liking for potent sweetness might also reflect a broader enhanced sensitivity to personality traits that feature aspects of reward processing or poor control of feeding such as disinhibited and restrained eating (Keskitalo et al., 2008) or impulsivity (Stevenson, 2017), complementary to the primary focus on anthropometry some common eating behavioural measures were also obtained.

The immediate conclusion drawn from analysing the two cohorts together was that the relationship between sweet-liking phenotypes and anthropometry was rather complex: significant age (but not country) interactions in the effect of sweet-liking phenotype on all associated anthropometric measures were found. Among younger participants (<21 years old), a single phenotypic difference was observed, that of SDs having the highest percentage body fat. Conversely, among the relatively older participants of the present dataset, i.e., those aged 21 years and older, SLs had higher fat free mass, but also higher BMI and waist circumference than did SDs. An increased energy intake and/or intake of carbohydrate-rich foods due to the signals from the elevated metabolically demanding fat free mass was suggested to underlie SLs' higher BMI and waist circumference. Further exploring the profile of participants younger than 21 years old versus those aged 21 years and older, age-specific differences in behavioural and lifestyle characteristics consistent with a lower versus an overt exposure to an obesogenic environment were identified. For participants classified into the SL phenotype, a relatively stable set of behavioural traits including enhanced interoceptive-like behaviours (hunger driven eating and seeking for intensity in experiences) and heightened reward sensitivity was found independent of the age group that is independent of the asserted level of exposure to the obesogenic environment. Considering the evolutionary basis of sweetness palatability alongside the current views that, due to the modern food environments, an increasing part of human ingestive behaviour is driven by pleasure and not simply by the need for energy, the novel finding that strong liking for potent sweetness is related to either decreased body fat or elevated fat free mass, i.e. that sweet liking may reflect an increased need for energy, is of significant interest. Regarding the elevated fat free mass in participants aged 21 years and older,

1.3.3 The role of sweet liking and disliking in sensing the internal body – Introduction to Paper 4

As it is evident from the foregoing sections, ingestion of sweet tasting and/or sugar-rich foods and beverages is influenced by two systems: the one associated with regulation of energy homeostasis and that involved in reward. In brief, immediately

after sweetness and/or sugars are sensed (mouth, gut), they are converted into neural and humoral signals which travel to the brain (Besnard et al., 2016; Chaudhari & Roper, 2010). The central nervous system integrates this information with internal parameters related to glycemia, adipose stores, past experience, and many others, producing appropriate regulatory behavioural, endocrine, and autonomic outputs (Clemmensen et al., 2017). As these feedback loops generate responses based upon existing need states, should the internal state of the body be sensed correctly, it could direct ingestive behaviour by affecting the hedonic value of the food stimuli, amongst other systems.

Interoception is defined as one's ability to perceive bodily sensations from various internal systems including homeostatic and emotional needs (Schleip & Jäger, 2012). Laboratory-based tasks (objective interoception measures: accuracy, awareness) and questionnaires (subjective interoception measures: sensibility) have been developed to quantify one's sensitivity to such internal cues (Garfinkel et al., 2015, 2016). From a neural perspective, insula that has been posited as key brain region in interoception, is also known for its role in gustation and, in particular, in central processing of the taste quality and intensity of gustatory stimuli (Small, 2010). Nevertheless, it Is likely to relate to affective valence of tastants: Small has proposed that, in response to palatable taste stimuli, functional connectivity of the insula and the taste hedonics-specific OFC is increased (Small, 2010).

Modern humans have engineered a food environment that is unnaturally affluent and hyper-palatable (Sørensen et al., 2003). Exposure to that obesogenic environment has been suggested to supersede peripheral signals related to energy stores and energy needs (Sample et al., 2016), and even 'exploit' the limbic system (Yeomans & Gray, 2002). Given that all individuals are exposed to similar environmental cues, it has been argued that the variability in the susceptibility to these cues and consequently to overconsumption might be due to interpersonal variability in intrinsic psychobiological processes (Blundell & Finlayson, 2004). Hedonic response pattern to sweetness may contribute to this susceptibility and interoceptive signalling could be a potential candidate to empirically establish this hypothesis.

1.3.3.1 The role of sweet liking and disliking in sensing the internal body – Summary of Paper 4

Despite the proliferation of studies demonstrating a role of interoception in eating disorders (Quadt et al., 2018) and an increasing interest in the association between interoceptive abilities and BMI (Herbert & Pollatos, 2014; Koch & Pollatos, 2014; Murphy et al., 2017) or neural density/activation in the insula (Rasmussen et al., 2017; Smucny et al., 2012), little attention has been given in directly contrasting known drivers of ingestive behaviour with interoceptive abilities. In Paper 3, there was preliminary evidence that SLs may use satiation signals and signals generated from body's energy stores (adipose tissue, fat free mass) rather efficiently and even independently of the influences of the obesogenic environment. As taste hedonics is an important effector mechanism that contributes to the regulation of food intake, it is critical to measure what effects, if any, sweet-liking phenotypes have on objectively obtained interoceptive abilities and whether these differences are evident across different interoceptive modalities. To our knowledge, no study has investigated those links.

Sixty four females between 18 and 34 years of age participated in this study. In line with previous findings highlighting larger discrepancies in a number of characteristics (beyond sensory profiles) between SLs and SDs than between SLs and IUs (Paper 3), only SLs and SDs were recruited for this study. The classification method proposed in Paper 2 was used to discriminate between the distinct sweet-liking phenotypes. Besides obtaining the common measures of cardiac interoception, due to the overlap through the vagus nerve between gut-derived afferent signals related to sweetness/sugars and those related to satiety (Clemmensen et al., 2017), elucidating phenotypic differences in interoceptive performance directly linked to one's ability to sense internal signals generated from the stomach was deemed essential. Accordingly, a bimodal interoception protocol was administered which involved a water load task and a series of heartbeat tasks. A newly developed water load task was utilized a which has been developed to account for total stomach capacity in determining gastric interoceptive abilities (van Dyck et al., 2016). Regarding the cardiac interoception measures, classic heartbeat tasks were used (heartbeat tracking task: Schandry, 1981;

heartbeat discrimination task: Whitehead et al., 1977) accompanied by subjective measures of interoception that allow for metacognitive awareness (i.e., match between interoceptive accuracy and confidence in the correctness of associated responses), interoceptive sensibility (i.e., own beliefs about sensitivity to internal signals), and trait prediction error (i.e., discrepancy between interoceptive accuracy and sensibility) to be calculated (Garfinkel et al., 2015, 2016; Garfinkel & Critchley, 2013). Eating patterns and behaviours reflecting different components of interoception were also assessed through questionnaires.

As hypothesised, our exploratory analysis revealed that SLs outperformed SDs on all measures of interoceptive accuracy: that is accuracy in the heartbeat tracking task, accuracy in the heartbeat discrimination task and sensitivity to stomach distention in the water load task (i.e., SLs ingested less water than SDs to feel satiated). There was no evidence for phenotypic differences in any of the remainder interoceptive measures meaning that SLs might be unaware of their abilities in sensing internal signals accurately, albeit being better than SDs at doing so. Regarding the two eating patterns under investigation which have principles of interoception at their core, SLs scored higher on most components of both intuitive and mindful eating. This finding was only partially explained by individual variation in interoceptive accuracy suggesting that one's hedonic response to sweetness may have some independent contribution to homeostatic eating. SLs' enhanced interoceptive abilities were also evident with regards to perception of sensations related to emotions. Particularly, SLs scored higher than SDs in emotional eating (but not in external eating); negative relative to positive emotions were found to trigger greater increases in SLs' energy intake. Collectively, the SL phenotype emerged as a phenotype of enhanced responsiveness to internal cues with possible applications in understanding the underpinnings of the individual variation in responsiveness to the obesogenic environment.

1.4 Sugar 'addiction' as a driver for overconsumption – Introduction to Paper 5

Throughout our lives we learn to associate food choices and intake with the subsequent reinforcement from consuming the food. Within this conditioning learning framework whereby repeated exposure has a central role (O'Doherty et al., 2017), food

cues recruit decision-making brain regions across the prefrontal and cingulate cortices integrating signals from areas involved in taste hedonics and other extrinsic and intrinsic processes (Rangel, 2013). It has been proposed that 'food addiction' described as the hedonic-driven consumption of highly palatable foods and beverages beyond energy requirements (Kalon et al., 2016), is underpinned by the hijacked reward centres in the brain and associated impairment of ingestive decision-making processes caused by repeated choice and intake of hyperpalatabe foods in a viscous cycle (Wiss et al., 2018). Similar to individuals addicted to drugs of abuse when compared to healthy controls, those with 'food addiction' versus individuals who score low in the relevant 'food addiction' assessment scales (e.g., Yale Food Addiction Scale: Gearhardt et al., 2009, 2016) demonstrate different brain activation patterns and connectivity in reward circuits in response to the consumption of hyperpalatable foods (reviewed in Kalon et al., 2016). Additional neuroimaging data highlight differential effects of 'food addiction' on the hypothalamus with consequences for satiety networks (reviewed in Kalon et al., 2016).

Questioning the growing view that certain foods and beverages, particularly those high in sugars and fats, may be addictive (Meule, 2015), in a review on the foundations of 'food (sugar) addiction', authors noted that, despite the neural correlates shared by substance and food 'addicts', the overlapping is limited to the following five out of eleven criteria for substance use disorder (DSM-V: APA, 2013): use of larger amounts and for longer than intended, craving, hazardous use, tolerance, and withdrawal (Wiss et al., 2018). To incorporate the evidence that, similar to other behaviours, eating, can become addictive but overeating does not fully meet the criteria of other substance-related phenomena, Hebebrand and colleagues introduced the alternative term 'eating addiction' (Hebebrand et al., 2014).

Although the basic premise of 'food addiction' appears to be somewhat questionable (Westwater et al., 2016; Ziauddeen & Fletcher, 2013), the literature in 'sugar addiction' calls for special attention. Sugars that are a major component of foods palatability and have intrinsic reinforcing properties of both an evolutionary/homeostatic (1.1.4.2) and hedonic (1.1.4.3) basis, could clearly lead to habituation and even addiction thereby uniquely contributing to overconsumption and

the obesity epidemic. However, it should be noted that while there is an interaction between 'food addiction' and obesity, 'food addiction' is also extended to non-obese populations (Meule & Gearhardt, 2019). For instance, whilst 15% of the US population consider themselves as 'food addicts' (Schulte & Gearhardt, 2018), over two thirds of the adult population in the US are obese (Flegal et al., 2016). On the other hand, a relevant meta-analysis has reported an average prevalence of 'food addicts' as high as 19.9% (Pursey et al., 2014) which approximates the prevalence of other drugs of abuse like alcohol (Grant et al., 2015) and tobacco (Chou et al., 2016).

Considering the role of taste and particularly the role of sweetness in reward processing of gustatory stimuli (1.1.3), phenotypic differences in liking for sweetness could explain the reason why not all food-addicted people are obese and not all those with obesity are food-addicted. Being a SLs may then indicate a higher risk for sugar addiction relative to being a SD. Contrastingly, in this thesis, evidence of lower body fat and lower sensitivity to the influences of the external environment in ingestive behaviour were presented (Papers 3 and 4). These possibilities merit scrutiny. Secondly, the relationship between hedonic response patterns to sweetness and addiction or predisposition to addiction to drugs of abuse has been widely researched by Kampov-Polevoy and other groups that followed his methodological approach to identify distinct sweet-liking phenotypes. For example, alcoholics or individuals addicted to other drugs of abuse are more often SLs than SDs (Janowsky et al., 2003; Kampov-Polevoy et al., 1997, 1998, 2001; Krahn et al., 2006). Likewise, positive familial history of alcoholism (Kampov-Polevoy, Garbutt, et al., 2003; Kampov-Polevoy, Ziedonis, et al., 2003; Wronski et al., 2006) or individual risk for developing alcohol-related problems (Kampov-Polevoy et al., 2014; Lange et al., 2010) has been associated with the SL phenotype . Response to treatment for alcohol dependence has also found to differ by phenotype such that the SL phenotype attenuates effectiveness (Garbutt et al., 2009, 2016).

Drawing on the above, questions remain regarding the veracity of 'sugar addiction' and as to whether, on the basis of preventing short-term ingestive drives from being converted into compulsive behaviours, current initiatives to regulate sugar intake by taxing sugar-rich food products or restricting their advertising as it applies to other addictive commodities (e.g., alcohol, tobacco) are in the right direction (Wiss et al.,

2018). Addressing these questions by considering individual variation in sweet-liking might prove rather fruitful.

1.4.1 Repeated exposure to sugars as a driver for overconsumption; the role of distinct sweet-liking phenotypes – Summary of Paper 5

Considering the evidence about the potent reinforcing and appetitive properties of sugars and sweetness, it remains possible for overconsumption of sugars and/or sweet tasting foods to influence ingestive decision making towards intake beyond homeostatic needs. Should this 'sugar addiction' be empirically supported, it may threaten diet quality (Britten et al., 2000), weight control (Hu, 2013; Te Morenga et al., 2013), and metabolic health (Lean & Te Morenga, 2016; Te Morenga et al., 2014). In that context, over the past decade, initiatives aiming to curtail consumption of sugar-rich products through introducing dietary guidance for sugar intake (SACN, 2015; USDA, 2015; WHO, 2015) and/or sugar tax for beverages have been proposed to 'unsweeten' the world's diet (Yang, 2010) and fight the current obesity epidemic. As empirical evidence on the role of overconsumption of sugars in altering gustatory hedonics is very limited and often obtained from methodologically poor studies, the question remains as to whether the pleasure elicited by exposure to sugars feeds back to stronger liking for sweetness or even enhances a broader liking for highly palatable food options.

A randomized controlled trial was conducted where predetermined amounts of high-sugar/low-fat breakfast items and snacks tailored to individual energy needs were consumed for eight consecutive days (exposure condition: n = 62) relative to a no-exposure (control group: n = 31). The focus was to ensure a relatively high intake of sugars (at least 10% of individual energy requirements from sugars) to investigate how sugars' reinforcement properties may affect liking for both sweetness and a number of snack foods and beverages typical of a Westernised diet. Given the previously proposed phenotypic differences in the susceptibility to influences of the obesogenic environment (Paper 3) and interceptive abilities (Paper 4), whether or not individual variation in hedonic response to sweetness alters the effects of a high-sugar diet on broader gustatory hedonics was also explored through targeted recruitment of the three distinct sweet-liking phenotypes.

As was expected based on the principles of sensory specific satiety, analysis of post-exposure ratings for liking of 1 M sucrose solution revealed that, as opposed to the control group, participants exposed to the high-sugar diet significantly reduced their liking for sweetness whilst perceived sweetness intensity remained unaffected; sweet-liking phenotype failed to interact with the above results. However, findings focusing on changes in liking over time for the repeatedly consumed real food products (high-sugar breakfast items) among participants in the exposure condition did not align with the effect of overconsumption of sugars on liking for sweetness assessed using simple taste solutions: with the exception of orange juice that was even rated as more pleasant, no change in liking was observed. The view that the 'addiction-like' properties of sugars may override sensory fatigue in contexts which involve food sources that elicit pleasure (versus unconditioned/unfamiliar aqueous solutions), could be somewhat supported. Pertaining to the effect of overconsumption of sugars on liking for highly palatable foods without regards to their predominant taste quality, it was found to be fully dependent on individual differences in hedonic response patterns to sweetness: SDs were affected the most from the dietary intervention. Specifically, while SDs in the control group rated the snack foods and beverages as significantly less pleasant during the second food taste test compared to their baseline ratings, that decline in liking was attenuated (even borderline reversed) among SDs who were exposed to the high-sugar diet: in contrast, exposure had not effects on associated liking in SLs or IUs. Questions are raised as to whether such an effect of sugar overconsumption on liking may also project to alterations in ingestive decision making with regards to intake of hyperpalatable foods and beverages of low nutritional value and often high energy density.

1.5 General Conclusions

Despite improvements in obesity prevention and treatment strategies, the prevalence of individuals suffering from overweight or obesity is on the rise in most societies worldwide (Bentham et al., 2017; Livingston, 2018). This modern epidemic calls for further understanding of the individual drivers of food choice and intake and more effective approaches to monitoring them both. Although the relative importance of the multi-factorial causes of food choice and intake remains unknown, the role of sensory

aspects of feeding, and particularly of taste hedonics, on ingestive behaviour and hence on health outcomes including obesity, is evident throughout the literature (1.1.3). This thesis therefore focuses on hedonic responses to sweetness.

As detailed in Paper 1, over the 50 years that followed the pioneering work of Pangborn, who identified three distinct hedonic response patterns to sweetness and challenged the common belief that sweetness is universally liked, her approach has given way to different methods, which have often dichotomously classified individuals into SLs and SDs; classification criteria also varied between methodological approaches and researchers. Misclassifications aside, heterogeneity in aspects of psychometric protocols *per se* – such as the concentration range of taste stimuli, the rating scales where hedonic responses were captured and so forth (Bartoshuk et al., 2006) – also negated any consensus on the various implications of distinct hedonic responses to sweetness. Indeed, although there is no scarcity of empirical data in the literature, such data has failed to show clear relationships between sweet-liking and dietary intake (Tan & Tucker, 2019) or weight outcomes (Cox et al., 2016). Therefore, to effectively personalise the conversation about public health strategies targeting the underpinnings of overconsumption, this thesis aimed, first, to robustly identify the true number and nature of hedonic response patterns to sweetness; secondly, to develop a standard approach to assessing sweet-liking by establishing an agreed set of classification criteria, which will enable a broader use of sweet-liking phenotyping methodology; and finally, to re-evaluate the influences of sweet-liking phenotypes on aspects of human ingestive behaviour and on the consequences of food choice and intake, that is, weight status and body composition.

Using the statistical method that emerged as the most reliable method from reviewing the prior literature (Paper 1), in Papers 2 and 3 it was demonstrated that the hedonic value of sweetness could be expressed as a monotonic increase in liking as sucrose concentration increases (SL phenotype), an inverted U pattern (IU phenotype), or a monotonic decrease (SD phenotype). This conclusion aligns with other recent studies (Garneau et al., 2018; Kim et al., 2017; Qian Yang et al., 2019), which used the same phenotyping method to identify distinct hedonic responses to sweetness coupled with adequate sample sizes to allow for those different groups to emerge, and

chemosensory protocols similar to the protocol presented here regarding the nature of the sweet-tasting stimuli and participants' motivational state (hunger/thirst). Further supporting the robustness and meaningfulness of these sweet-liking phenotypes and their potential direct link with the secondary gustatory cortex in the OFC and ultimately the reward systems in the brain (Rolls, 2000), it was statistically and graphically demonstrated that observed phenotypic differences in sweetness perception had a non-significant aka menial role in the identification of the distinct hedonic response patterns to varying sweetness (see 3.5 for details). Moving a step forward, a quick but statistically robust phenotypic protocol classifying individuals into SLs, IUs, or SDs based upon whether their hedonic score for a single sucrose concentration was higher or lower than particular cut-off liking values was also developed (Paper 2). Its validity was tested and confirmed in a second population (Paper 3). Additionally, in Paper 5 it was demonstrated that utilising the proposed sweet-liking phenotype classification criteria reveals a stable taste hedonic trait.

As for the second objective, based upon the present datasets there was suggestive evidence that higher liking for potent sweetness, expressed as the SL phenotype, was related to a broader phenotype of enhanced responsiveness to internal cues. This link between the SL phenotype and the internal body was documented for both homeostatic and emotional needs, with possible indirect effects on ingestive behaviour (see next paragraph for details). Instead, SDs appeared to be more sensitive to influences from the external environment, which even interfered with their innate food preferences. Regarding the direct effects of sweet-liking phenotypes on dietary intake, with the exception of SLs using strong alcoholic drinks more frequently and consuming less fibre, the empirical work conducted in this thesis failed to suggest other significant links.

In more detail, in Paper 3 classification into the SL phenotype was linked to either higher fat-free mass or lower body fat, both reflecting an increased need for energy. According to the set-point hypothesis, the homeostatic system has the potential to respond to states of negative energy balance such as energy expenditure or caloric restriction by driving the return of energy stores to their biologically defended level (Speakman et al., 2011). Elevated fat-free mass, with its known increased energy

demands (Ravussin et al., 1986), can trigger this event cascade. Body fat that releases proportional amounts of leptin (Fried et al., 2000) may also create a feedback loop, whereby relatively low levels of leptin promote food choices that are rich in energy (lipostatic model: Kennedy, 1953). Considering the functionality of sweet-liking for rapid stages of growth (1.1.4.2), the well-established age-related decline in sweet-liking (Venditti et al., 2020), which due the small age range in the study samples recruited for thesis was only evident in Paper 4, may also imply some overlap between the degree of liking for sweetness and internal body state and needs. Strong liking for potent sweetness, i.e. the SL phenotype, has been reported to coincide with elevated growth markers during late childhood and early adolescence (Coldwell et al., 2009; Mennella et al., 2014).

The enhanced responsiveness to homeostatic- and emotional-specific internal needs in SLs as opposed to primarily SDs was also evident through phenotypic differences in objective measures of interoception, as well as questionnaires capturing interoceptive-like eating patterns and behaviours. In brief, in Paper 4, preliminary data indicated that SLs performed better than SDs in sensing both generic interoceptive signals (heartbeats) and relevant signals associated with gut-brain communication (gastric satiation and fullness). Mindfulness and intuitive eating (Paper 4), as well as trait hunger (Paper 3), i.e. eating patterns and behaviours suggesting enhanced reliance on internal signals to initiate and/or terminate food intake, were also linked to the SL phenotype. Consistent with contemporary theories of interoception pointing to a link between interoceptive abilities and higher-order cognition including emotional awareness (Murphy et al., 2017), in Paper 4 SLs who demonstrated high interoceptive abilities also reported increasing their usual food intake as a coping mechanism when they were experiencing negative emotions (and not positive emotions), presumably in an effort to secure some source of reward.

Examining the components of the proposed profile of SDs to understand the role of sweet-liking patterns in overconsumption, it is reasonable to suggest that SDs' relatively poor responsiveness to internal cues signifying the body's need state contributed to their increased susceptibility to influences from the external environment. Specifically, the SD phenotype was the subgroup most affected by

repeated exposure to a high-sugar diet, as described in Paper 5, shifting their innate food preferences (disliking for highly palatable snacks) in the opposite direction.

Finally, although both Papers 3 and 5 failed to match the proposed classifications of distinct sweet-liking phenotypes with most of the components of baseline dietary intake (i.e., SLs consume more sugars, sugar-rich snacks, or sweetened beverages than SDs), some special mentions should be made. First, the view empirically supported throughout this thesis that classification into sweet-liking phenotypes underpins differences in responsiveness to internal cues may highlight an indirect effect of sweet-liking on ingestive behaviour, with possible long-term outcomes in weight status. Indeed, any impairment in sensitivity to eating-related internal signals has been proposed as a major cause of overconsumption in modern affluent food environments (Sample et al., 2016); whereas the effects of such impairment appear to start as early as in infancy (e.g., breastfeeding versus bottle feeding: DiSantis et al., 2011; Fildes et al., 2015) and childhood (e.g., restrictive parental feeding practices, use of food as a reward, plate-clearing practices etc: Brunstrom et al., 2005), contributing to intake beyond homeostatic needs and ultimately obesity later in life. In Paper 4, the observation that, in SLs, enhanced sensitivity to the body's internal state was coupled with more efficient resistance to obesity (e.g., personal and familial history of effortlessly maintaining a healthy weight) dovetails with the above narrative.

Similar arguments could be made regarding the few phenotypic differences in dietary habits. Although there was no relationship between sweet-liking phenotypes and intake of sugars, two diet-related findings are worth noting. First, the higher habitual use of alcohol, with its well-established rewarding properties (Barker & Taylor, 2014) by SLs in comparison to SDs, and second, the lower intake of fibre by SLs in comparison to SDs which may underpin an evolutionary-based aversion toward the bitterness elicited from foods high in fibre such as vegetables and whole grains to protect against toxins and poisons (Bakke & Vickers, 2007; Drewnowski & Gomez-Carneros, 2000). Both findings suggest that SLs represent a phenotype characterised by enhanced sensitivity to internal signals hardwired to humans from birth. In fact, elevated sensitivity to reward was found to be a trait characterising those classified into the SL phenotype (Paper 3); this observation resonates with the wealth of evidence regarding

the rewarding effects of sweetness via both gustatory and post-ingestive pathways (1.1.4.3). Elevated sensitivity to reward in SLs could also call for a closer examination of the principles of delay discounting theory (i.e., depreciation of the value of a reward as reward's release time increases: reviewed in Odum, 2011) discussed in Paper 2 in relation to hedonic responses to sweetness. In the context of the modern environment which is saturated with hyperpalatable foods (Sørensen et al., 2003), the prospect of immediate gratification from these food over competing long-term goals of eating healthily and maintaining a healthy weight calls for action. Therefore, differences in cognitive biases such as in delay discounting may play a role in ingestive decision making by predisposing some (plausibly SLs) towards overconsumption of highly palatable foods and beverages, sweet tasting foods and beverages included. Although trait impulsivity, which includes delay discounting as one of its facets, did not differ by phenotype when we assessed it using a standardised questionnaire (Papers 3 and 4), more specialised measures of discounting, i.e., discounting tasks (Matta et al., 2012) could be considered by future studies. Steeper rates of discounting future rewards have, indeed, been proposed to predict unhealthy eating (Barlow et al., 2016) and obesity (Amlung et al., 2016) in human participants.

Furthermore, in this healthy, young, and lean sample, it is also plausible that other factors such as peer pressure, cost and access (Mela, 2001) may have had a stronger influence on food choice and intake than taste hedonics. In support of the latter, Tuorila and colleagues (2008) showed that liking a product explained roughly 60% more variance of likelihood to buy compared to use frequency. Indeed, in Paper 5, although ratings for liking and desire-to-eat of highly palatable snacks were lower in SDs, this phenotypic variability was not evident for reported intake of the same foods and beverages. It is worth noting that in the relatively older subgroup of participants in Paper 3, who were more exposed to the obesogenic environment, some variance in anthropometrics was explained by intake of sweetened beverages.

1.5.1 Limitations

Although reasonable efforts to ensure that all experiments carried out as part of this thesis were of a high standard were taken, before discussing potential future directions of the present work, some limitations that may, at least in some part, restrict the conclusions drawn should be considered. To note, experiment-specific limitations are addressed in the relevant papers, but an overview is presented here, too.

1.5.1.1 Participants

An important consideration is whether variables related to characteristics of the participant pool used for all experiments detailed within this thesis may limit a wider interpretation of the observed findings. Specifically, due to recruitment largely conducted on Psychology students at the University of Sussex, participants were educated and relatively young and lean; the majority self-identified as Caucasians; and women mostly outnumbered men. In epidemiological studies dietary measures are often mediated by socioeconomic status including education level (Maguire & Monsivais, 2014), while sex and age are variables that may also affect diet and eating behaviour (Arganini et al., 2012), as well as chemosensory ability (Venditti et al., 2020); the latter was found to differ by sex and age in the present dataset, too. Thus, caution should be taken in generalising this research to groups of individuals who are older or with obesity or may show more ethnic or socioeconomic diversity.

1.5.1.2 Sensory measures

All sweetness-related sensory evaluations were based on tasting and rating aqueous sucrose solutions. From the caloric sugars available, sucrose dissolved in water has been the most commonly used sweet tasting stimulus in recent sensory research (Calvert et al., 2020; Iatridi et al., 2019), while it has also long been studied in terms of taste receptors and neural processing (Han et al., 2019). As far as complex carbohydrates is concerned, human capacity to identify their taste quality has only recently been proposed (Low et al., 2017). There is also a growing appreciation that non-nutritive sweeteners (NNSs) may not fully share caloric sugars' known rewarding and appetitive

properties related to expression of sweet liking or disliking (1.1.4.3). Also, still more work is required to elucidate how NNSs interfere with the established links between sweetness and post-ingestive neuroendocrine signalling (Yunker et al., 2020). For instance, it has been suggested that incongruent exposure to sweetness such as through NNSs may undermine sweetness as a cue for the learned control of energy intake (Veldhuizen et al., 2017; Wittekind et al., 2018).

Regarding the use of food stimuli, a few issues require serious consideration. The first concerns the effect on perceived liking of the stored information (conditioned learning) about the sensory-mediated hedonic and satiety value and other post-ingestive consequences of the food stimulus, i.e. its intrinsic characteristics, derived from previous exposure to that or a similar product (Piqueras-Fiszman & Spence, 2015). Taste-related extrinsic information prior to ingestion has also been found to be associated with changes in liking ratings. For example, in Okamoto et al., participants liked basic taste solutions labelled with a food-related descriptor (e.g., caramel candy for sweet taste, lemon for sour taste, etc.) more than the same stimuli served with a numerical label (Okamoto et al., 2009). From a neuroimaging perceptive, providing taste-related information at pre-ingestion has been shown to increase activation in gustatory brain areas including the frontal operculum and the orbitofrontal cortex where the reward value of the sensed taste is coded (e.g., Barrós-Loscertales et al., 2011; Veldhuizen et al., 2012). Olfactory cues triggered by flavours within foods (Prescott, 2015) and visual appearance including colour (Piqueras-Fiszman & Spence, 2014) can also set up expectations about the stimulus one is about to experience; potential disadvantages in use of coloured or flavoured stimuli such as Kool-aid or fruit juices (e.g. Grinker, 1977; Kim et al., 2014; Weafer et al., 2014) to measure sweet-liking arise. Collectively, as one becomes exposed to a familiar food product or tastant to evaluate its taste, previously experienced information may turn into expectations that are likely to influence liking ratings in several ways (e.g., assimilation-contrast theory; reviewed in Piqueras-Fiszman & Spence, 2015).

The picture becomes more complicated when food products high in both sugars and fats are chosen to measure liking for sweetness (e.g., Jilani et al., 2019; Monteleone et al., 2017). From a purely sensory perspective, fats are known to mask sensory inputs

from sugars and vice versa (Drewnowski & Almiron-Roig, 2010; Hayes & Duffy, 2008; Mennella et al., 2012). Perceived sweetness also decreases with viscosity which in principle, is expected to be elevated in sugar-fat mixtures (Arabie & Moskowitz, 1971). With regards to investigation of the effect of hedonic response to sweetness on weight outcomes, an additional consideration relates to attitudes toward high-sugar/high-fat products that may be specific to sugar-fat mixtures (Yanovski, 2003). As an example, Drewnowski (1991) showed elevated preferences for sugar-fat mixtures in obese participants with history of repetitive dieting relative to those being obese but not having experienced major fluctuations in their body weight; a similar finding was reported when lean individuals who were previously obese were compared to always lean counterparts (Drewnowski et al., 1985).

Regardless of the taste stimuli used to investigate affective responses to sweetness, laboratory based sensory measures have been criticised as possibly unrelated to sensory interactions on real life consumption and/or unrepresentative of the way these abilities manifest outside of the laboratory (Bell & Meiselman, 1995; Rozin & Tuorila, 1993). As detailed above and stressed elsewhere too (Moskowitz & Krieger, 1995), due to the complexity of liking for real life food products and the multisensory aspects of feeding behaviour overall, the use of simple taste solutions was considered to best serve the present research hypotheses. Additionally, significant efforts were made toward following standardised (if available) and well-controlled procedures to eliminate possible confounders and aid comparisons with similar work by others. For example, participants were instructed against participating in sensory tests whilst being under extreme states of hunger or satiation. Besides the empirical evidence citing mechanisms involved in alliesthesia (Cabanac, 1979), a recent meta-analysis of neuroimaging studies also stressed that motivational state modulates activation in brain regions related to affective reactions elicited by sweetness (Chen & Zeffiro, 2020). Although the amount of energy contained in taste samples could be considered as negligible, decoupling oral response to sweetness from possible post-ingestive effects of sucrose was deemed critical: a strict sip-and-spit protocol was followed throughout (Running & Hayes, 2017).

Regarding quantification of the sensory information, acknowledging the clear lack of an ideal scaling method to collect subjective ratings of liking and intensity (Bartoshuk et al., 2003; Cardello, 2017), all participants received scale-specific standardised training (Bartoshuk et al., 2006; Green et al., 1996; Sharafi et al., 2015) ahead of the sensory tests. This might also allow for low or high scale users to be identified, i.e., when individuals systematically make less use of the extreme responses. This phenomenon is likely to be of significant relevance to the sweet-liking phenotyping method proposed in Chapter 3 where individuals are classified into the distinct sweet-liking phenotypes based on the evaluation of a single sucrose solution and pre-determined liking cut-off values. For example, SLs low scale users and SDs high scale users might rate liking for 1 M lower than +15 and higher than -15 on the -50/+50 VAS, respectively, resulting in their misclassification into the IU phenotype. This limitation might be mitigated, as in the proposed single solution sweet taste test, rating liking and intensity of a water blank solution preceded each series of the 1 M sucrose solution.

1.5.1.3 Dietary measures

The first limitation in relation to dietary measures relates to the inability to collect detailed dietary data from participants recruited in both the UK and the US. Regarding the 24h dietary recalls which were available for the UK sample only (Paper 3), it has to be noted that free-living measures of real life food intake are typically subject to random and systematic within person measurement errors varying in magnitude and direction depending on the method used (Gibson, 2005). Specifically, reporting dietary intake retrospectively has the disadvantage of relying on participant's memory, as well as their willingness to accurately and truthfully report all intake (Gibson, 2005). In fact, asking participants to keep their own dietary records to eliminate memory lapses would have added more noise to the dataset due to the nature of the food products of most interest, i.e. highly palatable foods and drinks rich in sugars: recording your own food intake is known to inadvertently reduce intake through self-monitoring (Yu et al., 2015), while there is evidence showing biased underreporting towards intake between meals (i.e., snacks) in women independent of their BMI (Poppitt et al., 1998). Finally, underreporting is a pervasive problem primarily in women with overweight or obesity

(Braam et al., 1998), which is a group significantly underrepresented in this thesis. Nevertheless, protocols that both prevented and addressed misreporting were employed (see 4.2.4 and 4.2.5 for details).

In similar lines, using population-specific validated FFQs, semi-quantitative information about the habitual use of beverages only was obtained. Given the mounting evidence highlighting that intake of SSBs predicts obesity development (1.2.1), analysing the habitual use of beverages with a special focus on products with both caloric and NNSs to gain insights into dietary habits in relation to sweet liking was deemed justified. The view that thirst is likely to be a more stable determinant of motivated behaviour relative to hunger (McKiernan et al., 2008), further supports the selection of beverages relative to focusing on other sweet tasting food products. Finally, despite FFQs considered an insufficiently valid measure of dietary intake on an individual basis due to the risk of underreporting, it should be born in mind that such issues call for serious caution primarily when absolute intakes of macronutrients are estimated (Molag et al., 2007). Thus, the cross-country approach used in Paper 3 to assess dietary intake that may relate to sweet liking should not be totally discredited. In addition, given the observed differences in the fibre content of SLs' and SDs' diets, as well as the research identifying bitterness as a sensory deterrent to consuming vegetables (Drewnowski & Gomez-Carneros, 2000), collection of FFQ data discriminating between the habitual intake of fibre-rich foods of different sensory characteristics (e.g. citrus *vs*. non-citrus or astringent *vs*. non-astringent fruit, cruciferous *vs*. non-cruciferous or starchy *vs*. non-starchy) would be of interest in future research (e.g., Catanzaro et al., 2013; Fogel 2015; Gervis et al., 2019).

1.5.2 Suggestions for future research

Given the inconsistencies in the scope of research evaluating the role of sweet-liking and disliking in overconsumption and the findings reported in this thesis, a number of directions may be taken to further understand the nature of the effects of distinct hedonic response patterns to sweetness.

Besides the broader use by future studies on gustatory hedonics of the proposed sweet-liking classification criteria to facilitate consensus in phenotyping results (Paper 2), it would be important to replicate the results found in Paper 3, suggesting phenotypic differences in fat-free mass and body fat, particularly as the hypotheses tested here have not been studied previously, with one exception in which the body composition assessment protocol was unstandardised (Garneau et al., 2018). That said, it is not known whether in the extant literature there would have been differences in studies focusing on BMI exclusively. BMI, although easily obtained and a convenient proxy measure of adiposity, has its limitations in capturing additional details about body composition at an individual level, such as differences between upper and lower body fat deposition (Vazquez et al., 2007), and discrimination between body fat and fat-free mass, particularly for values below 30 kg/m^2 (Okorodudu et al., 2010). This is not to suggest that BMI has absolutely no prediction value for overall fatness. As an example, in a prospective cohort of over 15,000 adults in the US, obese participants who were metabolically healthy at baseline had four times higher risk of developing metabolic syndrome after nine years of follow-up than the normal weight comparison group (Bradshaw et al., 2013). However, given the evidence from this thesis and other groups (Kim et al., 2017; Qian Yang et al., 2019, 2020) regarding the ethnic differences in the prevalence of the distinct sweet liking phenotypes, the use of BMI as an indirect index of adiposity may be particularly problematic in sweet-liking research. For example, Asian populations, who are classified into the SDs phenotype more often than Caucasians (Qian Yang et al., 2019, 2020), also display a greater proportion of body fat for a given BMI than those from a White ethnic background (Rush et al., 2007). On the basis of age-related decline in sweet-liking (Venditti et al., 2020), similar challenges may apply with middle-aged/older adults, for whom waist circumference is more important as an indicator of health (Huxley et al., 2010).

Taking the worldwide projections for obesity (Kelly et al., 2008) and calls for alternative public health strategies (Livingston, 2018) into account, shifting efforts and associated empirical investigation towards more tailored approaches that utilise interpersonal characteristics – including individual susceptibilities related to the multi-faceted forces of overconsumption and consequent unsuccessful weight management – appear promising (Shah et al., 2017). For example, one parameter of the failure to make progress in obesity management is that, over the long term, the majority of individuals regain most of the weight lost through hypocaloric dieting (Pronk & Wing, 1994; Safer, 1991). Defensive homeostatic (Speakman et al., 2011) and psychological mechanisms, including eating behaviours (van Strien, 2020), seem to act in concert with the increasingly tempting food environment and motivate overconsumption (Sørensen et al., 2003). Based upon the findings from Papers 3 and 4, in which different sweet-liking phenotypes reflect different levels of contribution of homeostatic signals to food choice and intake, a key goal of future research should investigate whether the development of lifestyle interventions tailored to one's sweet-liking phenotype could better address some of the outstanding challenges in counselling on weight loss. Clinical trials testing the relative effectiveness of interventions regulating emotional eating and reward sensitivity in SLs, whilst focusing on resetting homeostatic eating in those identified as SDs, would be of great value.

Pertaining to the effects of exposure to a high-sugar diet, there are few remaining questions other than those already addressed in Paper 5. Firstly, it would be interesting to explore whether it was sugars or sweetness that mediated the effects of the high-sugar diet on subsequent food preferences. This is particularly important for a number of reasons. As detailed in 1.1.2, a growing body of evidence has suggested causal links between sugar overconsumption and the risk of weight gain; multiple dietary recommendations on added sugars have been developed accordingly (SACN, 2015; USDA, 2015; WHO, 2015). On the other hand, Cox and colleagues argue that as taste, which is commonly identified by consumers as synonymous with palatability, determines food choice and intake, the food industry will not easily compromise on it and will seek ways to reformulate foods and beverages that retain their sweetness (Cox et al., 2016). Therefore, the use of non- NNSs has become a popular alternative to sugar,

contributing no calories while satisfying the craving for sweetness (Yunker et al., 2020). Furthermore, as part of national policies to tackle sugar overconsumption, numerous countries now tax sugar-rich products with an emphasis on SSBs (Backholer et al., 2017; Colchero et al., 2016; Lee et al., 2019; Zhong et al., 2018); Chile even introduced beverage warning labels as part of the country's relevant legislation (Correa et al., 2019). However, to date, sugar taxation has targeted caloric sugars and not overall sweetness in human diets; thus, the above mentioned policies have indirectly been facilitating use of beverages sweetened with NNSs (Winkler, 2019). Despite some preliminary evidence indicating that NNSs somewhat differ from caloric sugars in brain activation related to satiation and reward (Yunker et al., 2020), sweet-tasting molecules, regardless of caloric content, share most oral and gastrointestinal receptors which activate the known metabolic and neuroendocrine pathways related to sweetness (1.1.4.1). It is unclear whether switching to NNSs alters one's appetite for sweetness and/or hyper-palatable foods and beverages. Limited studies on the topic indicate that replacing SSBs with beverages sweetened with NNSs did not sustain the desire for sugar overconsumption over the period of intervention (Appleton et al., 2018), while others have shown that NNSs consumption early in life was associated with heightened motivation for sweet-tasting foods (Yunker et al., 2020).

Another consideration might be whether the observed phenotypic-specific shift in liking for highly palatable foods and beverages following the exposure to a high-sugar diet translates to consumption (Paper 5). Contrary to the simplified model of food choice and intake demonstrated in Figure 1.1, diverse signals originating from the gastrointestinal tract, internal energy stores, the external environment, cognitive, learned and social factors, and many other sources are implicated in ingestive decision-making (Woods, 2013). Indeed, unlike the significant effect of phenotype on baseline food likings reported in Paper 5, no equivocal phenotypic differences in associated intake frequency were revealed. Therefore, future research could benefit from monitoring one's dietary intake before and after such experimental protocols using rigorous dietary tools that do not undermine spontaneous consumption (e.g., 24h recalls over food diaries: Yu et al., 2015) and ultimately fill critical gaps in knowledge regarding how to approach sugar reduction strategies. For example, providing that

future research will corroborate the link between diet-induced alterations in liking for highly palatable snacks and overconsumption, taxing high-sugar products in a population with a large representation of SDs who were seen to be prone to influences from the external environment (Paper 5) might be fruitful. The opposite would be true for populations dominated by SLs who, due to their oversensitivity to reward (Paper 3) and enhanced interoceptive abilities (Paper 4), might be at risk of overconsumption when exposed to environments that promote restrained and disinhibited eating behaviours (Chen et al., 2018); criminalisation of food components and dieting messages are believed to sustain such problematic traits (Berg et al., 2018; Schaumberg et al., 2016).

While there are many additional aspects in research on sweet-liking phenotypes to consider, and much controversy still surrounds a large portion of the literature, the most prominent suggestive evidence that emerged in this thesis was that liking for ever-higher sweetness reflects a broader phenotype of enhanced responsiveness to internal cues. Taking into account the obstacles to universal changes in an environment where ample options of highly palatable foods and drinks are readily available, it is worthwhile to ensure that modern humans are equipped with coping strategies that match their individual eating styles and susceptibilities to broader eating behaviours. Programmes and interventions designed to address overconsumption and obesity might benefit by identifying individual differences in sweet-liking. I hope that my research, and my focus on the sweet-liking phenotype classification method developed in this thesis in particular, will contribute to future work in the above directions.

Chapter 2 (Paper 1)

Reconsidering the classification of sweet-liking phenotypes: a methodological review

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Abstract

Human ingestive behavior depends on myriad factors, including both sensory and non-sensory determinants. Of the sensory determinants, sweet taste is a powerful stimulus and liking for sweetness is widely accepted as an innate human trait. However, the universality of sweet-liking has been challenged. Sub-groups exhibiting strong liking (sweet likers) or having aversive responses to sweet taste (sweet dislikers) have been described, but the methods defining these phenotypes are varied and inconsistent across studies. Here, we explore the strengths and weaknesses of different methodological approaches in identifying sweet-liking phenotypes in a comprehensive review. Prior studies (N = 71) using aqueous sucrose solution-based taste tests and a definition of two or more distinct hedonic responses reported between 1970 and 2017 were summarized. Broadly speaking, four different phenotyping methods have been used: 1. Interpretation (visual or statistical) of the shape of hedonic response curves, 2. Highest preference using ratings, 3. Average liking above mid-point or Positive/Negative average liking method, and 4. Highest preference via paired comparisons. Key methodological weaknesses included the use of subjective or arbitrary criteria as well as adoption of protocols unsuitable for large-scale implementation. Overall, we did not identify a method distinctly superior to the others. Given the role of both hedonics and reward in food intake, a better understanding of individual variations in sweet taste perception could clarify how sweet-liking interplays with obesity or addictive behaviors such as alcohol misuse and abuse. The development of a universally used statistically robust and less time-consuming classification method is needed.

Highlights

- Hedonic responses to sweet taste vary: 'sweet tooth' is not universal
- Four phenotyping methods using liking ratings for sucrose are commonly used
- Responses vary from increasing liking as sweetness increases to strong aversions
- Use of hierarchical cluster analysis minimizes subjective and arbitrary decisions
- We suggest classification via a statistically defined sucrose stimulus and cut-off values

2.1 Introduction

Poor food choices and overeating are key contributors to the etiology of many modern chronic diseases, mainly by influencing the development of obesity and obesity-related conditions such as type II diabetes (Darnton-Hill et al., 2004; Swinburn et al., 2011). Human ingestive behavior involves a complex interaction between sensory and non-sensory factors. Biologically determined factors (taste, hunger/fullness mechanisms, sensory-specific satiety), experience/memory with food (physiological and social conditioning), person-related characteristics (perceptions, beliefs, values, knowledge, family and social networks etc.), and social and environmental determinants (cultural and religious norms; food availability, economic environment, public policies, media etc.) operate together and formulate discrete food choice patterns (Contento, 2016; Drewnowski, 1997; McCrickerd & Forde, 2016). Of the sensory determinants of food choice, sweet taste is widely accepted as a powerful stimulus that generally signals pleasure (Drewnowski et al., 2012). According to the delay discounting theory (reviewed in Odum, 2011), this attribute of sweetness could presumably serve as an additional driver of food choice when immediate rewards (e.g. pleasure) are optimized over long-term benefits (e.g. health). Evidence from animal studies and human neuroimaging experiments suggest common neural pathways between addictive substances such as drugs and alcohol and sweet foods and beverages (Alonso-Alonso et al., 2015; Stice et al., 2013), further supporting this key role for sweetness in food acceptance.

The pleasure derived from tasting sweet substances has been considered as an innate response evidenced by the positive facial reactions of newborns from a variety of species to the experience of sweet tastes (Desor et al., 1973; Steiner, 1979; Steiner et al., 2001). Sweet taste stimuli have been reported as more preferable even prior to birth (de Snoo, 1937; Liley, 1972). Although the underlying mechanisms have still to be fully determined, sweet taste liking has typically been hypothesized to have evolved as a signal for the presence of a safe source of energy to support development and survival (Mennella et al., 2016).

The substance most commonly used to investigate the affective reactions elicited by sweetness is sucrose. During a laboratory-based sweet taste test (STT), various concentrations of aqueous sucrose solutions are presented either individually in

a randomized single-blind manner (Tables 2.1-2.4) or in a sequential dyadic manner (Table 2.5) in an attempt to determine the concentration perceived to be mostly preferred (see 2.3.4 for additional details). As a rule, two or more replications of each series of solutions are completed, typically using a "sip and spit" protocol. In the traditional STT (individual presentation), participants rate the perceived liking of each solution before rinsing his or her mouth with water and proceeding to the next solution. The hedonic evaluation of each stimulus is collected using rating scales, although the choice of specific scale varies broadly between studies. The most widely used are either unipolar n-point category scales, or Visual Analog Scale (VAS) or similarly anchored lines scales where liking is rated on a continuous dimension between two extreme possibilities (e.g. "dislike extremely" and "like extremely"); such line scales may or may not include a defined neutral point in the middle (Tables 2.1-2.4). The hedonic version of the general Labeled Magnitude Scale (gLMS) and unbounded ratio scales (i.e., magnitude estimation) have also been used (Tables 2.1-2.4). Although there is no evidence that the use of a particular scale during a STT facilitates the identification of the distinct sweet-liking phenotypes (Yeomans et al., 2007), considering that individuals may attribute different meaning to the same descriptor within a specific sensory modality, stripping away the internal labels from the rating scales could be beneficial (Hayes et al., 2013).

Researchers who use laboratory-based STTs have repeatedly described different hedonic responses to the same sweet taste stimulus, challenging the view that the expression of sweet-liking is universal. Early reports of these differential responses include those by Pangborn, and Thompson and colleagues, who observed different types of sweet-liking responses after they tasted sucrose solutions of various concentrations (Pangborn, 1970; Thompson et al., 1976, 1977). In later reports, a simpler distinction between SLs and SDs dominated. Alternative expressions such as low or moderate *vs*. high concentration likers, non-likers *vs*. likers and low *vs*. high preference group, as well as an additional grouping interpreted as a neutral hedonic response (the 'neutrals') have also been described. (Tables 2.1-2.5)

Despite some degree of conceptual agreement that distinct sweet-liking phenotypes exist, the methods that have been used to identify these individual

differences in affective responses to sweetness vary widely across studies. It is thus possible that the use of different methodological approaches to classify participants as sweet likers or dislikers contributes to inconsistencies in the literature regarding the relationship between sweet-liking phenotypes and associated behaviors such as real life sugar intake (Holt et al., 2000; Methven et al., 2016; Tuorila et al., 2017). Likewise, the interplay between sweet-liking phenotypes and body weight (Asao et al., 2015; Drewnowski, Henderson, Shore, et al., 1997; Drewnowski & Schwartz, 1990; Garneau et al., 2018; Goodman et al., 2018; Grinker, 1977; Grinker & Hirsch, 1972; Holt et al., 2000; Johnson et al., 1979; Kim et al., 2014; Malcolm et al., 1980; Methven et al., 2016; Thompson et al., 1976; Weafer et al., 2017; Yeomans et al., 2007; Yeomans & Prescott, 2016) or body composition (Coldwell et al., 2009; Garneau et al., 2018; Mennella et al., 2014) remains inconclusive.

As the global health community is struggling to address obesity and its disease burden (Livingston, 2018), moving beyond the narrow view that liking for sweet taste is innate and universal and recognizing that people live in different hedonic worlds, could help in tailoring personalized treatments as well as targeted prevention policies. In the present paper, the various methods that have been applied for the identification of different sweet-liking phenotypes are systematically reviewed, towards a goal of identifying the most consistent and usable methodology for future studies to adopt. To the best of our knowledge, this is the first methodological review that considers the strengths and weaknesses of the different sweet taste liker phenotyping methods.

2.2 Material and Methods

2.2.1 Strategy & eligibility criteria

A comprehensive review using a narrative approach was undertaken. To identify papers, a search was performed in January 2018 using two electronic databases: Scopus (https://www.scopus.com/) and MEDLINE/PubMed (https://www.ncbi.nlm.nih.gov/pubmed/). Search limiters included human subjects and studies being reported between 1960 and 2017. Databases were searched using the key words 'sweet taste', 'sweet-liking', 'sweet taste liking', 'sweet preference', 'sweet taste test', 'sweet liker', 'sweet

disliker', 'sweet taste phenotype', or 'hedonic' and 'sucrose'. Reference sections of the collected articles were manually scanned for additional relevant studies.

To be eligible for inclusion, a clear definition of two or more different categories of sweet-liking phenotypes which were based on liking ratings of aqueous sucrose solutions was required. Studies classifying participants into different liking quartiles based on their responses to food, complex beverages or flavoured/coloured sweet solutions, either after they tasted the stimuli or after they completed relevant preference questionnaires, were beyond the scope of this review and were excluded. It should be noted that sensory perceptions of "real life" food and beverages are highly influenced by memory, experience, and product familiarity (Mela, 2001; Ventura & Worobey, 2013). Moreover, many sweet food products used in those studies are also high in fat (chocolate, cake, biscuits, ice cream etc.) with some evidence suggesting an effect of sugar on the sensory assessment of fats and vice versa (Drewnowski & Almiron-Roig, 2010; Hayes & Duffy, 2007, 2008; Mennella et al., 2012). The impact of the food matrix (Urbano et al., 2016), as well as of the tastants' spatial distribution (Mosca et al., 2013) on sweet taste perception have also been argued. Therefore, to ensure the approach taken truly identified responses solely to sweet taste, only studies conducted with simple sucrose solutions were included in this review.

To better assist methodological driven comparisons and reduce the diversity in taste test protocols, experiments which attempted to classify participants into distinct sweet-liking groups using sweet tastants other than sucrose (e.g. in Looy et al., 1992; Oleson & Murphy, 2017; Thai et al., 2011; Yeomans et al., 2009) were also excluded. Firstly, many consumers detect other taste or flavour elements when tested with artificial sweeteners, such as the well-known concentration-dependent bitterness of acesulfame potassium and saccharin (Bobowski et al., 2016; Horne et al., 2002; Roudnitzky et al., 2011; Schiffman et al., 1979, 1995), and so phenotypic differences in response to these compounds could reflect differences in sensitivity to these subtle non-sweet flavour elements. Secondly, although psychophysical evidence has suggested considerable similarity in the actions of all simple sweeteners on sweet taste receptors (Fernstrom et al., 2012), different pathways have been implicated with the detection and recognition thresholds of sugars and non-nutritive sweeteners (Low et al., 2017).

Pragmatically, we also recognised that the vast majority of studies have used sucrose as the sweet tastant. As long as taste protocols controlled for potential effects of ingestion and, therefore, the potentially diverse metabolic effects and effects on gut-brain axis elicited by different sweeteners (Low et al., 2014; Tan & Tucker, 2019) were minimized, it could be hypothesized that the current review's conclusions on the strengths and weaknesses of the sweet-liking phenotypes classification methods based on sucrose-based taste tests could be used more broadly. Moreover, studies directly contrasting the distribution of sweet-liking phenotypes using different sweeteners report highly overlapped figures (Looy et al., 1992; Oleson & Murphy, 2017; Thai et al., 2011). Conversely, recent evidence suggesting that complex carbohydrates can be perceived independently of the sweet taste oral receptors (Lapis et al., 2016) and that gustatory sensitivity to simple sugars might be, at least in part, dissociated from that of complex carbohydrates (Lapis et al., 2014; Low et al., 2017) does however suggest some caution needs to be used in interpretation of the cause of differences in sweet-liker phenotypes based on evaluation of sucrose.

2.2.2 Analysis of different methodological approaches

Most of the eligible studies used a single method to identify different sweet-liking phenotypes; accordingly, a methods-based structure was chosen to organize the eligible papers, versus a purely chronological summary. For each method, the relevant studies are discussed and their main characteristics are summarized in a table (Tables 2.1-2.5). In cases that used more than one method on the same group of participants, those studies are included in the relevant tables for each method they used. To assess the impact of these different approaches on phenotype identification, the proportions of the main sweet-liking phenotypes are graphically presented (Figure 2.2). A discussion of the strengths and weaknesses of each classification approach follows, along with recommendations for future research.

2.2.3 Statistical analysis

Across the studies reviewed, the proportions of individuals within each phenotype varied. These differences could be due to either the sensitivity of the method, or may reflect underlying differences in characteristics of the participant cohort being tested. To assess these hypotheses, two-tailed Z-tests for independent samples (Formula 1) were conducted to determine whether sweet-liking phenotypes and sex significantly differed across classification methods. The formula used considers the best available estimate for the variance of each pairwise difference under the null hypothesis. Differences in age and BMI between methods were estimated by non-parametric Kruskal Wallis tests (*H*) for independent samples, followed by Mann Whitney post-hoc tests with adjusted *p-values*. To account for the different sample sizes, raw age and BMI mean values were transformed into z-scores before these analyses (Formula 2). Effect sizes were calculated for the pairwise comparisons by dividing the Z statistic of the Mann Whitney test with the squared root of the study samples being relevant to each comparison (Field, 2013). Participants' characteristics are reported as percentages in case of categorical variables and as means (M) ± standard deviations (s.d.) for continuous data. All values were weighted based on the different sample sizes as seen below (Formula 3-5).

$$Z = \frac{(P_1 - P_2)}{\sqrt{\hat{P}(1 - \hat{P})\left[\frac{1}{N_1} + \frac{1}{N_2}\right]}} \text{ for null hypothesis } (H_0): P_1 = P_2 \text{ and } \hat{P} = \frac{N_1 P_1 + N_2 P_2}{N_1 + N_2}$$

Formula 1. Equation for z-statistic for independent proportions (*Z*)

$$Z\ score = \frac{M - M_{pooled}}{s.d.}$$

Formula 2. Equation for z-score estimation (*Z score*)

$$P_{pooled} = \frac{N_1 P_1 + N_2 P_2 + \ldots + N_k P_k}{N_1 + N_2 + \ldots + N_k}$$

Formula 3. Equation for pooled percentage estimation (*P*pooled)

$$M_{pooled} = \frac{N_1 M_1 + N_2 M_2 + \ldots + N_k M_k}{N_1 + N_2 + \ldots + N_k}$$

Formula 4. Equation for pooled mean estimation (M_{pooled})

$$s.d._{pooled} = \sqrt{\frac{(N_1 - 1)s.d._{\cdot 1}{}^2 + (N_2 - 1)s.d._{\cdot 2}{}^2 + \ldots + (N_k - 1)s.d._{\cdot k}{}^2}{(N_1 + N_2 + \ldots + N_k) - k}}$$

Formula 5. Equation for pooled standard deviation estimation ($s.d._{pooled}$)

Where:

- P_1, P_2, …, and P_k are the samples' proportions that have the characteristic in question
- N_1, N_2, …, and N_k are the samples' size
- k is the number of independent samples
- M is the mean
- $s.d.$ is the standard deviation

Studies with missing or incomplete data and those using incompatible measures (e.g. BMI percentiles or categories instead of BMI raw values, median instead of mean values, etc.) were excluded from analysis. To ensure the independence of the various study cohorts, studies with stated or suspected overlap in sampling were excluded. All formula-based calculations were performed in Microsoft Excel 2013 software for Windows. Remaining analyses were carried out using IBM SPSS Statistics version 24.0. An alpha level of .05 was considered for all statistical tests.

2.3 Results

2.3.1. Identification of key methodological approaches to classifying sweet-liking phenotypes

Our literature search identified sixty nine relevant papers describing seventy one studies that met the eligibility criteria including fourteen manually retrieved from the reference lists of the search results; 256 records in Scopus and 192 records in MEDLINE/PubMed were excluded after the screening process was completed. After

adjusting for possible overlapping samples, 7543 subjects (37% men; data from 61 studies) who were tested for their hedonic responses to sweet taste and classified to different sweet-liking phenotypes were included into the final analysis. All but six studies recruited only adults. Average age and BMI for adults were 31.9 years (*s.d.* = 10.3 years; data from 46 studies) and 26.9 kg/m^2 (*s.d.* = 6.6 kg/m^2; data from 24 studies), respectively. Research groups from the United States published the most (63%), followed by studies in the UK and elsewhere.

Across the eligible papers four different classification methods were identified: 1a. Visual discrimination of hedonic responses to multiple sucrose concentrations (*N* = 23 including 2 studies that used two classification methods; Table 2.1) where individual liking ratings are plotted as a function of concentration, 1b. Statistical discrimination of hedonic responses to multiple sucrose concentrations (*N* = 5; Table 2.2) where participants are statistically merged to homogenous groups based on their hedonic responses, 2. The 'highest preference using ratings' method (*N* = 32; Table 2.4) where the specific sucrose concentration associated with the highest liking rating was identified, 3. The 'average liking above mid-point' or 'positive/negative liking' method (*N* = 10 including 1 study that used two classification methods; Table 2.4) where liking ratings are compared to a particular cut-off score, and 4. The 'highest preference via paired comparisons' method (*N* = 5 including 1 study that used two classification methods; Table 2.5) where the sucrose concentration of optimal palatability is identified. These different approaches are described in detail in the subsequent sections.

Study populations also vary across methods. One reason for this is that some methodological approaches tend to be used consistently in particular academic fields of study. For example, Method 2 has been widely used in studies relating sweet taste responses to medical conditions such as alcoholism, a disorder being more prevalent among males (NSDUH, 2017). In contrast, Methods 1b and 3 are often used by researchers investigating different aspects of sweet-liking such as associations with other sensory characteristics in healthy (i.e. medication free) non-smoking individuals and, correspondingly, young (Kantor et al., 2015; Moody & Mindell, 2017) women (Jamal et al., 2016) of relatively low BMI (Conolly & Davies, 2018; Flegal et al., 2016) dominate

in those cohorts. Accordingly, as can be seen in Table 2.6, sex distribution differed significantly between methods across all but two pairwise comparisons (Method 4 *vs*. Method 1a: Z = 0.87, *p* = .384; Method 4 vs. Method 2: Z = 1.93, p = .054; *p* < .05 for remaining comparisons). Just over half of those who were assessed via the 'highest preference' rating method were men (51.1%), whereas the largest sex disparity was observed in studies using the 'average liking above mid-point'/'positive/negative liking' method with barely one out of 4 participants being men (22.9%). Likewise, BMI and age were significantly different across the various classification methods, H(3) = 12.30, *p* = .006, and H(3) = 9.37, *p* = .025, respectively. Note that because full data were only available from a study testing a paediatric population, Method 4 was not included in these comparisons. Follow-up analysis indicated that in studies using Method 2, participants had a considerably greater body size compared to those in Method 1a (*p* = .001, *r* = .583), and participants tested were also significantly older than those in Method 1a and 3 (*p* = .014, *r* = .299; *p* = .013, *r* = .363, respectively). Method 3 tended to test individuals with a lower BMI when contrasted with Method 1b (*r* = .756, *p* = .064). Overall, comparisons of age yielded slightly smaller effect sizes relative to the BMI contrasts.

Table 2.1 Z statistics for pairwise comparisons of sex proportions across the different sweet taste liker classifications methods

	% male	Method 1a (N = 1290)		Method 1b (N = 1335)		Method 2 (N = 2591)		Method 3 (N = 1990)		Method 4 (N = 82)	
		Z	*p*	*Z*	*p*	*Z*	*p*	*Z*	*p*	*Z*	*p*
Method 1a	35.5	0.00	1.000	**-3.24**	**0.001**	**9.16**	**< 0.001**	**-7.89**	**< 0.001**	0.87	0.384
Method 1b	29.6	**3.24**	**0.001**	0.00	1.000	**12.85**	**< 0.001**	**-4.36**	**< 0.001**	**2.04**	**0.041**
Method 2	51.1	**-9.16**	**< 0.001**	**-12.85**	**< 0.001**	0.00	1.000	**-19.41**	**< 0.001**	-1.93	0.054
Method 3	22.9	**7.89**	**< 0.001**	**4.36**	**< 0.001**	**19.41**	**< 0.001**	0.00	1.000	**3.64**	**< 0.001**
Method 4	40.3	-0.87	0.384	**-2.04**	**0.041**	1.93	0.054	**-3.64**	**< 0.001**	0.00	1.000

Z, Z-statistic; *p*, *p-value*

Bold text indicates a significant difference with a p-value less than 0.05

Table 2.2 Z statistics for pairwise comparisons of sweet-liking phenotypes proportions across the different classifications methods

	N (%)	Method 1a (N = 1371)		Method 1b (N = 1335)		Method 2 (N = 2283)		Method 3 (N = 1870)		Method 4 (N = 205)	
		Z	p	Z	p	Z	p	Z	p	Z	p
SL phenotype											
Method 1a	530 (38.6)	0.00	1.000	**4.06**	**< 0.001**	**3.28**	**0.001**	**13.98**	**< 0.001**	0.37	0.711
Method 1b	619 (46.3)	**-4.06**	**< 0.001**	0.00	1.000	-1.27	0.204	**9.63**	**< 0.001**	-1.70	0.089
Method 2	1009 (44.2)	**-3.28**	**0.001**	1.27	0.204	0.00	1.000	**12.38**	**< 0.001**	-1.16	0.246
Method 3	1187 (63.5)	**-13.98**	**< 0.001**	**-9.63**	**< 0.001**	**-12.38**	**< 0.001**	0.00	1.000	**-6.55**	**< 0.001**
Method 4	82 (40.0)	-0.37	0.711	1.70	0.089	1.16	0.246	**6.55**	**< 0.001**	0.00	1.000
SD phenotype											
Method 1a	795 (58.0)	0.00	1.000	**-6.75**	**< 0.001**	**-2.63**	**0.009**	**-12.80**	**< 0.001**	0.55	0.582
Method 1b	601 (45.0)	**6.75**	**< 0.001**	0.00	1.000	**4.94**	**< 0.001**	**-5.52**	**< 0.001**	**-4.00**	**< 0.001**
Method 2	1222 (53.5)	**2.63**	**0.009**	**-4.94**	**< 0.001**	0.00	1.000	**-11.71**	**< 0.001**	1.78	0.075
Method 3	661 (35.3)	**12.80**	**< 0.001**	**5.52**	**< 0.001**	**11.71**	**< 0.001**	0.00	1.000	**6.91**	**< 0.001**
Method 4	123 (60.0)	-0.55	0.582	**4.00**	**< 0.001**	-1.78	0.075	**-6.91**	**< 0.001**	0.00	1.000
Other/Undefined phenotype											
Method 1a	46 (3.4)	0.00	1.000	**5.78**	**< 0.001**	-1.95	0.051	**-4.28**	**< 0.001**	**-2.66**	**0.008**
Method 1b	115 (8.6)	**-5.78**	**< 0.001**	0.00	1.000	**-8.76**	**< 0.001**	**-10.26**	**< 0.001**	**-4.37**	**< 0.001**
Method 2	52 (2.3)	1.95	0.051	**8.76**	**< 0.001**	0.00	1.000	**-2.67**	**0.008**	**-2.18**	**0.029**
Method 3	22 (1.2)	**4.28**	**< 0.001**	**10.26**	**< 0.001**	**2.67**	**0.008**	0.00	1.000	-1.56	0.119
Method 4	0 (0.0)	**2.66**	**0.008**	**4.37**	**< 0.001**	**2.18**	**0.029**	1.56	0.119	0.00	1.000

Z, Z-statistic; *p*, *p-value*; SD, sweet disliker; SL, sweet liker

Bold text indicates a significant difference with a p-value less than 0.05

2.3.2 Classification by interpreting the shape of individual hedonic response curves (Method 1a & Method 1b)

The interpretation of the shape of individual hedonic response curves to different sweet taste stimuli was the first methodology used to identify distinct sweet-liking phenotypes, following a seminal report by Pangborn (1970). In brief, liking ratings (or average liking ratings in case of replicates) across different stimuli are plotted so that the effects of increasing sucrose concentration (x-axis) on the perceived liking at individual level (y-axis) can be visually inspected. A simplified summary of the most commonly reported sweet-liking phenotypes resulting from visual inspection of the shape of these individual hedonic response curves is shown in Figure 2.1.
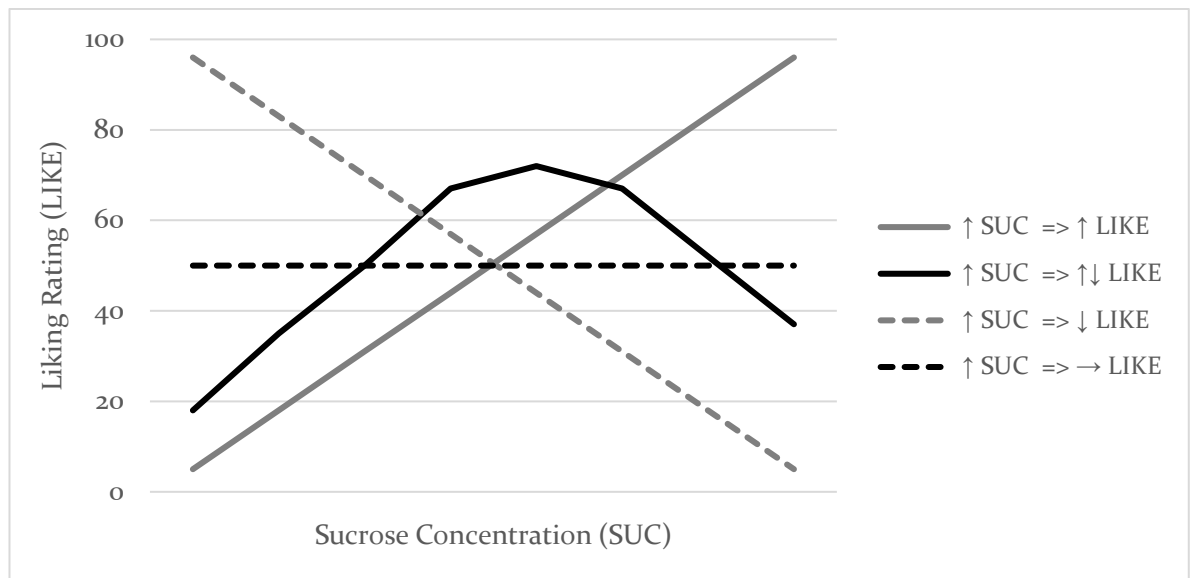
Fig. 2.1. Graphical representation of the most commonly reported sweet-liking phenotypes as they are illustrated by methods interpreting the shape of hedonic response curves

2.3.2.1 Visual discrimination of hedonic responses to multiple sucrose concentrations (Method 1a)

Simple visual interpretation of response curves to classify participants into different groups presumed to reflect different sweet-liking phenotypes prevailed for more than four decades (Table 2.1). In 1970, Pangborn observed three distinct hedonic responses to increasing sucrose concentrations among men: increased liking ('like'), increased disliking ('dislike'), and increasing liking ratings followed by a reduction for solutions with added sucrose above 0.094 M ('like-dislike') (Pangborn, 1970). When a range of stronger sucrose solutions was presented to an age diverse population including both men and women, although the intermediate ('like-dislike') phenotype was associated with a three times higher breakpoint, an otherwise consistent set of results was revealed (Enns et al., 1979). Specifically, the 'liker' phenotype was dominant in both experiments (55.0 and 63.3%, respectively), while the remaining of the participants were split roughly equally between the two other phenotypes. Age and sex differences aside, participants in Pangborn (1970) also tasted nearly twice as many solutions (replicates included) as those in Enns et al. (1979); adaptation (Lawless & Heymann, 2010) and sensory specific satiety (Rolls et al., 1981) could, then, partially explain the qualitative difference observed regarding the intermediate phenotype. A subsequent study exclusively in women using a similar range of sucrose concentrations as Enns and colleagues (1979) but reporting a sucrose concentration breakpoint closer to that of Pangborn (1970), identified the same three sweet-liking phenotypes, but failed to confirm these particular proportions (Franko et al., 1994). Half of those women had a current diagnosis of bulimia nervosa which is likely to underlie altered or biased sensory evaluations (Drewnowski, 1989).

Those three sweet-liking phenotypes continue to be reported in more recent studies (Table 2.1). However, participants who exhibit either an increasing disliking or an inverted U-shaped hedonic pattern are now typically considered as a single group, the SD phenotype. Interestingly, although relevant cohorts mainly consisted of young women of normal body weight and the concentration range of sweet taste stimuli tested was relatively similar, the representation of SL-SD phenotypes significantly varied: it ranged between 3:1 in Yeomans et al. (2007) to 1:5 in Holt et al. (2000), with almost a

50-50 proportion observed elsewhere (Drewnowski, Henderson, Shore, et al., 1997; Oleson & Murphy, 2017). This lack of concordant findings with regard to the number of SLs and SDs identified in studies where this oversimplifying merging occurred, is probably indicative of the implications of the subjectivity attached to visual inspection-dependent methods.

In contrast, Thompson and colleagues (1976) recognized only two different phenotypes when they visually interpreted the hedonic response curves to sweet taste stimuli; an inverted U-shaped curve characterized by an increased liking up to a sucrose concentration equal to 0.30 M and then a decline (Type I response/phenotype) and an increased liking with concentration (Type II response/phenotype). When they replicated their protocol in another sample of young adults, a similar 70:30 Type I to Type II sweet-liking phenotypes proportion to that of Group 1 in Thompson et al. (1976) was observed (Thompson, et al., 1977). In the other studies that used the same classification methodology (Drewnowski & Schwartz, 1990; Grinker & Hirsch, 1972; Johnson et al., 1979; Malcolm et al., 1980; Thai et al., 2011; Travers et al., 1993), different proportions of Type I and Type II responders, or sweet dislikers (SDs)-sweet likers (SLs) as they were subsequently renamed by Drewnowski & Schwartz (1990) were reported. It should be noted, though, that except the comparable sucrose concentration breakpoint observed in the Type I responders (0.18-0.32 M), participant characteristics greatly varied across the different studies (Table 2.1).

A potentially replicable methodology was suggested when the SL-SD classification was attributed to individuals exhibiting a simple monotonically ascending and monotonically descending hedonic function to increasing sucrose concentration; SLs were systematically outnumbered by SDs (Drewnowski et al., 1998; Drewnowski, Henderson, & Shore, 1997; Eikemo et al., 2016; Grinker, 1977; Looy et al., 1992; Looy & Weingarten, 1991, 1992). It is noteworthy that in the studies by Looy and colleagues, although additional sweet-liking phenotypes were also identified, no further details on those subjects exhibiting either a neutral, an erratic, or an inverted U-shaped response were provided.

Table 2.3. Papers included in this review using the 'Visual discrimination of hedonic responses' classification method (Method 1a) for the identification of the distinct sweet-liking phenotypes

Author(s), Publication Year	Country	Participants n (% men)	Health Status (%)	Age in years mean (±s.d.)*	Sucrose Solutions (x times of replicates)	Hedonic Scale	Sweet-liking phenotypes (%)
Oleson & Murphy (2017)	USA	40 (50)	Healthy (100)	19.0 (1.6)	0.058, 0.12, 0.23, 0.47, and 0.93 M[§] (x 2)	gLMS	- High concentration liker (47.5): $\uparrow_{SUC}$ => $\uparrow_{LIKE}$ - Moderate concentration liker (52.5): $\uparrow_{SUC}$ => $\downarrow_{LIKE}$ or $\uparrow\downarrow_{LIKE}$, breakpoint at 0.23 M
Eikemo et al. (2016)	Norway	49 (100)	Healthy (100)	24.7 (3.9)	0.05, 0.10, 0.20, 0.42, and 0.65 M (x 3)	VAS	- SL (46.9): $\uparrow_{SUC}$ => $\uparrow_{LIKE}$ - SD (53.1): $\uparrow_{SUC}$ => $\downarrow_{LIKE}$
Thai et al. (2011) [1]	Malaysia	325 (49)	Healthy (100)	21.0 (14.5)	0.087, 0.22, and 0.55 M[§] (x 1)	gLMS	- Type II (48.9): $\uparrow_{SUC}$ => $\uparrow\rightarrow_{LIKE}$ - Type I (51.1): $\uparrow_{SUC}$ => $\uparrow\downarrow_{LIKE}$, breakpoint at 0.22 M
Yeomans et al. (2007) (see also Table 2.6)	UK	60 (33)	Healthy (100)	23.1 (6.2[†])	0.05, 0.21, 0.42, and 0.83 M (x 2)	VAS	- SL (66.7): $\uparrow_{SUC}$ => $\uparrow_{LIKE}$ - SD (33.3): $\uparrow_{SUC}$ => $\downarrow_{LIKE}$ or $\uparrow\downarrow_{LIKE}$, breakpoint at 0.21 M
Holt et al. (2000)	Australia	132 (42)	Healthy (100)	Australian: 22.8 (4.3) Malaysian: 21.5 (1.2)	0.058, 0.12, 0.23, 0.47, and 0.93 M[§] (x 1)	3-point scale	- SL (12.1): $\uparrow_{SUC}$ => $\uparrow_{LIKE}$ - SD (87.9): $\uparrow_{SUC}$ => $\downarrow_{LIKE}$ or $\uparrow\downarrow_{LIKE}$, breakpoints at 0.12 or 0.23 M
Drewnowski et al. (1998) [2]	USA	121 (0)	Healthy (100)	27.7 (**)	0.058, 0.12, 0.23, 0.47, and 0.93 M (x **)	9-point category scale	- SL (41.3): $\uparrow_{SUC}$ => $\uparrow_{LIKE}$ - SD (52.1): $\uparrow_{SUC}$ => $\downarrow_{LIKE}$ + 8 participants with undefined sweet-liking phenotype

Study	Country	N (% male)	Group (N)	Age	Sucrose concentrations	Scale	Results
Drewnowski et al. (1997b)	USA	159 (0)	Healthy (100)	27.0 (8.8[††])	0.058, 0.12, 0.23, 0.47, and 0.93 M (x 1)	9-point category scale	- SL (41.5): $\uparrow_{SUC}$ => $\uparrow\rightarrow_{LIKE}$ - SD (51.6): $\uparrow_{SUC}$ => $\downarrow_{LIKE}$ *or* $\uparrow\downarrow_{LIKE}$, breakpoint at ** + 11 participants with undefined sweet-liking phenotype
Drewnowski et al. (1997a)	USA	87 (0)	Healthy (100)	25.4 (5.6[††])	0.058, 0.12, 0.23, 0.47, and 0.93 M (x 1)	9-point category scale	- SL (34.5): $\uparrow_{SUC}$ => $\uparrow\rightarrow_{LIKE}$ - SD (65.5): $\uparrow_{SUC}$ => $\downarrow_{LIKE}$
Franko et al. (1994)	USA	40 (0)	Bulimia nervosa (38) Bulimia nervosa with history of anorexia (12) Healthy (50)	Bulimia nervosa: 25.0 (4.0) Controls: 24.0 (4.0)	0.039, 0.078, 0.149, 0.30, 0.632, and 1.632 M[‡‡] (x 2)	analogue scale	- (37.5): $\uparrow_{SUC}$ => $\uparrow\rightarrow_{LIKE}$ - (50.0): $\uparrow_{SUC}$ => $\uparrow\downarrow_{LIKE}$, breakpoint at 0.078 M - (12.5): $\uparrow_{SUC}$ => $\downarrow_{LIKE}$
Travers et al. (1993)	USA	41 (61)	PD (61) Healthy (39)	PD patients M: 62.4 (5.0) F: 67.8 (8.3) Controls: M: 64.4 (7.8) F: 61.2 (3.8)	0.04 [3], 0.08, 0.15, 0.3, 0.6, 0.9, and 1.5 M (x 1)	6-point category scale	- (36.6): $\uparrow_{SUC}$ => $\uparrow\rightarrow_{LIKE}$ - (63.4): $\uparrow_{SUC}$ => $\uparrow\downarrow_{LIKE}$, breakpoint at 0.3 M

Reference	Country	N (%)	Status / Sig.	Age	Sucrose concentrations	Scale	Results
Looy et al. (1992)	Canada	Group 1: 22 (41)	** (**)	**(**)	0.05, 0.10, 0.21, 0.42, and 0.83 M (x 5)	VAS	*Group 1* - SL (40.1): $\uparrow_{\text{SUC}}$ => $\uparrow_{\text{LIKE}}$ - SD (31.8): $\uparrow_{\text{SUC}}$ => $\downarrow_{\text{LIKE}}$ + 6 participants with neutral, inverted U-shaped or erratic response
		Group 2: 38 (29)	** (**)	**(**)			*Group 2* - SL (34.2): $\uparrow_{\text{SUC}}$ => $\uparrow_{\text{LIKE}}$ - SD (36.8): $\uparrow_{\text{SUC}}$ => $\downarrow_{\text{LIKE}}$ + 11 participants with neutral, inverted U-shaped or erratic response
Looy & Weingarten (1992)	Canada	66 (42)	** (**)	20.3 (3.5)	0.05, 0.10, 0.21, 0.42, and 0.83 M (x 8)	VAS	- SL (33.3): $\uparrow_{\text{SUC}}$ => $\uparrow_{\text{LIKE}}$ - SD (50): $\uparrow_{\text{SUC}}$ => $\downarrow_{\text{LIKE}}$ - Neutral (10.6): $\uparrow_{\text{SUC}}$ => $\rightarrow_{\text{LIKE}}$ + 4 participants with erratic response
Looy & Weingarten (1991)	Canada	28 (43)	** (**)	20.5 (3.5)	0.03, 0.05, 0.10, 0.16, 0.21, 0.31, 0.42, 0.62, and 0.83 M (x 8)	VAS	- SL (32.2): $\uparrow_{\text{SUC}}$ => $\uparrow_{\text{LIKE}}$ - SD (46.4): $\uparrow_{\text{SUC}}$ => $\downarrow_{\text{LIKE}}$ - Neutral (21.4): $\uparrow_{\text{SUC}}$ => $\rightarrow_{\text{LIKE}}$
Drewnowski & Schwartz (1990)	USA	50 (0)	Healthy (100)	20.2 (1.7)	0.059, 0.24, 0.50, and 1.06 M[§§] (x 1)	9-point category scale	- Type II [4] (36.0): $\uparrow_{\text{SUC}}$ => $\uparrow_{\text{LIKE}}$ - Type I [4] (64.0): $\uparrow_{\text{SUC}}$ => $\downarrow_{\text{LIKE}}$ *or* $\uparrow\downarrow_{\text{LIKE}}$, breakpoint at 0.24 M
Frijters & Rasmussen-Conrad (1982)	NL	25 (0)	Overweight (51) Normal weight (48)	[24-53 years old]	0.06, 0.1148, 0.2089, 0.3082, 0.6918, and 1.3 M (x 3)	3-anchor line (midpoint for the ideal sweetness)	- Type II (4.0): $\uparrow_{\text{SUC}}$ => $\uparrow_{\text{LIKE}}$ - Type I (92.0): $\uparrow_{\text{SUC}}$ => $\uparrow\downarrow_{\text{LIKE}}$, breakpoint at ** - Neutral (4.0): $\uparrow_{\text{SUC}}$ => $\rightarrow_{\text{LIKE}}$

Malcolm et al. (1980)	USA	22 (0)	Healthy (100)	[18-40 years old]	0.006 [5], 0.012 [5], 0.03 [5], 0.06 [5], 0.09, 0.15, 0.3, 0.5, 0.8 and 1 M (1 x)	9-point category scale	- Type II (45.5): $\uparrow_{SUC}$ => $\uparrow\rightarrow_{LIKE}$ - Type I (54.5): $\uparrow_{SUC}$ => $\uparrow\downarrow_{LIKE}$, breakpoints at 0.3 M and 0.5 M
Johnson et al. (1979)	USA	49 (**)	Obese in weight loss (65) Normal weight (35)	Behavior modification weight loss: 36.0 (**) Meal replacement weight loss: 35.0 (**) Controls: 24.0 (**)	0.058, 0.10, 0.17, 0.32, 0.58, and 1.46 M[§] (x 2)	9-point category scale	- Type II (30.6): $\uparrow_{SUC}$ => $\uparrow_{LIKE}$ - Type I (69.4): $\uparrow_{SUC}$ => $\uparrow\downarrow_{LIKE}$, breakpoints at 0.17 and 0.32 M
Enns et al. (1979)	USA	Children: 21 (76) Young adults: 27 (63) Elderly: 12 (42)	** (**) ** (**) ** (**)	Children M: 10.5 (0.2[††]) W: 10.7 (0.3[††]) Young adults M: 19.0 (1.0[††]) W: 18.3 (1.6[††]) Elderly M: 71.6 (2.8[††]) W: 70.5 (3.6[††])	0.056, 0.1, 0.17, 0.32, 0.56, and 1.0 M (x 3)	9-point category scale	Children: (76.2): $\uparrow_{SUC}$ => $\uparrow_{LIKE}$ (23.8): $\uparrow_{SUC}$ => $\downarrow_{LIKE}$ Young adults: (63.0): $\uparrow_{SUC}$ => $\uparrow_{LIKE}$ (37.0): $\uparrow_{SUC}$ => $\uparrow\downarrow_{LIKE}$, breakpoint at 0.32 M Elderly: (41.7): $\uparrow_{SUC}$ => $\uparrow_{LIKE}$ (58.3): $\uparrow_{SUC}$ => $\downarrow_{LIKE}$

Grinker (1977) [6] (see also Table 2.7)	USA	56 (34)	Extremely obese (45)	Extremely obese: 34.2 (**)	0.057, 0.10, 0.17, 0.32, and 0.57 M[§] (x 1)	9-point category scale	- (30.4): ↑$_{SUC}$ => ↑→ $_{LIKE}$ - (69.6): ↑$_{SUC}$ => ↓$_{LIKE}$
			Moderately obese (25)	Moderately obese: 32.7 (**)			
			Normal weight (30)	Normal weight: 23.1 (**)			
Thompson et al. (1977)	USA	32 (**)	Obese (44) Normal weight (56)	20.0 (3.0)	0.075, 0.15, 0.3, 0.6, 0.9, 1.2, and 1.5 M (x 1)	Magnitude estimation method	- Type II (31.2): ↑$_{SUC}$ => ↑$_{LIKE}$ - Type I (68.8): ↑$_{SUC}$ => ↑↓$_{LIKE}$, breakpoint at 0.6 M
Thompson et al. (1976)	USA	*Group 1* 18 (61) *Group 2* 59 (19)	Normal weight (100) Overweight/ Obese (100)	*Group 1* Type II: 19.6 (1.5) Type I: 19.2 (1.3) *Group 2* Type II: 33.9 (15.9) Type I: 38.3 (13.4)	*Group 1* 0.075, 0.15, 0.3, 0.6, 0.9, 1.2, and 1.5 M *Group 2* 0.06, 0.1, 0.25, 0.4, 0.7, 1.0, and 2.0 M (x 1)	Magnitude estimation method	*Group 1* - Type II (27.8): ↑$_{SUC}$ => ↑→$_{LIKE}$ - Type I (72.2): ↑$_{SUC}$ => ↑↓$_{LIKE}$, breakpoint at 0.3 M[‡] *Group 2* - Type II (35.6): ↑$_{SUC}$ => ↑→$_{LIKE}$ - Type I (64.4): ↑$_{SUC}$ => (↑)↓$_{LIKE}$, breakpoint at 0.25 M[‡]
Grinker & Hirsch (1972) [7, 8]	USA	23 (**)	Obese (43) Normal weight (57)	**(**)	0.057, 0.10, 0.18, 0.33, and 0.61 M[§§] (x 1)	7-point category scale	- (56.5): ↑$_{SUC}$ => ↑↓$_{LIKE}$ with breakpoint at 0.18 M - (43.5): ↑$_{SUC}$ => ↓$_{LIKE}$

Pangborn (1970)	USA	29 (100) [8]	** (**)	**(**)	0.023, 0.059, 0.094, 0.13, 0.17, 0.20, and 0.24 $M^{§§‡}$ (x 5)	9-point category scale	- Like (55.0): $\uparrow_{SUC} => \uparrow_{LIKE}$ - Like-dislike (20.0): $\uparrow_{SUC} => \uparrow\downarrow_{LIKE}$, breakpoint at 0.094 M - Dislike (25.0): $\uparrow_{SUC} => \downarrow_{LIKE}$

*Age mean and s.d. rounded to one decimal place

**No information available

[†]s.d. calculated from standard error (SE) (SE=s.d./√sample size)

[††]s.d. calculated from standard error of the mean (SEM) (SEM=s.d./√sample size)

[§]Sucrose concentration in M (mol/L) calculated from % w/v based on sucrose's molecular weight (342.296 g) and the assumption that the solvent is pure/deionized water at 20°C (Haynes, 2016)

[§§]Sucrose concentration in M (mol/L) calculated from % w/w based on sucrose's molecular weight (342.296 g) and the assumption that the solvent is pure/deionized water at 20°C (% w/w = % w/v x Special Gravity$_{solution}$) (Haynes, 2016)

[‡]Based on reviewers' conclusion after interpreting the shape of the hedonic response curves

[‡‡]Based on reviewers' assumption that the sucrose concentration was initially expressed in % w/w

[1] The between-sex sweet-liking phenotypes results are presented.

[2] It is not clear whether there is an overlap between participants in the current report (Drewnowski, et al., 1998) and those in Drewnowski et al. (1997b).

[3] Only 28 of the 41 participants tasted and rated the 0.04 M solution.

[4] Type I and II sweet-liking phenotypes' description is adjusted based on Thompson and colleagues original paper (Thompson, et al., 1976)

[5] The relevant liking ratings weren't included in the sweet-liking phenotype classification.

[6] It is not clear whether the presented sweet-liking phenotypes results being were collected before or after the red "cherry" colour manipulation of the sucrose solutions.

[7] Original reference in Grinker, J., Smith, D. V. & Hirsch, J. (1971). Taste preferences in obese and normal weight subjects. *Proceedings of the IVth International Conference on the Regulation of Food and Water Intake*, Cambridge, England (abstract).

[8] It is not clear whether there is an overlap between participants rating stimuli on a hedonic scale (Table 2.1) or those tested via the paired-comparison technique (Table 2.5).

[9] Only 20 of the 29 participants completed the entire series of replicates.

$\uparrow_{SUC}$: Increasing sucrose concentration

$\downarrow_{LIKE}$: Descending liking rating

$\uparrow\downarrow_{LIKE}$: Inverted U-shaped hedonic response curve

$\uparrow_{LIKE}$: Ascending liking rating

$\uparrow\rightarrow_{LIKE}$: Ascending liking rating followed by a plateau

$\rightarrow_{LIKE}$: Consistent liking rating

AN, anorexia nervosa; BMI, body mass index; gLMS, generalized Labeled Magnitude Scale; liking ratingM, men; NL, The Netherlands; PD, Parkinson disease; SUC, sucrose concentration; s.d., standard deviation; SD, sweet disliker; SL, sweet liker; VAS, Visual Analog Scale; W, women

2.3.2.2 Statistical discrimination of hedonic responses to multiple sucrose concentrations (algorithmic classification: Method 1b).

To overcome the possible limitations resulting from the subjective visual discrimination of the different sweet-liking phenotypes, a statistically-based approach has been suggested recently (Table 2.2). The hierarchical cluster analysis (HCA) technique produces relatively homogeneous sub-groups (clusters) of cases based on selected characteristics either through an agglomerative (successive fusion of individuals into groups) or a divisive (successive separation of individuals into finer groups) approach (Everitt et al., 2011). Essentially, this method determines how many likely clusters of data are present in the dataset based on the statistical relationship between liking ratings and sucrose concentration for each individual. Wherever the information has been available (Asao et al., 2015; Garneau et al., 2018; Methven et al., 2016), the agglomerative method was selected, i.e. hierarchical decomposition was formed in a "bottom-up" fashion.

Researchers in Korea were the first to introduce the use of HCA in the relevant literature (Kim et al., 2014). In their initial experiment in a sample of young healthy Korean women three clusters were recognized: two clusters where both the hedonic response curves followed the inverted U-shaped pattern but with different breakpoints (0.35 and 0.70 M), and one with increasing liking with increasing sucrose concentration (Kim, et al., 2014). It should be noted that in Cluster 2 the gap between the highest and the lowest ratings was only 2 points, similar to the neutral response noted using the visual inspection method discussed earlier. When the protocol was replicated in a comparable study sample (Kim et al., 2017), five clusters were reported and interpreted as three distinct sweet-liking phenotypes evenly distributed across participants. However, unlike their first experiment, only one inverted U-shaped pattern was observed with the maximum liking at 0.35 M. A strong disliking (SDs) and a strong liking (SLs) pattern were also reported each representing approximately one third of the study sample.

Irrespective of the divergent representation of the distinct sweet-liking phenotypes, the relatively steep increasing slope with increasing sucrose concentration (SL phenotype) was also consistent across the rest of the experiments using HCA (Table

2.2). In a US-based large-scale study of 953 participants from various ethnicities and age groups (Garneau, et al., 2018) children's hedonic responses were classified into two clusters: a SL cluster representing 3 out of 4 children and a second cluster for those with a SD phenotype. HCA for the adults' sub-group revealed an additional cluster that included both individuals with a relatively neutral liking pattern and those with the inverted U-shaped hedonic response (40.3% and 17.7% of the total adult sample, respectively). In Methven et al. (2016) where only two clusters of hedonic responses were identified among UK adults, there were almost half as many SLs as there were SDs. It is worth mentioning that ratings for the two lower sucrose concentrations were only slightly above neutral across those SDs. Another study with a similar small sample size as that in Methven et al. (2016) but which used double the number of sweet taste stimuli, reported an equal number of SLs and SDs in a US cohort (Asao, et al., 2015). SD phenotype was, however, expressed by a definite inverted U-shaped hedonic response curve.

Table 2.4 Papers included in this review using the 'Statistical discrimination of hedonic responses' classification method (algorithmic classification: Method 1b) for the identification of the distinct sweet-liking phenotypes

Author(s), Publication Year	Country	Participants n (% men)	Health Status (%)	Age in years mean (±s.d.)*	Sucrose Solutions (x times of replicates)	Hedonic Scale	Sweet-liking phenotypes (%)
Garneau et al. (2018) [1]	USA	Children: 303 (41) Adults: 650 (38[†])	Healthy (**) Unhealthy (**) Healthy (**) Unhealthy (**)	Children: 10.9 (2.2) Adults: 41.8 (16.5)	0.070, 0.13, 0.22, and 0.40 M[§] (x 1)	VAS	*Children* - Cluster 1 -- SL (78.2): $\uparrow_{SUC}$ => $\uparrow_{LIKE}$ - Cluster 2 -- SD (21.8): $\uparrow_{SUC}$ => $\downarrow_{LIKE}$ *Adults* - Cluster 1 -- SL (33.5): $\uparrow_{SUC}$ => $\uparrow_{LIKE}$ - Cluster 2 -- Neutrals (17.7 + 40.3): $\uparrow_{SUC}$ => $\uparrow\downarrow_{LIKE}$, breakpoint at ** *and* => $\rightarrow_{LIKE}$ - Cluster 3 -- SD (8.5): $\uparrow_{SUC}$ => $\downarrow_{LIKE}$
Kim et al. (2017)	Republic of Korea	120 (0)	** (**)	24 (**)	0.087, 0.17, 0.35, 0.70, and 1.05 M[§] (x 1)	9-point category scale	- Cluster 4+5 -- SL (32.5): $\uparrow_{SUC}$ => $\uparrow_{LIKE}$ - Cluster 1 (35.8): $\uparrow_{SUC}$ => $\uparrow\downarrow_{LIKE}$, breakpoint at 0.35 M - Cluster 2+3 -- SD (31.7): $\uparrow_{SUC}$ => $\downarrow_{LIKE}$
Methven et al. (2016) (see also Table 2.6)	UK	36 (34 [2])	** (**)	26 (**)	0.087, 0.17, 0.35, 0.70, and 1.05 M[§] (x 1)	VAS	- Cluster 1 -- SL (36.1): $\uparrow_{SUC}$ => $\uparrow_{LIKE}$ - Cluster 2 -- SD (63.9): $\uparrow_{SUC}$ => $\uparrow\downarrow_{LIKE}$, breakpoint at 0.17 M

Asao et al. (2015) (see also Table 2.7)	USA	26 (46)	Healthy (100)	32.6 (14.5)	0.035, 0.053, 0.079, 0.118, 0.177, 0.266, 0.399, 0.598, 0.897, and 1.346 M (x 2)	VAS	- Cluster 2 -- High concentration liker (50.0): $\uparrow_{SUC}$ => $\uparrow_{LIKE}$ - Cluster 1 -- Low concentration liker (50.0): $\uparrow_{SUC}$ => $\uparrow\downarrow_{LIKE}$, breakpoints between 0.118 M-0.266 M
Kim et al. (2014)	Republic of Korea	200 (0)	** (**)	22 (**)	0.087, 0.17, 0.35, 0.70, and 1.05 M§ (x 1)	VAS	- Cluster 1 (49.5): $\uparrow_{SUC}$ => $\uparrow_{LIKE}$ - Cluster 2 (31.5): $\uparrow_{SUC}$ => $\uparrow\downarrow_{LIKE}$, breakpoint at 0.70 M *or* ≈> $\uparrow\rightarrow_{LIKE}$ - Cluster 3 (19.0): $\uparrow_{SUC}$ => $\uparrow\downarrow_{LIKE}$, breakpoint at 0.35 M

*Age mean and s.d. rounded to one decimal place

**No information available

§Sucrose concentration in M (mol/L) calculated from % w/v based on sucrose's molecular weight (342.296 g) and the assumption that the solvent is pure/deionized water at 20°C (Haynes, 2016)

[1] The paper was available online on the 12th of October 2017.

[2] One participant denied the relevant information.

$\uparrow_{SC}$: Increasing sucrose concentration

$\downarrow_{LIKE}$: Descending liking rating

$\uparrow\downarrow_{LIKE}$: Inverted U-shaped hedonic response curve

$\uparrow_{LIKE}$: Ascending liking rating

$\rightarrow_{LIKE}$: Consistent liking rating

BMI, body mass index; gLMS, general labeled magnitude scale; LIKE, liking rating; SUC, sucrose concentration; s.d., standard deviation; SD, sweet disliker; SL, sweet liker; VAS, visual analog scale

2.3.3 Highest preference using ratings classification method (Method 2)

Identifying the sweet taste stimuli associated with the highest preference using ratings from a small set of samples (see Table 2.3 for the range of stimuli used) and accordingly assigning participants into particular sweet-liking phenotypes is another commonly used classification method. Following the lead of Kampov-Polevoy and colleagues as originators of this approach (Kampov-Polevoy et al., 1997, 1998), most subsequent studies investigating links between sweet-liking and addictive behaviors or mental disorders have used a similar approach. Two distinct sweet-liking phenotypes were described: a SL phenotype and a SD phenotype. The SL phenotype was defined as preferring the highest sucrose concentration (or the two higher sucrose concentrations) typically being at 0.83 or 0.97/0.99 M, whereas subjects rating one of the remaining concentrations (or one of the two lower concentrations) as the most likable were classified as SDs.

A first screening for addiction-related experiments listed in Table 2.3 revealed that in 6 out of 8 studies under a case-control design that tested participants with a diagnosed alcohol or substance dependence, SLs represented more than 50% of the total study sample (Bogucka-Bonikowska et al., 2001; Kampov-Polevoy et al., 1997; Krahn et al., 2006; Kranzler et al., 2001; Tremblay et al., 2009; Wronski et al., 2006). Notably, in half of those studies, the classification criteria that were used for the identification of the distinct sweet-liking phenotypes may influence the final count in favor of the SL group. For example, Kampov-Polevoy and colleagues (1997) and Kranzler and colleagues (2001) attributed the SL phenotype to subjects expressing preference for either the first or the second highest sucrose concentration, while Tremblay and colleagues (2009) used a much stricter definition for the SDs (maximum liking rating for the lowest sucrose concentration). The two remaining addiction-related studies are split between those where the two discrete sweet-liking phenotypes were evenly distributed across participants (Bogucka-Bonikowska et al., 2002), and those where SLs were less than one third of the total study sample (Kampov-Polevoy et al., 1998).

Regarding studies testing psychiatric patients and their matched healthy controls, regardless of the heterogeneity in age and underlying disorders, less variability among the proportions of the distinct sweet-liking phenotypes was reported. In these

studies, SLs were either more than (Sienkiewicz-Jarosz et al., 2013; Swiecicki et al., 2009, 2015) or as many as (Damiano et al., 2014) the SDs in all but one (Dichter et al., 2010) study. Unlike with the addiction-related trials, women overall outnumbered men, while in Sienkiewicz-Jarosz et al. (2013), Swiecicki et al. (2015), and Swiecicki et al. (2009), where a higher proportion of SLs was reported, a sweet taste test protocol including three different sucrose solutions being served twice (i.e. a 3 x 2 design) was used instead of the more commonly used 5 (sweet taste stimuli) x 5 (replicates) design. Accordingly, it is not unreasonable to speculate that individuals are more likely to be classified as having the SL phenotype when tested in a protocol with less opportunity for fatigue, adaptation (Lawless & Heymann, 2010) and sensory specific satiety effects (Rolls et al., 1981).

Confirming this hypothesis, non-case-control addiction-related studies (Garbutt et al., 2016; Janowsky et al., 2003; Kampov-Polevoy, Ziedonis, et al., 2003; Kampov-Polevoy et al., 2004; Langleben et al., 2012) and a very recent trial including binge eaters (Goodman et al., 2018) that did apply the usual 5 (sweet taste stimuli) x 5 (replicates) sweet taste test protocol, all reported lower proportions of SLs. Comparably, when the same protocol was exclusively used with healthy participants, the SL phenotype was either less common than (Eiler et al., 2018; Kampov-Polevoy et al., 2001; Turner-McGrievy et al., 2013, 2016) or approximately as common as the SD phenotype (Kampov-Polevoy et al., 2006, 2014; Kampov-Polevoy, Garbutt, et al., 2003; Kareken et al., 2013; Lange et al., 2010; Weafer et al., 2017) Likewise, a study of Polish adolescents using a 3 (sweet taste stimuli) x 1 (replicate) version of the 'highest preference using ratings' method indicated a SL phenotype prevalence of 67%. However, the confounding effect of the well-established enhanced hedonic response to sweet tastes in underage populations (De Graaf & Zandstra, 1999; Garneau et al., 2018; Mennella et al., 2014) should also be considered.

Table 2.5. Papers included in this review using the 'Highest preference using ratings' classification method (Method 2) for the identification of the distinct sweet-liking phenotypes

Author(s), Publication Year	Country	Participants n (% men)	Health Status (%)	Age in years mean (±s.d.)*	Sucrose Solutions (x times of replicates)	Hedonic Scale	Sweet-liking phenotypes (%)
Eiler et al. (2018) [1]	USA	74 (43)	Healthy (100)	22.8 (1.6)	0.05, 0.10, 0.21, 0.42, and 0.83 M (x 3)	**	- SL (35.1): $LIKE_{max}$ at 0.83 M - SD (63.5): $LIKE_{max}$ at 0.05, 0.10, 0.21, or 0.42 M + 1 participant with no available data
Goodman et al. (2018) [2]	USA	41 (15)	Binge-eating disorder (100)	38.0 (11.5)	0.05, 0.10, 0.21, 0.42, and 0.83 M (x 5)	analogue scale	- Highest sweet preferer (43.9): $LIKE_{max}$ at 0.83 M - Other sweet preferer (56.1): $LIKE_{max}$ at 0.05, 0.10, 0.21, or 0.42 M
Weafer et al. (2017)	USA	71 (51 [3])	Healthy (100)	[21-35 years old]	0.05, 0.10, 0.21, 0.42, and 0.83 M (x 5)	VAS	- SL (50.7): $LIKE_{max}$ at 0.83 M - SD (47.9): $LIKE_{max}$ at 0.05, 0.10, 0.21, or 0.42 M + 1 participant with non-appropriate concentration-response curve
Turner-McGrievy et al. (2016)	USA	209 (16)	Obese in weight loss (100)	42.3 (11.0)	0.05, 0.10, 0.21, 0.42, and 0.83 M (x 5)	VAS	- SL (33.5): $LIKE_{max}$ at 0.83 M - SD (66.5): $LIKE_{max}$ at 0.05, 0.10, 0.21, or 0.42 M
Garbutt et al. (2016)	USA	80 (71)	Alcoholic (100)	47.0 (8.6)	0.05, 0.10, 0.21, 0.42, and 0.83 M (x 5)	analogue scale	- SL (27.5): $LIKE_{max}$ at 0.83 M - SD (72.5): $LIKE_{max}$ at 0.05, 0.10, 0.21, or 0.42 M

Study	Country	N (%)	Groups	Age	Concentrations	Scale	Results
Swiecicki et al. (2015)	Poland	72 (29)	Depressed with SAD (25) Depressed without SAD (33) Healthy (42)	Depressed with SAD: 36.3 (9.3[†]) Depressed without SAD: 36.8 (10.3[†]) Controls: 35.4 (11.5[†])	0.029, 0.30, and 0.99 M[§§] (x 2)	2-anchor line	- SL (71.0): $LIKE_{max}$ at 0.99 M - SD (29.0[‡]): $LIKE_{max}$ at 0.029 or 0.30 M
Weafer et al. (2014)	USA	20 (**)	Healthy (100)	[18-30 years old]	0.05, 0.10, 0.21, 0.42, and 0.83 M (x 5)	VAS	SL (**): $LIKE_{max}$ at 0.83 M SD (**): $LIKE_{max}$ at 0.05, 0.10, 0.21, or 0.42 M + 1 participant with non-appropriate concentration-response curve
Kampov-Polevoy et al. (2014)	USA	150 (49)	Alcohol use disorders+ (50) Alcohol use disorders- (50)	21.0 (1.8)	0.05, 0.10, 0.21, 0.42, and 0.83 M (x 5)	VAS	- SL (50.0): $LIKE_{max}$ at 0.83 M - SD (50.0): $LIKE_{max}$ at 0.05, 0.10, 0.21, or 0.42 M
Damiano et al. (2014)	USA	57 (88)	ASD (33) Healthy (67)	ASD patients: 26.0 (8.0) Controls: 20.4 (5.6)	0.05, 0.10, 0.21, 0.42, and 0.83 M (x 5)	analogue scale	- SL (49.1): $LIKE_{max}$ at 0.83 M - SD (50.9): $LIKE_{max}$ at 0.05, 0.10, 0.21, or 0.42 M
Kareken et al. (2013)	USA	16 (75)	Healthy (100)	26.1 (4.4)	0.05, 0.10, 0.21, 0.42, and 0.83 M (x 3)	VAS	- SL (50.0): $LIKE_{max}$ at 0.83 M - SD (50.0): $LIKE_{max}$ at 0.05, 0.10, 0.21, or 0.42 M
Sienkiewicz-Jarosz et al. (2013)	Poland	40 (38)	PD (50) Healthy (50)	PD patients: 60.6 (27.7[††]) Controls: 56.3 (7.2[††])	0.029, 0.30, and 0.99 M[§§] (x 2)	2-anchor line	- SL (70.0): $LIKE_{max}$ at 0.99 M - SD (30.0[‡]): $LIKE_{max}$ at 0.029 or 0.30 M

Turner-McGrievy et al. (2013)	USA	196 (16)	Overweight/Obese (100)	42.6 (11.0)	0.05, 0.10, 0.21, 0.42, and 0.83 M (x 5)	analogue scale	- SL (35.2): $LIKE_{max}$ at 0.83 M - non-SL (64.8[‡]): **
Langleben et al. (2012)	USA	15 (87)	Opioid-dependent (100)	34.3 (8.2)	0.05, 0.10, 0.21, 0.42, and 0.83 M (x 3)	Likert scale	- SL (33.3): $LIKE_{max}$ at 0.83 M - SD (66.7): $LIKE_{max}$ at 0.05, 0.10, 0.21, or 0.42 M
Dichter et al. (2010)[‡‡]	USA	31 (**)	Depressed (52) Healthy (48)	Depressed: **(**) Controls: **(**)	0.05, 0.10, 0.21, 0.42, and 0.83 M (x 5)	analogue scale	- SL (12.9): $LIKE_{max}$ at 0.83 M - SD (87.1[‡]): $LIKE_{max}$ at 0.05, 0.10, 0.21, or 0.42 M
Lange et al. (2010)	USA	158 (39)	Healthy [4] with FHA+ (50) Healthy [4] with FHA- (50)	[20-25 years old]	0.05, 0.10, 0.21, 0.42, and 0.83 M (x 5)	analogue scale	- SL (55.1): $LIKE_{max}$ at 0.83 M - SD (44.9[‡]): $LIKE_{max}$ at 0.05, 0.10, 0.21, or 0.42 M
Tremblay et al. (2009)	USA	215 (55)	Alcoholic (43) Healthy (57)	Alcoholics: 47.7 (9.1) Controls: 25.9 (6.0)	0.05, 0.10, 0.21, 0.42, and 0.83 M (x 5)	VAS	- SL (40.5): $LIKE_{max}$ at 0.83 M - SD (14.0): $LIKE_{max}$ at 0.05 M + 85 participants with $LIKE_{max}$ at 0.10, 0.21, or 0.42 M + 13 participants with no preference
Swiecicki et al. (2009)	Poland	76 (32)	Depressed (61) Healthy (39)	Depressed: 38.2 (10.9[†]) Controls: 35.4 (11.5[†])	0.029, 0.30, and 0.99 M[§§] (x 2)	2-anchor line	- SL (63.2): $LIKE_{max}$ at 0.99 M - SD (36.8[‡]): $LIKE_{max}$ at 0.029 or 0.30 M
Garbutt et al. (2009)	USA	40 (73)	Alcoholic (100)	49.0 (9.0)	0.05, 0.10, 0.21, 0.42, and 0.83 M (x 5)	analogue scale	- SL (37.5): $LIKE_{max}$ at 0.83 M - SD (62.5): $LIKE_{max}$ at 0.05, 0.10, 0.21, or 0.42 M

Wronski et al. (2006)	Poland	78 (100)	Alcoholic (58) Healthy (42)	Alcoholics: 44.3 (10.1[††]) Controls: 42.8 (11.5[††])	0.029, 0.30, and 0.99 M[§§] (x 2)	2-anchor line	- SL (60.3): LIKE$_{max}$ at 0.99 M - SD (**): **
Kampov-Polevoy et al. (2006)	USA	163 (39)	Healthy (100)	22.1 (2.6[††])	0.05, 0.10, 0.21, 0.42, and 0.83 M (x 5)	analogue scale	- SL (52.8): LIKE$_{max}$ at 0.83 M - SD (46.0): LIKE$_{max}$ at 0.05, 0.10, 0.21, or 0.42 M + 2 participants with no available data
Krahn et al. (2006)[‡‡]	USA	65 (100)	Alcoholic (100)	[18-65 years old]	0.05, 0.10, 0.21, 0.42, and 0.83 M (x 5)	VAS	- SL (56.9): LIKEmax at 0.83 M - SD (**): **
Kampov-Polevoy et al. (2004) [5]	USA	165 (49)	Alcohol or drug abuse disorder and/or psychiatric disorder (100)	37.7 (11.6[††])	0.05, 0.10, 0.21, 0.42, and 0.83 M (x 5)	analogue scale	- SL (31.5): LIKE$_{max}$ at 0.83 M - SD (68.5[‡]): LIKE$_{max}$ at 0.05, 0.10, 0.21, or 0.42 M
Kampov-Polevoy et al. (2003b)	USA	163 (39)	Healthy with PHA+ (50) Healthy with PHA- (50)	22.1 (2.6[††])	0.05, 0.10, 0.21, 0.42, and 0.83 M (x 5)	analogue scale	- SL (50.9): LIKE$_{max}$ at 0.83 M - SD (49.1[‡]): LIKE$_{max}$ at 0.05, 0.10, 0.21, or 0.42 M
Kampov-Polevoy et al. (2003a)	USA	180 (48)	Alcohol or drug abuse disorder and/or psychiatric disorder (100)	37.7 (12.1[††])	0.05, 0.10, 0.21, 0.42, and 0.83 M (x 5)	analogue scale	- SL (31.0 [6]): LIKE$_{max}$ at 0.83 M - SD (69.0 [6]): LIKE$_{max}$ at 0.05, 0.10, 0.21, or 0.42 M

Study	Country	N (%)	Group	Age	Concentrations	Scale	Results
Janowsky et al. (2003)	USA	32 (34)	Cocaine dependent (50)	Cocaine dependent: 34.6 (6.6)	0.05, 0.10, 0.21, 0.42, and 0.83 M (x 5)	10-point analogue scale	- SL (28.1): LIKEmax at 0.83 M - SD (**): ** + 1 participant with $LIKE_{max}$ at both 0.42 and 0.83 M
			Depressed (50)	Depressed: 31.7 (9.4)			
Bogucka-Bonikowska et al. (2002)	Poland	60 (100)	Opioid-dependent (47)	Opioid-dependent: 40.5 (5.9)	0.029, 0.29, and 0.87 M§ (x 1)	2-anchor line	- SL (50.0): $LIKE_{max}$ at 0.87 M - SD (**): ** -
			Healthy (53)	Controls: 41.3 (9.0)			
Bogucka-Bonikowska et al. (2001)	Poland	62 (100)	Alcoholic (48)	Alcoholics: 43.6 (8.8††)	0.029, 0.29, and 0.87 M§ (x 1)	2-anchor line	- SL (58.1): $LIKE_{max}$ at 0.87 M - SD (**): **
			Healthy (52)	Controls: 41.3 (8.5††)			
Kranzler et al. (2001)	USA	122 (48)	Healthy with PHA+ (47)	PHA+: 26.0 (5.8)	0.05, 0.10, 0.21, 0.42, and 0.83 M (x 5)	VAS	- SL (57.4): $LIKE_{max}$ at 0.42 or o.83 M - SD (17.2): $LIKE_{max}$ at 0.05 or o.1 M + 25 participants with $LIKE_{max}$ at 0.21 M + 6 participants with no preference
			Healthy with PHA- (53)	PHA-: 25.8 (6.1)			
Kampov-Polevoy et al. (2001)‡‡	Russia	57 (100)	Alcoholic (56)	Alcoholics: 37.6 (7.9††)	0.05, 0.10, 0.21, 0.42, and 0.83 M (x 5)	analogue scale	- SL (31.6): $LIKE_{max}$ at 0.83 M - SD (68.4‡): $LIKE_{max}$ at 0.05, 0.10, 0.21, or 0.42 M
			Healthy (44)	Controls: 32.0 (9.0††)			
Scinska et al. (2001)	Poland	42 (100)	PHA+ (48)	PHA+: 15.4 (4.0††)	0.029, 0.29, and 0.87 M§ (x 1)	2-anchor line	- SL (66.7): $LIKE_{max}$ at 0.87 M - SD (**): ** -
			PHA- (52)	PHA-: 14.0 (3.8††)			

Kampov-Polevoy et al. (1998)[7]	USA	78 (100)	Alcoholic (33) Healthy (67)	Alcoholics: 40.0 (10.4) Controls: 38.8 (10.9)	0.05, 0.10, 0.21, 0.42, and 0.83 M (x 5)	analogue scale	- SL (34.6): $LIKE_{max}$ at o.83 M - SD (33.3): $LIKE_{max}$ at 0.05 or o.1 M - + 25 participants with $LIKE_{max}$ at 0.21 or 0.42 M or with no preference $(LIKE_{max})$[‡]
Kampov-Polevoy et al. (1997)	USA	57 (100)	Alcoholic (35) Healthy (65)	Alcoholics: 40.1 (10.1) Controls: 38.8 (11.3)	0.05, 0.10, 0.21, 0.42, and 0.83 M (x 5)	analogue scale	- SL (54.4): $LIKE_{max}$ at 0.42 or o.83 M - SD (38.6): $LIKE_{max}$ at 0.05 or o.1 M + 4 participants with $LIKE_{max}$ at 0.21 M[‡]

*Age mean and s.d. rounded to one decimal place

**No information available

[†]s.d. calculated from standard error (SE) (SE=s.d./√sample size)

[††]s.d. calculated from standard error of the mean (SEM) (SEM=s.d./√sample size)

[§]Sucrose concentration in M (mol/L) calculated from % w/v based on sucrose's molecular weight (342.296 g) and the assumption that the solvent is pure/deionized water at 20°C (Haynes, 2016)

[§§]Sucrose concentration in M (mol/L) calculated from % w/w based on sucrose's molecular weight (342.296 g) and the assumption that the solvent is pure/deionized water at 20°C (% w/w = % w/v x Special Gravity$_{solution}$) (Haynes, 2016)

[‡]Based on reviewers' calculation from the sweet-liking phenotypes' description provided by authors

[‡‡]Based on participants' baseline data

[1] The paper was available online on the 12th of December 2017.

[2] The paper was available online on the 17th of November 2017.

[3] Data were derived from the 70 participants who were classified as SLs or SDs.

[4] Regardless the current medical problems exclusion criterion, 18.3% of the study sample was later identified as positive to alcohol-related problems.

[5] Sample was derived from Kampov-Polevoy et al. (2003a).

[6] Percentages were calculated based on data from 161 participants with available sweet-liking data.

[7] Three quarter of the sample (57 participants) was derived from Kampov-Polevoy et al. (1997).

ASD, autism spectrum disorder; BMI, body mass index; FHA-, negative family history of alcoholism; FHA+, positive family history of alcoholism; LIKE, liking rating; $LIKE_{max}$, maximum liking rating; PD, Parkinson disease; PHA-, negative paternal history of alcoholism; PHA+, positive paternal history of alcoholism; SAD, seasonal affective disorder; s.d., standard deviation; SD, sweet disliker; SL, sweet liker; VAS, visual analog scale

2.3.4 Average liking above mid-point or Positive/Negative average liking classification method (Method 3)

A less commonly reported method of discriminating between the distinct sweet-liking phenotypes is the 'average liking above mid-point' method or 'positive/negative average liking' method (Table 2.4). It relies on a dichotomous classification of SLs/SDs analogous to that of the 'highest preference' rating method. However, in this case the discrimination depends on whether the individual average hedonic score ('average liking') for all the presented sweet taste stimuli is higher or lower than a particular cut-off liking value ('mid-point') or if it is higher or lower than zero when bipolar scales with a zero neutral response are used ('positive/negative'). In some cases, classification in the distinct sweet-liking phenotypes is established after averaging the liking scores of a single sucrose concentration presented at least twice. In addition, 'mid-point' does not usually refer to one predetermined point at half the distance between the hedonic scales' anchors, but it stands for values ranging from 40 to 60 on a 100-point scale.

Yeomans and colleagues were the first to suggest such a methodological framework for the identification of distinct sweet-liking phenotypes advocating for a single sweet taste stimulus design based on 0.29 or 0.30 M sucrose (Yeomans et al., 2006). Except for two studies where the SL phenotype was defined in the inclusion criteria (Mobini et al., 2007; Yeomans et al., 2008), the approximate 3:1 ratio of SLs to SDs they reported was comparable with most of the relevant studies (Coldwell et al., 2009; Yeomans et al., 2007, 2009), including a twin cohort of more than 1400 British and Finnish subjects (Tuorila, et al., 2017). Interestingly, the relative proportion of SLs and SDs in these studies was consistent irrespective of the number of different sweet taste stimuli served or the specific cut-off liking scores set in each study. Yeomans & Prescott (2016), who exclusively recruited female subjects, found an even larger number of SLs. In contrast, when comparably small samples were tested, the SL and SD phenotypes were about evenly distributed across participants (Methven et al., 2016; Sartor et al., 2011; Yeomans et al., 2006).

Table 2.6 Papers included in this review using the 'Average liking above mid-point or positive/negative average liking' classification method (Method 3) for the identification of the distinct Sweet-liking phenotypes

Author(s), Publication Year	Country	Participants n (% men)	Health Status (%)	Age in years mean (±s.d.)*	Sucrose Solutions (x times of replicates)	Hedonic Scale	Sweet-liking phenotypes (%)
Tuorila et al. (2017)	UK & Finland	1455 (20)	** (**)	British: [17-82 years old] Finnish: [17-39 years old]	0.58 M§ (x 1)	LAM scale	- Liker (63.6): LIKE > 0 - Non-liker (36.4): LIKE < 0
Yeomans & Prescott (2016)	UK	84 (0)	Healthy (100)	22 (4)	0.29 M§ (x 2)	VAS	- consistent SL (72.6): $LIKE_{Replicate\ 1}$ > 60 *and* $LIKE_{Replicate\ 2}$ > 60 - consistent SD (27.4): $LIKE_{Replicate\ 1}$ < 40 *and* $LIKE_{Replicate\ 2}$ < 40
Methven et al. (2016) (see also Table 2.2)	UK	36 (34 [1])	** (**)	26 (**)	0.087, 0.17, 0.35, 0.70, and 1.05 M§ (x 1)	VAS	- SL (52.8): $LIKE_{t\_mean}$ > 50 - SD (47.2): $LIKE_{t\_mean}$ < 50
Sartor et al. (2011)	UK	12 (42)	Healthy (100)	26 (6)	0.056, 0.10, 0.18, 0.32, and 1 M (x 1)	gLMS	- Sucrose likers (50.0): LIKE at 1 M > 55 - Sucrose dislikers (50.0): LIKE at 1 M < 55
Yeomans et al. (2009)	UK	92 (17)	Healthy (100) [2]	21 (**)	0.21 and 0.83 M (x 1)	VAS	- SL (59.8): $LIKE_{t\_mean}$ > 50 - SD (40.2): $LIKE_{t\_mean}$ < 50

Coldwell et al. (2009)	USA	143 (55)	Healthy (100)	13.5 (14.4[†])	0.056, 0.1, 0.17, 0.32, 0.56, and 1 M (x 3)	5-point category scale (+ face expression)	- High preference (61.5): [LIKE$_{mean}$ at 0.56 and 1 M] – [LIKE$_{mean}$ at 0.056 and 0.1 M] > 0 - Low preference (37.1): [LIKE$_{mean}$ at 0.56 and 1 M] – [LIKE$_{mean}$ at 0.056 and 0.1 M] < 0 + 2 participants with [LIKE$_{mean}$ at 0.56 and 1 M] – [LIKE$_{mean}$ at 0.056 and 0.1 M] = 0
Yeomans et al. (2008)	UK	60 (38)	Healthy (100)	23.5 (6.4)	0.30 M[§§‡] (x 2)	VAS	- SL (100.0 [3]): LIKE$_{t\_mean}$ > 55 - SD (0.0 [3]): **
Yeomans et al. (2007) (see also Table 2.3)	UK	60 (33)	Healthy (100)	23.1 (6.2[†])	0.05, 0.21, 0.42, and 0.83 M (x 2)	gLMS	- SL (68.3): LIKE at 0.42 *and/or* 0.83 M > 0 - SD (31.7): LIKE at 0.42 *and/or* 0.83 M < 0
Mobini et al. (2007)	UK	60 (30)	Healthy (100)	23.5 (6.4)	0.30 M[§§‡] (x 2)	2-anchor line	- SL (100.0 [3]): LIKE$_{Replicate 1}$ > 55 *and* LIKE$_{Replicate 2}$ > 55 - SD (0.0 [3]): **
Yeomans et al. (2006)	UK	24 (17)	Healthy (100)	22 (**)	0.30 M[§§‡] (x 2)	2-anchor line	- SL (50.0): LIKE$_{t\_mean}$ ≥ 60 - SD (50.0): LIKE$_{t\_mean}$ ≤ 45

*Age mean and s.d. rounded to one decimal place

**No information available

[†]s.d. calculated from standard error (SE) (SE=s.d./√sample size)

[§]Sucrose concentration in M (mol/L) calculated from % w/v based on sucrose's molecular weight (342.296 g) and the assumption that the solvent is pure/deionized water at 20°C (Haynes, 2016)

[§§]Sucrose concentration in M (mol/L) calculated from % w/w based on sucrose's molecular weight (342.296 g) and the assumption that the solvent is pure/deionized water at 20°C (% w/w = % w/v x Special Gravity$_{solution}$) (Haynes, 2016)

[‡]Based on reviewers' assumption that the sucrose concentration was initially expressed in % w/w

[1] One participant denied the relevant information.

[2] Information from personal communication.

[3] The sweet taste test was conducted at screening level.

BMI, body mass index; gLMS, general labeled magnitude scale; LIKE, liking rating; LIKE$_{mean}$, average hedonic score; LIKE$_{t\_mean}$, average hedonic score across all sucrose solutions and replicates; LAM scale, labelled affective magnitude scale; NL, The Netherlands; SC, sucrose concentration; s.d., standard deviation; SD, sweet disliker; SL, sweet liker; VAS, visual analog scale

2.3.5 Highest preference via paired comparisons classification method (Method 4)

A rather different approach to distinguish hedonic responses to sweet stimuli is by contrasting the most preferred levels of sweetness for each individual (i.e. based on preferences between stimuli and not on the rated liking for those stimuli). In this protocol developed by researchers at the Monell Chemical Senses Center (Mennella et al., 2011), sucrose solutions of varying concentrations are presented in a dyadic sequential mode. Participants are forced to point to the solution they "like better" and each subsequent pair is determined by the preceding preference choice (similar to an adaptive method for taste thresholds). The task continues until the participant chooses the same sucrose concentration relative to both a higher and a lower concentration or the highest or lowest concentration two consecutive times. Participants can then be split into groups which correspond to different sweet-liking phenotypes depending on the geometric mean of the most preferred concentrations or the number of times a sucrose solution is selected over all the others (i.e. the percentage preference).

Only a few studies which used this sweet-liking assessment protocol then go on to define sweet-liking groups (Table 2.5). In Grinker's reports the graphical representation of the percentage preference as a function of concentration revealed a group that systematically preferred the lowest sucrose concentration they tasted (two thirds of adults and one third of children tested) and a second group showing either an inverted U-shaped response with optimal preference at 0.18 M (Grinker & Hirsch, 1972) or a monotonically ascending one (Grinker, 1977). A half century later, Mennella and colleagues (2014) also identified two approximately equally distributed sweet-liking phenotypes after they split a subgroup of their children study population at the median sucrose preference value. Asao and colleagues (2015) reported a 3:1 ratio between low and high concentration likers when they compared the geometric mean of the most preferred sucrose concentrations with a concentration threshold they had previously identified via HCA. It is notable that despite large differences in BMI across the adult studies using the 'highest preference via paired comparisons' method, it provided fairly consistent proportions of the SD phenotype.

Table 2.7 Papers included in this review using the 'Highest preference via paired comparisons' classification method (Method 4) for the identification of the distinct sweet-liking phenotypes

Author(s), Publication Year	Country	Participants n (% men)	Health Status (%)	Age in years mean (±s.d.)*	Sucrose Solutions (x times of replicates)	Hedonic Scale	Sweet-liking phenotypes (%)
Asao et al. (2015) (see also Table 2.2)	USA	26 (46)	Healthy (100)	32.6 (14.5)	0.035, 0.053, 0.079, 0.118, 0.177, 0.266, 0.399, 0.598, 0.897, and 1.346 M (x 2)	- [††]	- High concentration liker (38.5): geometric mean of most preferred SUC at ≥ 0.598 M - Low concentration liker (61.5): geometric mean of most preferred SUC at < 0.598 M
Mennella et al. (2014)	USA	100 (**)	Healthy (100)	Group B: 8.14 (1.8[†]) Group A: 7.54 (1.9[†])	0.088, 0.18, 0.35, 0.70, and 1.05 M[§] (x 2)	- [††]	- Group B (47.0): geometric mean of most preferred SUC at ≥ 0.609 M - Group A (53.0): geometric mean of most preferred SUC at < 0.609 M
Grinker (1977) [1] (see also Table 2.3)	USA	56 (34)	Extremely obese (45) Moderately obese (25) Normal weight (30)	Extremely obese: 34.2 (**) Moderately obese: 32.7 (**) Normal weight: 23.1 (**)	0.057, 0.10, 0.17, 0.32, and 0.57 M[§] (x 1)	- [††]	- (30.4): ↑$_{SUC}$ => ↑ optimal preference with SUC more often preferred at 0.57 M - (69.6): ↑$_{SUC}$ => ↓ optimal preference with SUC more often preferred at 0.057 M

Grinker (1977) [2]	USA	26 (53.8)	Overweight in weight loss (31) Overweight (31) Normal weight (38)	[8-10 years old]	0.057, 0.10, 0.17, 0.32, and 0.57 M[§] (**)	- [††]	- (69.2): $\uparrow_{SUC}$ => $\uparrow$ optimal preference with SUC more often preferred at 0.57 M - (30.8): $\uparrow_{SUC}$ => $\downarrow$ optimal preference with SUC more often preferred at 0.10 M
Grinker & Hirsch (1972) [3, 4]	USA	35 (**)	Obese (63) Normal weight (37)	**(**)	0.057, 0.10, 0.18, 0.33, and 0.61 M[§§] (x 1)	- [††]	- (37.1): $\uparrow_{SUC}$ => $\uparrow\downarrow$ optimal preference with SUC more often preferred at 0.18 M - (62.9): $\uparrow_{SUC}$ => $\downarrow$ optimal preference with SUC more often preferred at 0.057 M

*Age mean and s.d. rounded to one decimal place

**No information available

[†]s.d. calculated from standard error (SE) (SE=s.d./√sample size)

[††]Sweet-liking calculated via paired-comparison procedure

[§]Sucrose concentration in M (mol/L) calculated from % w/v based on sucrose's molecular weight (342.296 g) and the assumption that the solvent is pure/deionized water at 20°C (Haynes, 2016)

[§§]Sucrose concentration in M (mol/L) calculated from % w/w based on sucrose's molecular weight (342.296 g) and the assumption that the solvent is pure/deionized water at 20°C (% w/w = % w/v x Special Gravity_solution) (Haynes, 2016)

[1] It is not clear whether the presented sweet-liking phenotypes results being were collected before or after the red "cherry" colour manipulation of the sucrose solutions.

[2] The presented data are reviewed in Grinker et al. (1977); the original cited paper didn't match.

[3] Original reference in Grinker, J., Smith, D. V. & Hirsch, J. (1971). Taste preferences in obese and normal weight subjects. *Proceedings of the IVth International Conference on the Regulation of Food and Water Intake*, Cambridge, England (abstract).

[4] It is not clear whether there is an overlap between participants tested via the paired-comparison technique (Table 2.5) and those rating stimuli on a hedonic scale (Table 2.1).

SUC, sucrose concentration; s.d., standard deviation

2.3.6 Outcome of the different methods compared

Figure 2.2 shows the sweet-liking data from Tables 2.1-2.5 focusing on the weighted average proportions of the different sweet liker phenotypes both within and between the different classification methods. Breaking down the relevant proportion within each method, participants who were classified algorithmically (Method 1b) were approximately evenly distributed between the SL and the SD phenotype (46.3% vs. 45.0%, respectively). Interestingly, the majority of participants considered SDs in studies using Method 1a and 1b did not actually exhibit strong aversive responses to sweet stimuli, but rather liking for intermediate concentrations (63.8% and 73.5%, respectively). In contrast, studies employing Method 3 identified 63.5% SLs across the total sample, and notably tested younger and leaner subjects, as well as the fewest men as described above (2.3.1). On the other hand, participants exhibiting erratic responses or presenting no particular preference to any of the sweet stimuli accounted for less than 10% of the population in all methods reviewed here.

When we statistically compared the frequency distributions of the different sweet-liking phenotypes between methods (Table 2.7), except Method 4 where, as expected, the disproportionally small number of listed studies led mainly to non-effective contrasts, most of the remaining paired comparisons revealed significant differences in the proportion of SLs between the different phenotyping methods; a similar conclusion was drawn for SDs.
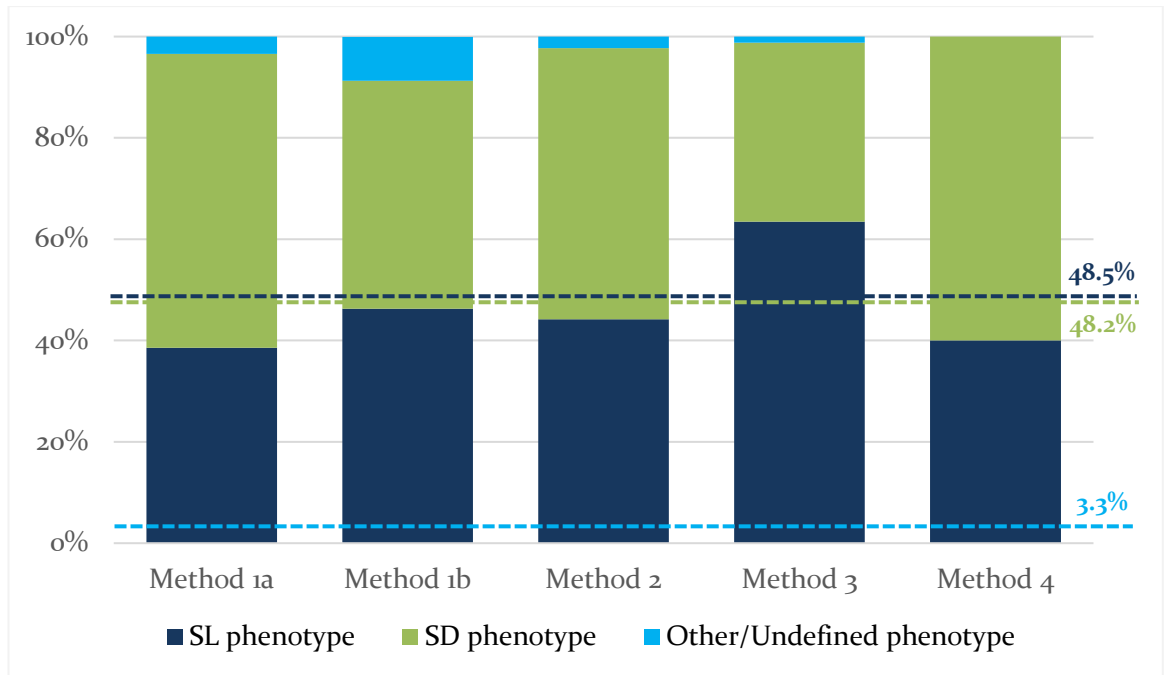
Fig. 2.2 Proportions (%) of sweet-liking phenotypes by classification method

The dashed lines denote the total weighed average proportions of the different sweet-liking phenotypes across all methods under review. The dark blue line represents the SL phenotype, the green line represents the SD phenotype, and the light blue line the other/undefined phenotype.

SL, sweet liker; SD, sweet disliker

Method 1a: Visual discrimination of hedonic responses; Method 1b: Statistical discrimination of hedonic responses (algorithmic classification); Method 2: Highest preference using ratings; Method 3: Average liking above mid-point/positive-negative average liking; Method 4: Highest preference via paired comparisons

2.4 Discussion

In reviewing the various approaches used previously to identify sweet-liking phenotypes, it is clear different methods have evolved out of the specific needs of the set of research questions being addressed, but in doing so the lack of consistency across studies makes it difficult to draw broader strong conclusions on questions such as "is sweet-liking associated with higher body weight". It is also clear that all methods have some degree of utility but no single existing method stands without criticism, and for this research area to move forward, there needs to be a more universal adoption of a common method that can quickly identify sweet-liking phenotypes while minimizing the

risks of misclassification. After reviewing the various strengths and weaknesses of existing methods, we propose a way forward that could achieve a more unified approach.

2.4.1 Strengths and weaknesses in identifying sweet-liking phenotypes using different classification methods

2.4.1.1 Interpreting the shape of hedonic response curves (Method 1a & Method 1b)

The interpretation of individual hedonic response curves was recognized as the most promising of the classification methods currently used. The main argument in favour of this approach is the absence of the need for an arbitrary pre-defined sucrose concentration cut-off value which is an essential element of other methods reviewed here. However, interpreting individual hedonic response curves does not come without its own challenges. A major concern is with the original visual approach, which was based on the interpretation of the individual examining each curve, leading to a risk of subjective or worse yet, unblinded classification of participants. This was particularly an issue when participants deviated from a monotonic response by neither showing linear increases nor decreases in liking ratings as a function of sucrose concentration, or when more than two different patterns of liking curves were evident in the tested sample. Many studies using the visual-interpretation approach tended to classify both participants whose responses had an inverted U-shaped pattern and those who showed descending liking ratings with increasing concentration as a single "negative" group, which potentially conflates two distinct phenotypes for the sake of simplicity. The shape of hedonic response functions also depends on the range of sucrose concentrations being tested, and the lack of a widely accepted concentration range for use in all studies is a major limitation when trying to contrast responses across studies.

The more recent introduction of algorithmic methods and of the agglomerative HCA in particular to interpret hedonic response curves removes most potential bias or inconsistency from visual inspection, and provides an unbiased method to classifying individuals into different sweet-liking phenotypes. Unlike the visual inspection approach, the steps required for the identification of the distinct groups (clusters) are

part of the statistical process. To eliminate the risk of low quality grouping, subsequent to selecting, for example, the agglomerative over the divisive clustering approach, further decisions are left for the researcher to make (Rani & Rohil, 2013). This allows for customization of the steps integrated into the clustering process, such as the selection of the exact linkage method (unweighted pair-group method, maximum or minimum method, Wards' algorithm) and truncation method (manual via incorporating data of the agglomeration schedule into the dendrogram or automatic determined by inertia or entropy) that best fit with a particular study design (Yim & Ramdeen, 2015). Correspondingly, those specific steps taken along with the relevant line of reasoning warrants to be reported. Robustness of the clusters generated needs to be checked and reported also: split-sample validation (Everitt et al., 2011) or simply contrasting the difference in individual values within a cluster from the cluster mean could be suggested. In addition, as with the visual interpretation method, the outcome of HCA will still be influenced by the concentration range of sucrose solutions used, and limiting this range may lead to misclassification. Moving forward, for direct comparability across different studies, a common range of test stimuli or one common single stimulus is needed. Moreover, unless a prior dataset is already available for a particular cohort and has already been analysed, HCA also requires advanced statistical techniques subsequent to data collection and therefore it is not as viable as, for example, Method 3 as a screening method to quickly identify distinct sweet-liking phenotypes when that is needed early in a study. Finally, we should note that, "*HCA suffers from the defect that it can never repair what was done in previous steps*" (Kaufman & Rousseeuw, 2009). That is, once a merge or split decision has been executed, no adjustments are possible.

2.4.1.2 Highest preference using ratings classification method (Method 2)

The 'highest preference using ratings' classification method provides a comparatively easy-to-interpret method for discrimination between SLs and SDs. It is noteworthy that this method had the highest consistency in terms of the relative proportions of SL and SD. Considering the most preferred sucrose solution for investigating individual hedonic responses has a precedent in Sensory Science: the forced-choice paired-comparison technique is based on a wider psychophysical

approach to determining an individual's most preferred level of a tastant after a series of dyadic contrasts (Meilgaard et al., 2016; Mennella & Bobowski, 2016).

However, the 'highest preference using ratings' method also has a few clear limitations. First, it uses the liking rating of an arbitrary sucrose concentration (usually 0.83 M) to discriminate SLs from SDs. Kampov-Polevoy and colleagues rationalized this concentration relative to the sucrose content of a commercially available beverage (Coca Cola at 0.33 M). However, to our knowledge, this choice has not been challenged or justified statistically in any subsequent work. Also, beyond the simple discrepancy (0.83 M versus 0.33 M), a direct comparison between model sucrose solutions and commercial beverages that contain acids, caffeine and aromatic flavors is questionable at best. A further issue is that under their operational definition, anyone who gives the highest rating to the highest concentration of sucrose is classified as SL regardless of the actual valance of their rating for that stimulus. That is, if an individual's highest rating falls below the mid-point of the scale (i.e., below the neutral point), representing an aversive response, they would still be classified as SL. Contrary to the rest of the methods reviewed here, it is also of note that studies using this technique have primarily focused on psychiatric populations (primarily those with alcohol or substance dependence, or other mental health concerns). While this does not invalidate the methodology per se, it does make contrasts of the outcome of studies using that method with other methods more problematic, since these populations are likely to differ from the general population in terms of reward response (Zald & Treadway, 2017).

2.4.1.3 Average liking above mid-point or positive/negative average liking classification method (Method 3)

Concerning the 'average liking above mid-point' or 'positive/negative average liking' method, the relative proportions of SLs and SDs identified by this method was remarkably consistent despite variations in the exact definition of the SL and the SD phenotype between different studies. Still, educated young women made up the majority of participants, and the homogeneity of the population tested may explain the consistency in proportions of SLs and SDs. One clear advantage of this simple method is that it uses only a single test stimulus and so is very quick and easy to administer, which

may be the reason it was selected for the largest study reviewed here (Tuorila, et al., 2017).

Nonetheless, the concentration of sucrose used and the specific cut-off points determining which phenotype a participant belongs to remains arbitrary. Another important point is that the 0.29/0.3 M sucrose solution used in many studies is close to the breakpoint concentration of the inverted U-shaped hedonic response curve typically associated with the SD phenotype (Table 2.1), suggesting this concentration is possibly too low and risks misclassification errors. Moreover, in studies using the 'average liking above mid-point' or 'positive/negative average liking' method and averaging liking ratings of all stimuli tested, is associated with the large number of low sucrose concentrations included in those sweet taste tests. A high average overall rating that could have resulted from strong liking for low sweetness is interpreted as indicative of the SL phenotype in such studies although it is actually more characteristic of the SD. Indeed, Methven and colleagues highlighted a 16.7% misclassification between this method and the statistically robust interpretation of hedonic response curves (Methven, et al., 2016).

2.4.1.4 Highest preference via paired comparisons classification method (Method 4)

The sweet-liking assessment protocol associated with the 'highest preference via paired comparisons' approach has been claimed to be a reliable and valid sweet taste test (Mennella et al., 2011; Mennella & Bobowski, 2016) and the method of choice in pediatric populations (Coldwell et al., 2013) as it allows for cognitive limitations in this population (Guinard, 2000; Mennella et al., 2011). However, unlike other approaches reviewed here, the paired-comparison approach is a measure of preference which by definition reflects a selection process made within a choice paradigm and not a measure of elicited liking per se (Hayes, 2015). This may be especially subject to experimental and methodological concerns, like adaptation. Indeed, more intense sucrose solutions tend to be preferred in subsequent series within the given task (Leon et al., 1999; Mennella et al., 2011), in direct contrast to the decreasing liking observed with replicates in other sweet taste test approaches. In addition, in the case of inverted U-shaped response phenotypes where stimuli of diametrically opposed levels of sweetness can be liked or

disliked to the same degree, a preference between two items will be forced. On the other hand, a relatively low misclassification rate of 11.5% in favor of the 'low concentration' likers was suggested when Asao and colleagues compared the 'highest preference via paired comparisons' method with the algorithmic interpretation of hedonic curves (Asao, et al., 2015). Likewise, Grinker's sweet-liking phenotype findings from the 'highest preference via paired comparisons' method were identical to those using the visual interpretation of hedonic curves method (Grinker, 1977). However, the limited number of studies that have used the 'highest preference via paired comparisons' approach potentially undermines a well-substantiated judgment of this classification method. It could be argued, for instance, that plotting the number of times a solution is selected over all the others as a function of sucrose concentration shares similar subjectivity issues with the visual interpretation of the hedonic curves. Moreover, if the majority of participants prefer the very high or very low sucrose concentrations tested, a subsequent grouping that depends on a median-driven dichotomization could be also problematic.

2.4.2 Future directions

Overall, none of the four classification methods reviewed here is clearly superior to the others. Considering the well-established nature of research into impaired reward system in addicted, depressed, and other psychiatric patients (Zald & Treadway, 2017), continued use of Kampov-Polevoy's original (Kampov-Polevoy et al., 1997) or adjusted (Kampov-Polevoy et al., 2001) sweet taste test protocols (Method 2) for discriminating SL/SD might ensure continuity within this specific research field. However, to overcome the issues we identified with Method 2, a decrease in number of sweet taste test replicates and a liking threshold score to classify SLs are recommended. Regarding Method 4, some would suggest that it could serve as a 'gold standard' approach for the identification of the distinct sweet-liking phenotypes in pediatric populations (Mennella & Bobowski, 2016; Mennella et al., 2011). Nonetheless, more cognitive demanding sweet taste protocols have been successfully used in both children (Enns et al., 1979; Garneau et al., 2018) and adolescents (Coldwell et al., 2009; Scinska et al., 2001) implying that when the language, attentional, or memory barriers are raised, both

underage and adult populations can conceptually collapse to a common classification method.

Those special cases aside, insights gained from this comprehensive methodological review highlight the need for a universally accepted and statistically-founded approach that amalgamates the best aspects of existing approaches into a single reliable method for use in future work. Whether the same approach can be translated to multi-ethnic populations or participants from different countries remains elusive (Coldwell et al., 2009; Holt et al., 2000; Thai et al., 2011; Tuorila et al., 2017; Turner-McGrievy et al., 2013, 2016), and therefore further exploratory work in this area is necessary. The well-established effect of age on sweet-liking (Bobowski & Mennella, 2017; De Graaf & Zandstra, 1999; Mennella & Bobowski, 2015) along with compelling evidence from the few studies directly contrasting the distribution of sweet-liking phenotypes in children and adults (Enns et al., 1979; Garneau et al., 2018; Grinker, 1977), frame a clear call for a common but age-specific classification method.

Taking the strengths and weaknesses of the reviewed methods together, we see a strong need for a single large scale study involving multiple sweet stimuli analyzed via HCA to identify the true number of sweet-liking phenotypes (i.e., binary SL and SD classification, versus 3 or more groupings as seen in recent large studies). Subsequent sensitivity and specificity analysis of such data could facilitate the identification of a single sucrose concentration and associated cut-off values that most reliably allow classification into the appropriate number of phenotypes under a less time-consuming scheme that the use of multiple taste stimuli and/or of sophisticated analysis by most prior methods dictates. Encouragingly, one relatively recent study piloted that (Asao, et al., 2015).

As for the baseline cohort size per se, it is advised to opt for a figure that allows for, at the minimum, the three primary sweet-liking patterns to be identified; that is increasing liking as concentration increases, an initial rise in liking ratings followed by a decline, and descending liking with concentration. The two studies from Korea using HCA (Kim, Prescott, & Kim, 2014, 2017) highlight that more participants do not necessarily reveal the expected sweet-liking patterns if testing conditions lean towards extreme motivational states. Taking collectively the findings from studies using Method

1b into account (Table 2.2), the robustness of HCA as a grouping method that assists identification of distinct sweet-liking patterns even when subtle differences in liking ratings are observed (Garneau, et al., 2018), a minimum cohort of at least 100 participants is recommended.

With regard to the range of taste stimuli required for the initial analysis, a low concentration at the age-specific sucrose recognition threshold (e.g. in Easterby-Smith et al., 2018; Kennedy et al., 2010; Wiriyawattana et al., 2018) or at a concentration just below that level could provide a reasonable lower extreme. We then recommend a sample set of not less than five to six but no more than nine to ten stimuli (control stimulus, i.e., water, included), with an upper concentration level close to the most broadly used strongest sucrose solutions in the relevant literature (1.0-1.1 M). This would be conducted by incorporating serial dilution principles with a log scale equal spacing approach. Including a stimulus within the most commonly reported sucrose concentration breakpoint range which is associated with the intermediate phenotype (0.2-0.3 M: Tables 2.1 & 2.2) would also be recommended. Nonetheless, limiting the use of moderate concentrations that may impede reproducibility of the liking responses (Asao et al., 2015) should be considered. Is then the notion 'less is more' true? The answer depends on counterbalancing the need for adequate individual ratings in order to generate meaningful liking patterns and to enhance reliability of the subsequent sensitivity and specificity checks with the need to minimize fatigue, adaptation (Lawless & Heymann, 2010) and contrast effects (Lim, 2011) multiple-stimuli sweet taste test protocols suffer from.

2.5 Conclusions

There remains no consensus on the best method to identify the different sweet-liking phenotypes: subjective approaches, arbitrary definitions and differences in protocols undermine consistency across prior studies. Considering that sweetness is not uniformly experienced as pleasurable, especially at high concentrations, a better understanding of the individual variations in affective responses to sweetness might shed some light on the complex aspects of human eating behavior and consequently, it may support strategies promoting health and well-being. The development of a

statistically robust and less time-consuming and resource-intensive sweet-liking phenotype discrimination method that enables both the adoption by future studies of some common classification criteria and its application in large epidemiological studies is needed.

Authors' contribution

VI conducted the literature search and drafted the manuscript. JEH and MRY commented on the manuscript.

Conflict of Interests

The funding sources had no involvement in the literature search, in the interpretation of findings, in writing the report, or the decision to submit the article for publication. JEH has received speaker fees, travel reimbursements, and/or consulting fees from federal agencies, nonprofit organizations, trade/commodity groups, and corporate clients in the food industry. MRY has received direct research funding from numerous sources including national and international companies, as well as speaker fees, travel reimbursements and consultancy fees from various companies, none of which impact on the work reported here. VI does not have any potential conflicts to disclose.

Chapter 3 (Paper 2)

Quantifying Sweet-liking phenotypes: Time for Some Consistency in the Classification Criteria

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Abstract

Taste hedonics is a well-documented driver of food consumption. The role of sweetness in directing ingestive behavior is largely rooted in biology. One can then intuit that individual differences in sweet-liking may constitute an indicator of variations in the susceptibility to diet-related health outcomes. Despite half a century of research on sweet-liking, the best method to identify the distinct responses to sweet taste is still debated. To help resolve this issue, liking and intensity ratings for eight sucrose solutions ranging from 0 to 1 M were collected from 148 young adults (29% men). Hierarchical cluster analysis (HCA) revealed three response patterns: a sweet-liker (SL) phenotype characterized by a rise in liking as concentration increased, an inverted U-shaped phenotype with maximum liking at 0.25 M, and a sweet-disliker (SD) phenotype characterized by a decline in liking as a function of concentration. Based on sensitivity and specificity analyses, present data suggest the clearest discrimination between phenotypes is seen with 1.0 M sucrose, where a liking rating between -15 and $+15$ on a $-50/+50$ scale reliably distinguished individuals with an inverted U-shaped response from the SLs and the SDs. If the efficacy of this approach is confirmed in other populations, the discrimination criteria identified here can serve as the basis for a standard method for classifying sweet-liking phenotypes in adults.

3.1 Introduction

Hedonic responses to taste stimuli are dissociable constructs from motivation or a desire to eat (i.e., "liking" vs. "wanting") as proposed by Berridge (1996), and these responses influence dietary intake (de Graaf & Boesveldt, 2017; Duffy, 2007; Finlayson & Dalton, 2012). Elsewhere, a conceptual model linking sensation to intake via affective/hedonic responses has also been proposed (Hayes, 2015). Under these models, it is highly plausible that interpersonal variations in hedonic responses to sweet taste—in conjunction with genetic and epigenetic inputs, environmental forces, and other acquired individual characteristic—may contribute to variations in the susceptibility for obesity and obesity-related diseases. For almost half a century, observations of distinct individual liking patterns to sweet taste stimuli have repeatedly been made, thereby challenging the widespread belief that sweetness is universally highly liked. Witherly and colleagues, for example, speculated that humans exhibit up to four distinguishable responses to various sweetened beverages (Witherly et al., 1980), which, as was also illustrated later by Drewnowski (Drewnowski, 1987), could be described as a rise in liking with increasing sweetener concentration followed by a decline (Type I), a rise and then a plateau (Type II), a monotonic decline (Type III), and a non-systematic change in liking (Type IV).

Since the pioneering work of Pangborn (1970), sensory scientists using simple sucrose solutions and multiple different scaling methods in laboratory settings have similarly identified at least four different sweet-liking phenotypes. As summarized in Figure 3.1, the associated response patterns are characterized by either a positive slope, a horizontal ("flat") slope, an inverted U-shape, or a negative slope. Simpler schemes also exist, where participants are dichotomized into sweet likers (SLs) and sweet dislikers (SDs). The SL phenotype (sometimes reported as the Type II phenotype) generally refers to liking for ever-higher sweetness (e.g. in Kim et al., 2017; Looy & Weingarten, 1991) and accounts for 48.5% of the published literature (Iatridi et al., 2019). In contrast, the SD phenotype, which shares a very similar distribution (48.2%) with the SL phenotype

(Iatridi et al., 2019), has been defined differently across various studies: it can describe either as a monotonically decreasing liking as sucrose concentration increases (e.g. in Drewnowski, Henderson, & Shore, 1997; Garneau et al., 2018), or a liking for moderate levels of sweetness, which is graphically presented as an inverted U (e.g. in Methven et al., 2016) and sometimes also called Type I phenotype (e.g. in Drewnowski & Schwartz, 1990; Thompson et al., 1976). To note, a few studies identifying both subtypes of the SD response pattern classified them into a single group reported as SD phenotype, as well (e.g. in Holt et al., 2000; Yeomans et al., 2007).
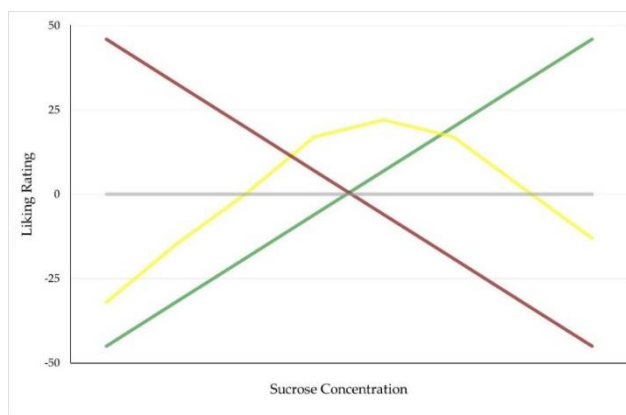
Fig. 3.1 Graphical representation of the most commonly reported sweet-liking phenotypes. The green line corresponds to a phenotype characterized by a rise in liking with increasing sucrose concentration (e.g., sweet liker phenotype), yellow line illustrates an inverted U-shaped hedonic response as a function of sucrose concentration (e.g., inverted-U phenotype), grey line represents an insensitive response to changes in sucrose concentration, and red line corresponds to a phenotype characterized by a decline in liking as sucrose concentration increases (e.g., sweet disliker phenotype). Adapted with permission from Reference (Iatridi et al., 2019).

Accordingly, an important question to be addressed is how these distinct hedonic responses to sweet taste can be defined and identified. Among 71 studies we recently reviewed (Iatridi et al., 2019), four main phenotyping methods (each relying on different classification criteria) were identified: the visual or algorithmic interpretation of hedonic responses from multiple sucrose concentrations (Method 1a and Method 1b, respectively), the "highest preference using ratings" method that dichotomizes

participants based on whether they like the highest sucrose concentration tested the most (Method 2), the "average liking above mid-point" or "positive/negative liking" method where liking ratings are compared to one or two predefined cut-off scores (Method 3), and the "highest preference via paired comparisons" method that categorizes participants based on which sucrose concentration they prefer the most (Method 4). As detailed in our recent review (Iatridi et al., 2019), Method 2 and Method 3 suffer from arbitrariness associated with the strength of the taste stimuli and/or the classification rating thresholds, and both methods are prone to misclassification. The dependence on visual inspection in Method 1a raises the potential for subjective interpretation, and Method 4 involves a choice paradigm based on preference rather than liking per se.

Considering these methodological challenges, along with the ongoing debate over the role of sugar intake as a factor in obesity (Hu, 2013; Khan & Sievenpiper, 2016; Stanhope, 2016; Te Morenga et al., 2013), there is strong need for a more precise and consistent method to identify sweet taste phenotypes. The numerous prior studies that have investigated the presence of different sweet-liking phenotypes and their potential relationship to dietary intake (e.g. in Holt et al., 2000; Methven et al., 2016; Tuorila et al., 2017) or to body mass index (BMI) (e.g. in Garneau et al., 2018; Grinker, 1977; Mennella et al., 2014; Sartor et al., 2011; Thompson et al., 1976) have used widely different methods to define phenotypes; presumably, this has contributed to the inconsistencies reported across studies. Accordingly, in our recent review (Iatridi et al., 2019), we suggested that a rapid and reliable phenotyping method is needed to facilitate comparisons across future studies. In our review, we proposed that an optimal sucrose concentration be identified that best separates distinct sweet-liking phenotypes, in terms of sensitivity and specificity. In 2015, Asao et al. (2015) piloted this idea in order to discriminate SLs from SDs. However, as commonly happens with small pilot studies, their sample size likely affected the phenotyping process, potentially leading to an

underestimation of the true number of distinct response patterns, a limitation the authors noted in their report. Further, the total number of stimuli they used was rather large (Keiko Asao et al., 2015), raising additional issues of fatigue, adaptation, and inattentiveness. Finally, their participants were tested after they had fasted for an average of 12.1 hours (Keiko Asao et al., 2015), which may influence the appetitiveness of the stimuli.

The present study aimed to extend the approach used by Asao et al. (2015) while also eliminating some of the methodological issues mentioned above toward a goal of defining a new standardized phenotyping method. We had three aims. First, we identified different sweet-liking phenotypes statistically. Second, we analyzed these phenotyping data to identify a single sucrose concentration where an application of one or two specific cut-off liking scores ensures the most reliable and replicable definition of each of the identified phenotypes. Last, potential relationships between the motivational state and baseline characteristics of our participants with these sweet-liking phenotypes were explored.

3.2 Materials and Methods

3.2.1. Participants

A total of 148 non-diabetic participants aged 18–34 were recruited from students and staff at the University of Sussex between September and December 2017 (Table 3.1). Cohort size was determined by the suggested minimum of 100 participants in our recent methodological review for the successful identification of the main sweet-liking phenotypes (Iatridi et al., 2019), which was further increased to adjust for the expected underrepresentation of the SD phenotype in our young adult population. Inclusion criteria comprised being medication free (other than oral contraception), smoking less than five cigarettes a week, and having no history of diagnosed eating disorders. Individuals with a current respiratory illness or having recently (less than two weeks) undergone a dental procedure, those being on a weight loss or a medically induced special diet, and women with an irregular menstrual cycle were also excluded. At

enrollment, participants gave their written informed consent for inclusion in the study, but they were naive to the study's hypothesis until they had completed all tasks (debriefing provided). The University of Sussex Science and Technology Cross-Schools Research Ethics Committee approved the protocol on the September 22, 2017 (ER/VI40/1), and the study was conducted in accordance with the 1964 Declaration of Helsinki.

Table 3.1 Participant characteristics.

	Total	Sweet Taste Like Phenotype [1,2]		
		Sweet Liker	Inverted U-Shaped	Sweet Disliker
	n = 148	*n* = 46	*n* = 73	*n* = 27
Gender, N (%)				
Woman	105 (70.9)	33 (71.7)	48 (65.8)	22 (81.5)
Man	43 (29.1)	13 (28.3)	25 (34.2)	5 (18.5)
Ethnicity, N (%)				
Caucasian	112 (75.7)	39 (84.8)	53 (72.6)	19 (70.4)
Asian	14 (9.4)	2 (4.3)	9 (12.3)	3 (11.1)
Other	22 (14.9)	5 (10.9)	11 (15.1)	5 (18.5)
Dieting, N (%)				
Once or more times in the past	52 (35.6)	15 (32.6)	23 (31.9)	12 (46.2)
Never	94 (64.4)	31 (67.4)	49 (68.1)	14 (53.8)
Added sugar in drinks/cereals, N (%)				
More when being younger	72 (48.6)	18 (39.1)	39 (53.4)	14 (51.9)
Same as when being younger	27 (18.2)	11 (23.9)	9 (12.3)	7 (25.9)
Never	49 (33.1)	17 (37.0)	25 (34.3)	6 (22.2)
Age range (median) in years	18.2–34.0 (20.2)	18.3–32.8 (19.8)	18.2–34.0 (20.2)	18.2–34.0 (20.9)
BMI range (median) in kg/m^2	17.8–32.4 (22.1)	17.9–29.1 (23.0)	17.8–32.4 (21.6)	18.2–30.3 (22.7)

BMI, body mass index; Q1, 25th percentile; Q3, 75th percentile. All frequencies reported refer to valid percentages. [1] Participants demonstrating erratic responses to sweet stimuli (*n* = 2) were excluded from this analysis. [2] $p > 0.05$ for all between group comparisons performed with chi-square or Kruskal Wallis tests.

3.2.2. Taste Test

3.2.2.1. Taste Stimuli

To ensure sufficient individual ratings for the development of hedonic curves while trying to minimize confounding effects of adaptation (Lawless & Heymann, 2010) and sensory specific satiety (Rolls et al., 1981), the taste test consisted of seven different aqueous sucrose solutions (0.03125, 0.0625, 0.125, 0.25, 0.5, 0.67, and 1 M) and one water blank, replicated in two separate blocks, for a total of 16 tastings.

The particular concentration range tested was equivalent to sucrose solutions between 1.07% and 34.23% (*w/v*) based on density at 20 °C (Haynes, 2013), and were chosen to reflect four different considerations: (1) previously reported effects of age on sucrose recognition thresholds (Easterby-Smith et al., 2018; Kennedy et al., 2010; Wiriyawattana et al., 2018); (2) the most commonly used sucrose concentrations in prior relevant studies (reviewed in Iatridi et al., 2019); (3) the sweetness typically encountered in sugar-sweetened beverages (Ventura et al., 2011); and (4) a compromise between equal log spacing and serial dilution for sample preparation.

All sweet stimuli were prepared at least 24 hours in advance by dissolving food-grade sucrose in mineral water at room temperature. Solutions were stored at 4 °C until used. On the experimental day, solutions were allowed to warm up to room temperature prior to presentation, and were presented as 10 mL samples in transparent 60 mL glass cups labelled with random three digit codes. For the solute and rinsing, we used a commercial mineral water with the lowest dry residue concentration available at the time (Volvic, Danone Waters London and Ireland Ltd., London, UK).

3.2.2.2. Rating Scales

Participants evaluated liking and intensity for each stimulus using a horizontal visual analogue scale (VAS) end-anchored with "dislike extremely" (scored −50) and "like extremely" (scored +50) and a vertical generalized labeled magnitude scale (gLMS) with properly positioned descriptors ranging from "no sensation" (scored 0) to "strongest

imaginable sensation of any kind" (scored +100), respectively. To ensure within and between-subjects compliance, training for both scales was provided. The practice session for VAS involved rating liking for a series of non-food items, while training in the use of gLMS was applied by evaluating responses to noise and light (Green et al., 1996).

On the basis of Cabanac's theory regarding possible enhancement of stimulus value by internal state ("alliesthesia": Cabanac, 1971), two series of VAS appetite ratings (Stubbs et al., 2000) were completed before the first and after the second taste test block. All ratings were collected using the Sussex Ingestion Pattern Monitor (SIPM version 2.0.13, University of Sussex, Falmer, UK), a computer-based system developed to record and score rating data.

3.2.2.3. Procedure

The taste test was conducted approximately 2 h after breakfast (between 09.30 am and 12.30 pm depending on each participant's personal routine). Participants were also asked to abstain from smoking, chewing gum, and tooth brushing for the 2 h prior to testing; no restrictions applied to water consumption. During both taste test blocks, a "sip and spit" protocol was followed: participants were instructed to place the entire 10-mL solution in their mouth, swirl it around for 10 seconds, and expectorate it. They then rated their liking and sweetness intensity before rinsing their mouth with water and proceeding to the next sample. Stimuli were presented in randomized order with participants blinded to the concentration of sucrose tasted each time. After the taste test was complete, demographic (date of birth, sex, and ethnicity) and lifestyle characteristics ("Have you ever been on a diet in order to lose weight?" with possible answers "Yes, one or more times in the past" or "Never," and "Did you usually add more sugar in your coffee, tea or cereals when you were younger?" with possible answers "Yes, I used to add more sugar in my coffee, tea or cereals when I was younger," or "No, I add the same sugar as I did in the past," or "Never added sugar in my coffee, tea or cereals") were collected.

3.2.3. Anthropometry

To minimize any possible interactions between the sensory ratings and anthropometric measures, participants revisited the laboratory for a separate early morning session (08:30–10:30) for anthropometry; this visit was scheduled between two days and two weeks after the taste test. Height was measured to the nearest 0.1 cm using a stadiometer and weight to the nearest 0.1 kg using a calibrated body composition analyzer (MC-780MA P, TANITA, Tokyo, Japan). Standardized procedures were followed, including wearing light clothing and no shoes (WHO, 1995).

3.2.4. Statistical Analysis

Our primary goals were to (a) algorithmically identify the different sweet-liking phenotypes in our study cohort and (b) to determine the specific sucrose concentration and associated cut-off score(s) for liking ratings that most reliably allowed for the identification of those distinct phenotypes. Assumptions of normality were tested prior to the main statistical analyses using visual inspection (histograms, Q-Q plots, and bloxplots), and summary statistics (skewness and kurtosis z-scores computed by dividing skewness or kurtosis values with the associated standard errors). Z-scores (absolute values) larger than 1.96 were indicative of a normal distribution. All ratings are reported as means and standard errors (normally distributed), while medians and ranges are used for age and BMI (not normally distributed); categorical characteristics are expressed as percentages.

Interclass correlation coefficients (ICCs) were calculated to assess test–retest reliability of liking ratings over the two taste test blocks. Given our experimental design, an average measures absolute agreement two-way mixed-effects model was selected (Trevethan, 2016). Per the guidelines, an ICC value less than 0.5 indicates poor reliability, values between 0.5 and 0.75 reflect moderate reliability, and values between 0.75 and 0.9 indicate good reliability (Portney & Watkins, 2009).

As the first step to achieve the principle aim of the current study, an agglomerative hierarchical cluster analysis (HCA) was performed and meaningful groups (clusters) of participants who shared similar liking patterns within each group but were heterogeneous in the between-group contrasts were identified. The mean liking ratings from the eight replicated concentrations in the two taste test blocks were treated as the dimensions for the HCA. The squared Euclidean distance between pairs of cases or clusters and the between-groups (average) linkage method were selected to assist with the merging process (Yim & Ramdeen, 2015). The final decision on the true number of clusters in our dataset was dictated graphically by interpreting the scree plot of coefficients of the agglomeration schedule we designed (Office Excel 2013 for Windows, Microsoft, Washington, DC, USA) and then applying this information ("stopping rule") to the dendrogram provided by the statistical software on the HCA output (Yim & Ramdeen, 2015).

We then implemented a two-by-two cross tabulation function to estimate the dyads of sucrose concentration and liking score with the highest sensitivity and specificity in predicting the three distinct sweet-liking phenotypes. In each two-by-two cross tabulation table, the phenotyping results emerged when a specific dyad of sucrose concentration and liking score was used as the classification criteria for the identification of the sweet-liking phenotype under investigation were contrasted with the associated phenotyping results suggested by the HCA. The number of true positives (e.g., classified as SL by both the dyad tested and the HCA) and the number of true negatives (e.g., not classified as SL by both the dyad tested and the HCA) indicated the sensitivity and specificity attached to that particular dyad of sucrose concentration and liking score, respectively. Reported liking ratings for stimuli from 0.03125 M to 1.0 M sucrose and potential cut-off values ranging between −20 and +20 in 5-point increments were tested for their prediction value. A K-1 series of sensitivity-specificity tests were conducted, where k represents the number of main clusters previously identified in the HCA.

To test the hypothesis that the sucrose concentration (within subject factor) and the initial clusters or subsequent sweet-liking phenotypes (between subject factor), as well as their interaction, affect liking and intensity ratings of the presented sweet taste

stimuli, repeated measures ANOVAs with Greenhouse-Geisser correction were carried out. We also employed separate one-way ANOVAs to contrast liking and intensity (both mean ratings and ratings across each of the eight concentrations) by sweet-liking phenotype. In cases of violation of the equal variances assumption, Brown–Forsythe tests were applied, instead (Tomarken & Serlin, 1986). Post hoc Fisher's least significant difference (LSD) and Games-Howell tests were used as appropriate to further understand the nature of specific paired comparisons.

Nonparametric (Mann–Whitney) tests for the previously reported not normally distributed continues variables (age and BMI) and Pearson's chi-square tests for the categorical variables (gender, ethnicity, dieting history, and habitual use of table sugar) were used to investigate for differences in participant characteristics across the distinct sweet-liking phenotypes. To explore whether there were also gender differences in measures of interest, additional chi-square tests were performed. Phi symmetric measures instead of Pearson's results are reported in cases of cells with an expected count less than 5.

To ensure participants' compliance with the taste test protocol, changes in hunger and thirst before and after delivering the taste test were explored using paired t-tests. We also calculated multiple linear regressions to investigate the degree to which pre- and post-test hunger and thirst predicted liking and intensity ratings across the study sample. The influence of pre- and post-test levels of hunger and thirst was further explored using either one-way ANOVAs or Brown–Forsythe tests (Tomarken & Serlin, 1986) to detect differences across the distinct sweet-liking phenotypes.

The extent to which our method for the identification of the distinct sweet-liking phenotypes agrees with those in previous literature (see Introduction for details) was assessed by Cohen's Kappas and 95% confidence intervals (CIs) based on the "Estimate ± 1.96 × Standard Error" formula (Landis & Koch, 1977); participants exhibiting an inverted U-shaped response were excluded from this analysis due to the bimodal nature of the phenotyping results elicited by Method 2 and 3. The relevant frequency distributions were also estimated. For the comparison with Method 2 participants who rated the highest sucrose concentration, namely the 1 M solution, as the most pleasant

were considered as SLs, whilst all remainder liking patterns were classified into the SD phenotype (Kampov-Polevoy et al., 2003, 2004). The agreement with Method 3 was tested using the 0.5 M sucrose solution and the corresponding neutral cut-off hedonic score of 0 (zero) as the classification criteria to discriminate SLs from SDs (Tuorila et al., 2017).

Unless otherwise stated, data were analyzed using SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk, NY, USA). An alpha level of 0.05 was set as the threshold for statistical significance and all performed statistical tests were two-tailed.

3.3 Results

3.3.1. Participant Characteristics

Participant characteristics are summarized in Table 3.1; three (two women and one man) failed to report to the laboratory for both sessions. As a whole the cohort tested here was relatively young and lean (Mdn = 20.2 years and Mdn = 22.1 kg/m^2, respectively) and was mainly comprised of women (70.9%); most self-identified as Caucasian (75.7%). Nearly half of the participants reported that they currently add less sugar in their drinks and cereals than when they were younger, and one in three had been on a diet for weight loss at least once in the past. Overall, the women were slightly younger than the men (Mdn = 21.1 years for men and Mdn = 20.1 years for women; U = 1454.5, Z = −3.263, p = 0.001), and had a lower average BMI (Mdn = 23.4 kg/m^2 for men and Mdn = 21.6 kg/m^2 for women; U = 1475.5, Z = −2.861, p = 0.004). This was expected, as it reflects the typical differences in BMI between men and women and the differences in BMI across different age groups in the U.K. (Conolly & Davies, 2018).

3.3.2. Taste Test

Test-retest reliability analysis comparing liking ratings across the two taste test blocks indicated moderate to good reproducibility based on the ICC cut-offs suggested by Portney and Watkins (2009) for all but the 0.125 M solution (Figure 3.2). The two highest sucrose concentrations (0.67 and 1.0 M), and water were associated with the

strongest agreement between the two repetitions. As expected, there was a main effect of concentration on liking across all participants with significantly different mean hedonic scores reported for different solutions ($F(2.12, 312.15] = 10.65$, $p < 0.001$, $\eta p^2 = 0.068$).
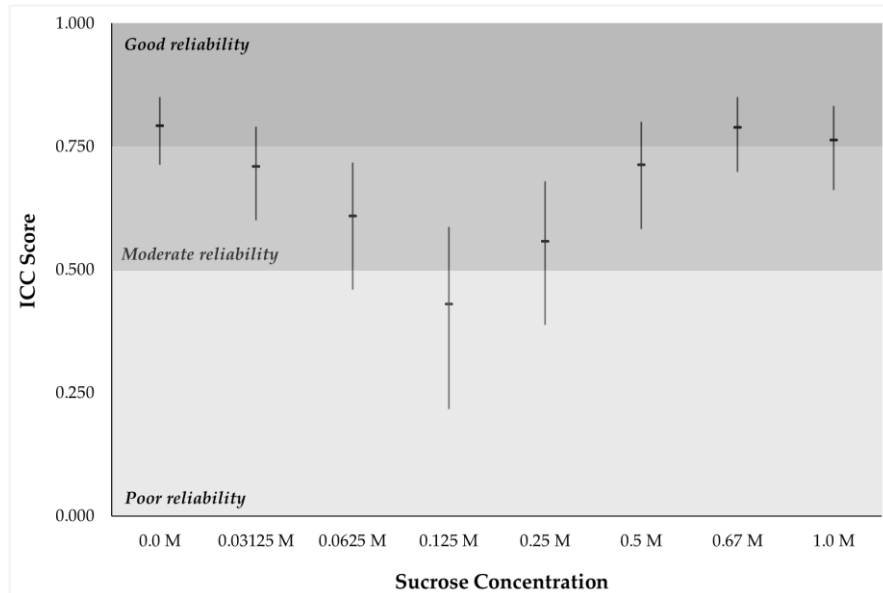
Fig. 3.2 Interclass correlation coefficient (ICC) scores (95% confidence interval) for liking ratings from the two taste test blocks across the different taste stimuli.

3.3.2.1. Identifying Distinct Responses to Sweet Taste: HCA

HCA resulted in ten subgroups of distinct responses to sweet taste with a significant effect of cluster on liking ($p < 0.001$ for all eight sucrose concentrations and effect sizes ranged from 0.22 for the 0.125 M solution to 0.80 for the 1.0 M solution). Three main clusters that accounted for 92% of the study sample were observed. Cluster 1 ($n = 44$) and cluster 3 ($n = 22$) described hedonic response patterns consistent with the sweet liker (SL) and sweet disliker (SD) phenotypes. Both trends were particularly evident for solutions with added sucrose above 0.125 M. Notably however, almost half of the study sample fell into cluster 2 ($n = 70$), where liking increased modestly with concentration up to an intermediate level of sucrose (0.25 M) and then decreased as the concentration continued to increase. Remarkably, participants who were classified into cluster 2 rated both the lowest ($M = 1.0$, $SEM = 0.76$ for 0.03125 M) and the highest ($M = -1.5$, $SEM =$

1.44 for 1.0 M) sucrose concentration as neutral; that is, they neither liked them nor disliked them (t(69) = 1.46, p = 0.148 for the paired comparison between the lowest versus the highest concentration).

Regarding the 12 participants classified into one of the remaining clusters (clusters 4 to 10), plotting liking as a function of concentration revealed that participants in cluster 9 (n = 2) and those in cluster 10 (n = 3) followed a classical SL and a SD liking pattern, respectively. Their ratings from the eight different sucrose concentrations resulted, however, in steeper liking curves ("extreme" responses) than those in our main SL and SD clusters, which explains why they emerged as separate groups during the clustering procedure. Indeed, before we applied the "stopping rule" as appropriate (see 3.2.4 for details), participants grouped into clusters 9 and 10 and those grouped into clusters 1 and 3, respectively, had been considered as homogenous only subsequent to the inverted U-shaped phenotype merged with the SL phenotype. Likewise, an inverted U-shaped response corresponding to corresponding to that of cluster 2 was observed for participants classified into cluster 4 (n = 2), cluster 7 (n = 2), and cluster 8 (n = 1): among the heterogeneous mean liking ratings to those of cluster 2, a different optimal sweetness (0.5 M for cluster 4 and 0.67 M for cluster 8) and a higher rating for the breakpoint concentration of 0.25 M sucrose (M = 8.9, SEM = 1.15 for cluster 2 and M = 28.5, SEM = 4.50 for cluster 7, t(70) = −2.84, p = 0.006) stand out. Two single cases of erratic responses were also identified and eliminated from further analysis (cluster 5 and cluster 6).

3.3.2.2. Identifying Distinct Sweet Taste Like Phenotypes: New Classification Criteria

With regard to the specific sucrose concentration and liking thresholds that best discriminated between the three main clusters, the 1 M solution and liking scores of −15 or lower for the identification of SDs and +15 or higher for the identification of SLs were associated with the lowest number of false negative classifications (90.9 and 97.7 percentage sensitivity for SDs and SLs, respectively) and the lowest number of false positive classifications (93.9 and 93.5 percentage specificity for SDs and SLs, respectively). The results are shown in Table 3.2 and Table 3.3.

We then applied these classification criteria individually to participants who were assigned to the remaining clusters. The revised grouping (SL phenotype: $n = 46$; 31.5%, inverted U-shaped phenotype: $n = 73$; 50%, SD phenotype: $n = 27$; 18.5%) was in agreement with the classification suggested by the visual interpretation of the shape of the relevant liking curves in all participants except those initially classified into cluster 4. Those participants met the new SD phenotype criteria rather the criteria associated with the inverted U-shaped response pattern. A closer inspection of their hedonic responses revealed that they actually had rated all sucrose solutions as neutral or unpleasant. In addition, integrating the very small clusters into the main groups of responses reduced overfitting and allowed for the subsequent statistical analyses required.

Confirming the diverse nature of the sensory responses to sweet taste among participants classified into the three main sweet-liking phenotypes, overall liking and intensity significantly varied across these newly defined distinct groups, $F(2, 56.21) = 89.44$, $p < 0.001$ for liking and $F(2, 77.95) = 5.74$, $p = 0.005$ for intensity. A main effect of sucrose concentration ($F(4.44, 635.19) = 8.53$, $p < 0.001$, $\eta p^2 = 0.056$), as well as a strong interaction effect between sucrose concentration and phenotype ($F(8.88, 635.19) = 78.65$, $p < 0.001$, $\eta p^2 = 0.524$) on liking were also found. As shown in Figure 3.3, follow-up analysis indicated that participants with an inverted U-shaped response liked the three lower sucrose concentrations at a similar level when compared with both SLs and SDs. When liking ratings of those stimuli were separately contrasted between the two extreme phenotypes, we found that SLs rated them as less pleasant than SDs did. Liking for the 0.125 M sucrose solution did not differ between groups, whereas liking ratings for the rest of the sweet taste stimuli significantly differed by cluster ($p < 0.001$ for most paired comparisons).

We next sought to examine the perceived variations in sweetness for the different stimuli between the three sweet liker phenotypes. Paired comparisons between the intensity ratings for each successive concentration and the intensity ratings for the previous indicated that participants were clearly able to distinguish between the different sucrose concentrations ($p = 0.002$ for water and 0.03125 M, and $p's < 0.001$ for all remainder pairs). Rated intensity also increased as sucrose concentration increased

across all three sweet taste like phenotypes, $F(2.32, 336.30) = 535.25$, $p < 0.001$, $\eta p^2 = 0.787$ (Figure 3.4). SDs overall perceived the taste stimuli as sweeter ($M = 23.3$, $SEM = 1.62$) than both SLs ($M = 17.2$, $SEM = 0.73$; $p = 0.001$) and participants classified in the inverted U-shaped phenotype ($M = 19.2$, $SEM = 0.96$; $p = 0.015$). No interaction effect between concentration and sweet taste like phenotype on intensity was, however, observed, $F(4.67, 333.68) = 521.10$, $p = 0.082$, $\eta p^2 = 0.027$.

Table 3.2. Sensitivity and specificity checks to discriminate sweet dislikers (cluster 3) from the rest of sweet-liking phenotypes.

Liking Cut-off Scores	Sucrose Concentration (M)							
	0.25		0.5		0.67		1.0	
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
−20	13.6	100.0	36.4	100.0	45.5	99.1	81.8	96.5
−15	13.6	100.0	54.5	97.4	68.2	95.6	90.9*	93.9*
−10	27.3	99.1	63.6	94.7	77.3	92.1	95.5	87.7
−5	50.0	94.7	77.3	93.0	95.5	86.0	100.0	77.2
0	59.1	89.5	90.9	86.8	100.0	76.3	100.0	68.4

Percentages (%) with an asterisk (*) indicate the dyad of sucrose concentration and liking cut-off score with the highest combined sensitivity and specificity for the prediction of the sweet disliker phenotype across all dyads tested.

Table 3.3 Sensitivity and specificity checks to discriminate sweet likers (cluster 1) from the rest of sweet-liking phenotypes.

Liking Cut-off Scores	Sucrose Concentration (M)							
	0.25		0.5		0.67		1.0	
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
0	95.5	26.1	100.0	40.2	100.0	55.4	100.0	64.1
5	79.5	43.5	100.0	54.3	97.7	63.0	100.0	77.2
10	56.8	67.4	100.0	67.4	97.7	76.1	97.7	89.1
15	38.6	84.8	88.6	79.3	88.6	87.0	97.7*	93.5*
20	20.5	88.0	63.6	87.0	79.5	96.7	84.1	97.8

Percentages (%) with an asterisk (*) indicate the dyad of sucrose concentration and liking cut-off score with the highest combined sensitivity and specificity for the prediction of the sweet liker phenotype across all dyads tested.
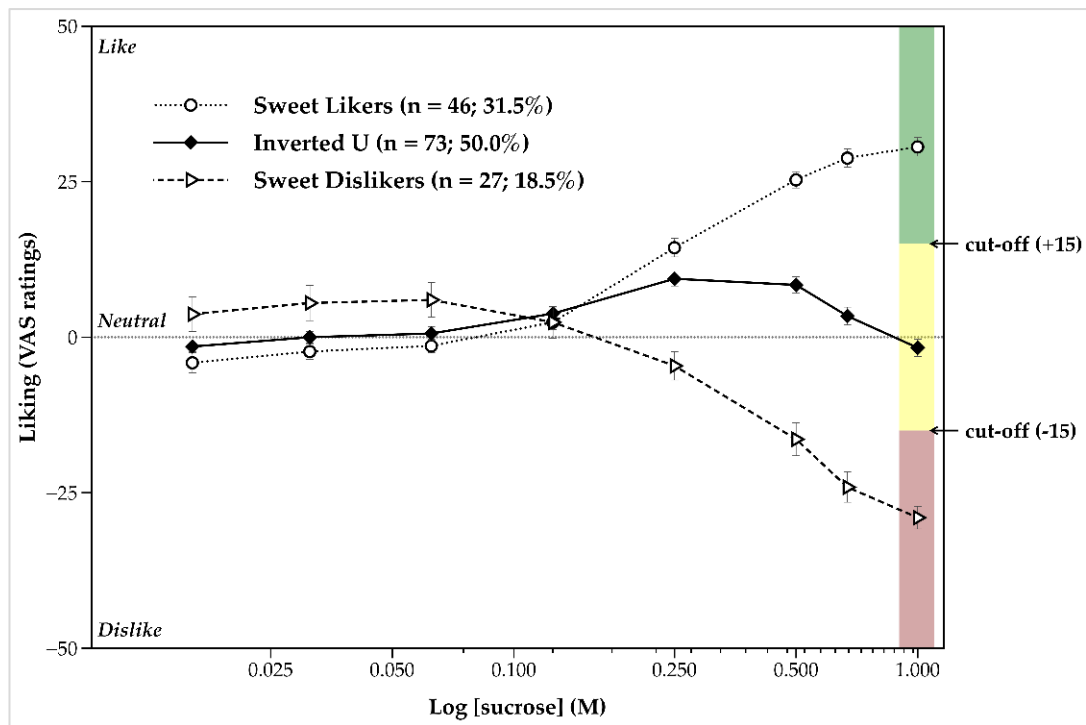
Fig. 3.3 Liking ratings (mean ± standard error of the mean) as a function of sucrose solutions by the three sweet-liking phenotypes. Ratings were averaged across the two taste test blocks. The response pattern for the sweet liker phenotype is displayed with a dotted line, the response pattern of inverted U-shaped phenotype with a solid line, and the response pattern of sweet disliker phenotype with a dashed line. Different colors denote the different ranges of liking ratings for 1 M sucrose which, according to the relevant sensitivity and specificity checks (see Tables 3.2 and 3.3 for details), could be used for the reliable discrimination between the three distinct sweet-liking phenotypes: green color corresponds to the range of liking ratings for 1 M sucrose representing sweet likers, yellow color indicates the hedonic response spectrum to 1 M sucrose characteristic of the inverted U-shaped phenotype, and red color corresponds to the range of liking ratings for 1 M sucrose for sweet dislikers.
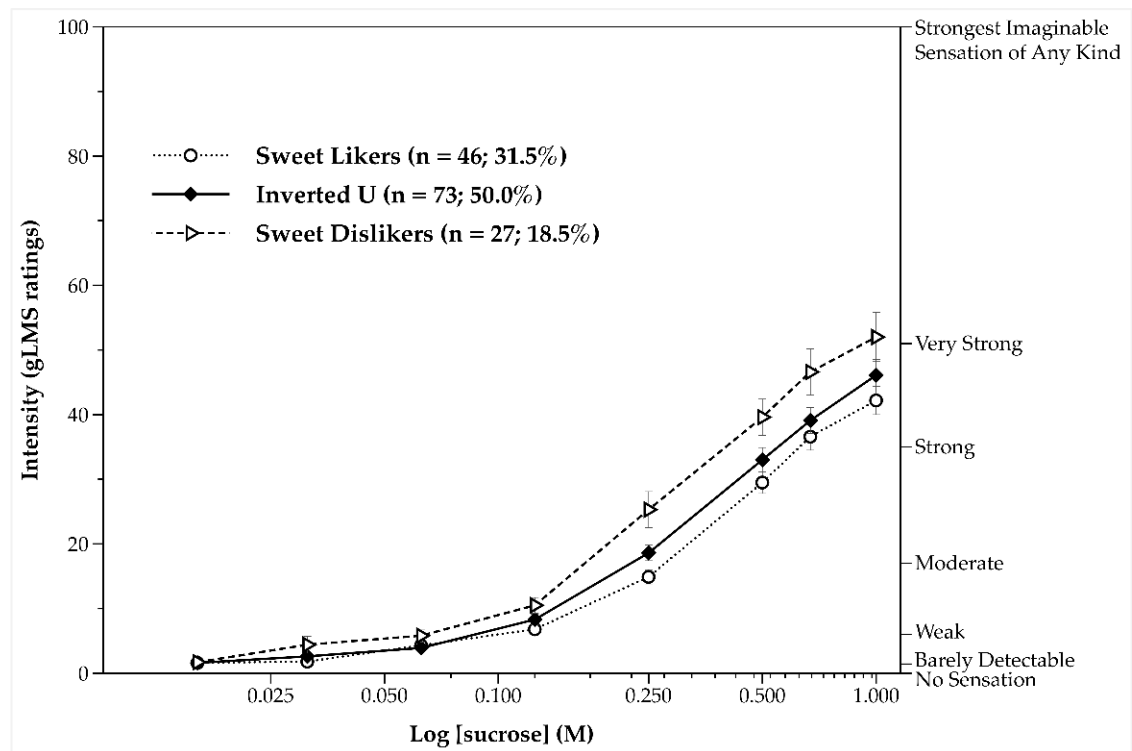
Fig. 3.4 Intensity ratings (mean ± standard error of the mean) as a function of sucrose solutions by the three sweet-liking phenotypes. Ratings are averaged across the two taste test blocks. The intensity curve of the sweet liker phenotype is displayed with a dotted line, the intensity curve of the inverted U-shaped phenotype with a solid line, and the intensity curve of the sweet disliker phenotype with a dashed line.

To explore whether the identified sweet-liking phenotypes were merely indirect consequences of differences in perceived intensity rather than true differences in hedonics per se, liking ratings were also plotted as a function of intensity separately for the three main clusters. As shown in Figure 3.5a–c, no such indication was found.
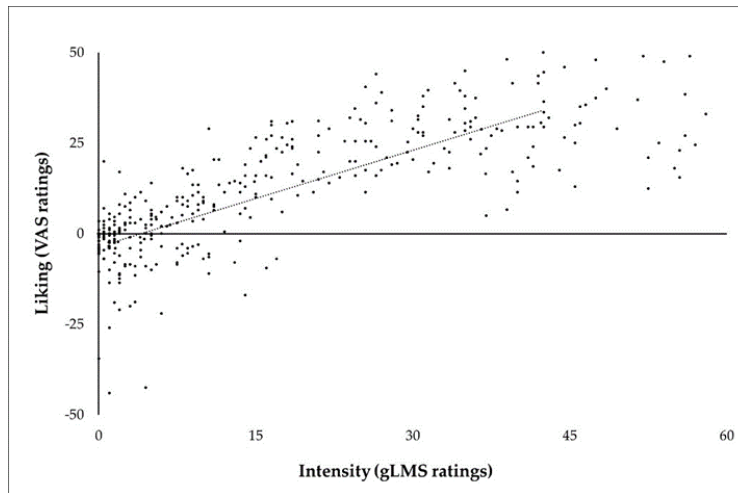
(a)
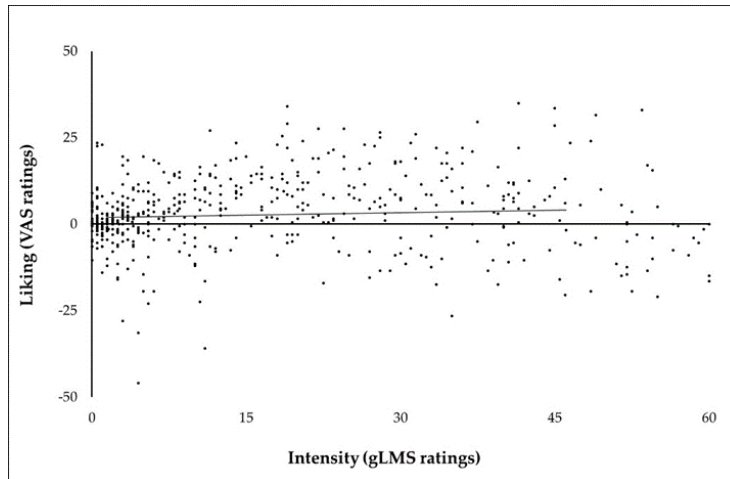
(b)
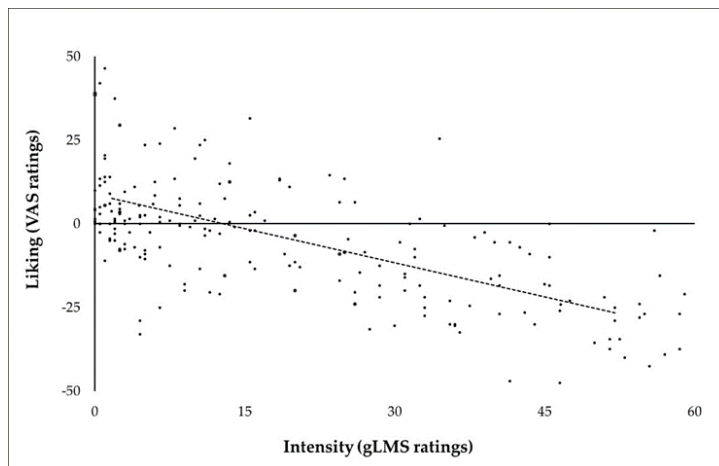
(c)

Fig. 3.5 Individual ratings of liking as a function of perceived intensity for the sweet taste stimuli in (**a**) sweet likers, (**b**) individuals exhibiting an inverted U-shaped hedonic response, and (**c**) sweet dislikers. Lines represent the average ratings across individuals classified within each phenotype.

3.3.2.3. Pre- and Post-Test Levels of Hunger and Thirst

Pre-test levels of hunger (*M* = −7.5, *SEM* = 2.11) and thirst (*M* = 0.3, *SEM* = 1.68) confirmed participants' compliance with the taste test preparation instructions, whereas the increase in hunger ($t(147)$ = −3.25, *p* = 0.001) and decrease in thirst ($t(147)$ = 2.32, *p* = 0.022) over time was also in line with the effects of the "sip and spit" and "mouth rinsing with water" parts of the taste protocol. Neither hunger nor thirst ratings before taste test block 1 or after taste test block 2 predicted liking ($F(2, 145)$ = 2.065, *p* = 0.130 for pre-test levels of hunger and thirst; $F(2, 145)$ = 0.607, *p* = 0.546 for post-test levels of hunger and thirst) or intensity ($F(2, 145)$ = 1.041, *p* = 0.356 for pre-test levels of hunger and thirst; $F(2, 145)$ = 0.403, *p* = 0.669 for post-test levels of hunger and thirst) across the study sample. When ratings of hunger and thirst were examined against the three distinct sweet-liking phenotypes, non-significant differences were found ($F(2, 143)$ = 2.410, *p* = 0.093, and $F(2, 143)$ = 0.094, *p* = 0.910 for pre-test levels of hunger and thirst, respectively; $F(2, 76.22)$ = 0.986, *p* = 0.378, and $F(2, 143)$ = 0.107, *p* = 0.899 for post-test levels of hunger and thirst, respectively). These data clearly show that the group differences in sweet-liking cannot be attributed to the observed changes in hunger or thirst.

3.3.3. Participant Characteristics by Sweet-liking phenotype

Possible variations in participant characteristics relative to sweet-liking phenotype were also examined. Gender ($\chi^2(2, N = 146)$ = 2.39, *p* = 0.302), ethnicity (φ = 0.152, *p* = 0.496), dieting history ($\chi^2(2, N = 144)$ = 1.84, *p* = 0.400), habitual use of table sugar (φ = 0.194, *p* = 0.240), age ($H(2)$ = 2.60, *p* = 0.273) and BMI ($H(2)$ = 0.67, *p* = 0.717) did not differ between groups. All associated values by phenotype are summarized in Table 3.1.

3.3.4. Comparison to Existing Classification Methods

When Method 2 (rating the 1 M sucrose solution or not as the most pleasant) and Method 3 (rating the 0.5 M sucrose solution higher than 0 or not) were used to distinguish the different sweet-liking phenotypes, the proportions of SD and the SL were

respectively overestimated: 113 participants were classified as SDs according to Method 2 and 108 as SLs according to Method 3. Compared with our phenotyping method, in both cases, the majority of those participants (56.6% of SDs in Method 2 and 53.7% of SLs in Method 3) exhibited an inverted U-shaped response. Focusing on Method's 2 phenotypic classification, all 27 participants classified as SDs using our method were also identified as SDs using Method 2. Regarding the SL phenotype, 22 out of 46 participants initially fell into the SL phenotype were classified as SDs using Method 2. Those 22 participants liked the 1 M sucrose solution significantly lower than the previous concentration (M = 25.3 for 1 M versus M = 30.6 for 0.67 M, p = 0.014), while no significant difference was observed when compared with the third higher sucrose concentration (M = 25.3 for 1 M versus M = 28.4 for 0.5 M, p = 0.222). The kappa coefficient was accordingly low at 0.447 (95% CI: 0.286 to 0.608). In contrast, the agreement with Method 3 was good with a Kappa coefficient at 0.879 (95% CI: 0.764 to 0.993). All SLs identified using our method were also classified as SLs by Method 3. The two phenotyping approaches were also in line regarding the SD phenotype: only four SDs using our method were discordantly classified as SLs using Method 3. Those participants had a mean liking for the 0.5 M barely over the neutral point (M = 1.1) and their liking rating for the 1 M, which was our concentration of choice for distinguishing sweet-liking phenotypes, was as low as −28.7. A graphical representation of the level of consistency/disagreement among the methods compared here is provided in Figure 3.6.
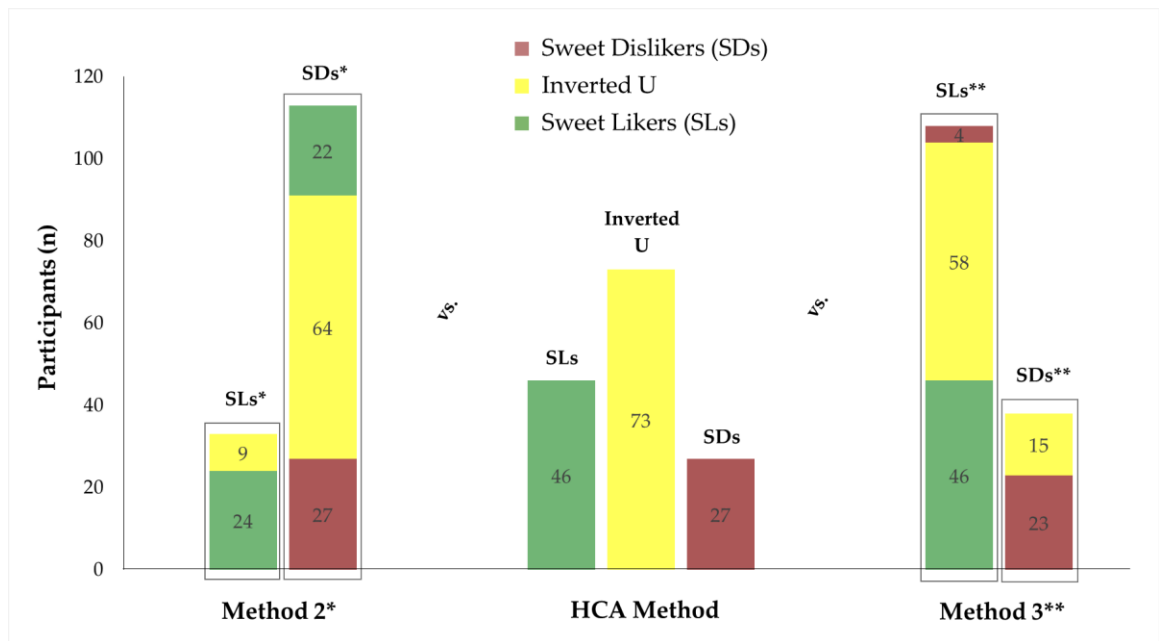
Fig. 3.6 Comparison of the distribution of sweet-liking phenotypes in our study sample when different classification methods were used. Method 2 (rating the 1 M sucrose solution or not as the most pleasant) and Method 3 (rating the 0.5 M sucrose solution higher than 0 or not) were, by definition, limited to a two-response group phenotyping outcome (binomial distribution), while HCA method (rating the 1 M sucrose solutions higher than +15, lower than −15, or between −15 and +15) allowed for the identification of three distinct sweet-liking phenotypes. 133 participants (77.4%) versus 27 (18.5%) were classified as SDs and 108 participants (74.0%) versus 46 (31.5%) were classified as SLs when Method 2 and Method 3 were contrasted with the method we proposed here (HCA method), respectively. Different colors of the stacked columns and the associated data labels (numbers) correspond to the number of participants classified into the phenotype of the same color when the HCA method was used. Data labels (numbers) within each column add up to the total number of participants classified into the phenotype illustrated at the upper end of the relevant column. Asterisks (*/**) denote alternatives to our definition for SLs and SDs. SDs, sweet dislikers; SLs, sweet likers.

3.4 Discussion

3.4.1. General Findings

The present report describes how hedonic responses to taste stimuli of varied sweetness can be algorithmically interpreted using HCA, and clustered into groups that represent similar sweet-liking patterns. For the current dataset, consistent differences in liking ratings across the eight sucrose solutions were found, which then allowed a clear characterization of participants as SLs, those with an inverted U-shaped response, or as SDs. Another key feature of the study was the subsequent identification of the 1 M aqueous sucrose solution and the VAS-based cut-off liking scores of −15 and +15 as the statistically reliable criteria to efficiently categorize individuals into these three different sweet-liking phenotypes.

3.4.2. HCA Selection Advantages

Regarding our decision to use HCA for the identification of different sweet-liking phenotypes, this was principally driven by the need for a statistically robust and unbiased merging of individuals into groups. Indeed, using an advanced statistical clustering technique allowed the three sweet-liking phenotypes to emerge, whereas this would have been difficult to discern using more traditional visual inspection methods, particularly if the inspector was assuming a simple dichotomous mode. HCA is also based on hedonic responses across multiple stimuli rather than based on an arbitrarily selected single liking rating or the average value of hedonic scores of different stimuli. Accordingly, most elements of subjectivity and arbitrariness noted in the other phenotyping methods discussed earlier were controlled for. When we re-analyzed our current data using other widely used methods (defined as Methods 2 and 3 in the introduction, and in our recent review: Iatridi et al., 2019), many participants were misclassified relative to the cluster analysis performed here, as the bimodal phenotyping approach in those methods assumes a priori that there are only two distinct response patterns. Critically, the HCA analysis shown here, as well as other recent studies (Garneau et al., 2018; Kim et al., 2017), all suggest that response patterns for sweet stimuli are better described by three distinct phenotypes. Regarding the observed

overestimation of SDs by Method 2 and of SLs by Method 3, this was a consistent feature of those methods in our recent evaluation of the impact of different sweet taste liker classification approaches (Iatridi et al., 2019). In contrast, discriminating participants between the different sweet-liking phenotypes based on a single sucrose concentration and predetermined cut-off liking scores as used in Method 3, led to the least misclassifications, further supporting the utility of such a phenotyping approach.

3.4.3. Phenotyping Results

Our findings confirm some (Enns et al., 1979; Franko et al., 1994; Garneau et al., 2018; Kim et al., 2017; Pangborn, 1970) but not all, studies using phenotyping methods that allowed for a non-dichotomous identification of sweet-liking patterns. Indeed, in some published reports, participants with an inverted U-shaped response were considered as outliers (Drewnowski, Henderson, & Shore, 1997; Drewnowski & Schwartz, 1990; Yeomans et al., 2007), whilst elsewhere they were treated as homogeneous with the SDs (Coldwell et al., 2009; Drewnowski et al., 1998; Looy et al., 1992). Here, the generated icicle plot of our statistical output (not shown) revealed that during the final stages of the clustering process, SLs merged with those from the inverted U-shaped phenotype before SDs joined them both, uncovering a greater resemblance of the SL rather than of the SD phenotype to the inverted U-shaped response group. It is then plausible to assume that eliminating or misclassifying this intermediate phenotype is problematic and possibly obfuscates potential relationships between sweet-liking phenotypes and health outcomes of interest. We also noticed that the sucrose concentration associated with the highest liking in the inverted U-shaped response group (i.e., the 0.25 M), was in line with the concentration observed in most previous work (Keiko Asao et al., 2015; Drewnowski & Schwartz, 1990; Holt et al., 2000; Oleson & Murphy, 2017; Thai et al., 2011; Thompson et al., 1976; Yeomans et al., 2007), although lower values have also been reported (Franko et al., 1994; Grinker & Hirsch, 1972; Methven et al., 2016; Pangborn, 1970). Practically speaking, this commonly

identified 0.21–0.3 M range of sucrose concentration threshold in individuals who like intermediate levels of sweetness is lower than the sugars composition of the commercially available sweetened beverages (Ventura et al., 2011). This may potentiate the argument for reexamining the utility of sugar-tax policies (Thow et al., 2018). The multisensory aspects of tasting real-life products should not, however, be disregarded (Piqueras-Fiszman & Spence, 2016), as well as the possible attenuating or enhancing effects of other flavor components on perceived sweetness in complex products (Drewnowski & Almiron-Roig, 2010; Hayes & Duffy, 2007, 2008; Mennella et al., 2012). As sagely noted by Pangborn, "a change in one ingredient can cause multiple physical-chemical interactions which alter several sensory attributes simultaneously: appearance, aroma, texture, taste etc." (Pangborn, 1987) (p. 65).

Turning now to the frequency distribution of the identified sweet-liking phenotypes, one third of our participants were classified as SLs, a proportion consistent with observations by others who also used HCA as their phenotyping method of choice (Garneau et al., 2018; Kim et al., 2017; Methven et al., 2016). Conversely, results in Asao et al. (2015) and Kim et al. (2014) indicate that this sweet-liking pattern accounted for roughly 50% of their study samples. Two possible explanations can be considered. First, the absence of a monotonically negative slope implies that individuals in both cohorts generally exhibited stronger liking for sweetness. Notably, in Kim et al. (2014), two thirds of those classified in the inverted U-shaped phenotype rated 0.7 M as the most liked, a sucrose concentration breakpoint twice as high as the concentration we identified. Second, in those studies, sweet-liking was assessed under extreme motivational states with participants' hunger (Keiko Asao et al., 2015; Kim et al., 2014) and/or satiety (Kim et al., 2014) being manipulated. Critically, when the same Korean researchers replicated their study using a more typical pretest protocol (i.e., refraining from eating for one to two hours prior to the taste test), their measures generally correspond with the data shown here. Focusing on the frequency distribution of the monotonically negative slope regardless of the SD label, our findings disagree with previous observations. For

example, of the 650 age diverse adults tested by Garneau et al. (2018), only 55 exhibited decreasing liking as concentration increased. Presumably, this is due to the relatively low sucrose concentrations they used; indeed, the highest concentration they used (0.40 M) fell near the concentration breakpoint we identified for our inverted U-shaped phenotype. In contrast, SDs in Kim et al. (2017) were approximately as frequent as SLs and as participants in the inverted U-shaped phenotype (31.7, 32.5, and 35.8%, respectively). Nonetheless, they reported that, for the purposes of the study, two distinct clusters were treated as a single sweet-liking pattern representing the SD phenotype, with no further information provided; each of those clusters accounted for 10 and 21.7% of the total sample, respectively (Kim et al., 2017).

Here, despite the similar liking ratings of the lowest and the highest sucrose concentration by participants classified into the inverted U-shaped phenotype, perceived sweetness varied considerably when intensity ratings of those stimuli were contrasted. Therefore, this type of response cannot be attributed to reduced sensitivity to taste stimuli or from differences in recognition thresholds; rather, it appears to reflect a distinct liking pattern. Figure 3.5a,c indicated that this is also true for the SL and the SD phenotype, since inclusion of intensity ratings in the liking plots generated the expected liking patterns. In previous research, any differences in sweetness intensity between participants, when reported, were interpreted independent of the associated phenotyping results (e.g. in Kampov-Polevoy et al., 2003, 2006; Kranzler et al., 2001). The few studies that have contrasted sweetness intensity between the defined sweet-liking phenotypes have had mixed outcomes: some studies report greater overall sweetness intensity in SDs than in SLs and/or than in other phenotypes in line with what we observed here (Coldwell et al., 2009; Drewnowski, Henderson, & Shore, 1997; Drewnowski & Schwartz, 1990; Looy & Weingarten, 1992), but the majority found no differences in sweet taste perception (Garneau et al., 2018; Kampov-Polevoy et al., 2014; Lange et al., 2010; Looy & Weingarten, 1991; Thompson et al., 1976, 1977; Weafer et al., 2017; Yeomans et al., 2006, 2009). These inconsistencies could arise from several

factors including the phenotyping methods and the stimuli concentrations used in these studies. Many of the most relevant studies did not, however, specifically report differences in sweetness intensity between their defined sweet-liking phenotypes, limiting meaningful contrasts between our findings and prior work.

3.4.4. Recommended Criteria for the Identification of Distinct Sweet-liking phenotypes

Except for a pilot experiment (Keiko Asao et al., 2015), this is the first study suggesting specific criteria for the identification of the distinct sweet-liking phenotypes that could be considered as both statistically robust and easy-to-apply. One core element of the proposed simpler approach is the administration of a single sucrose concentration that allows for both a less time-consuming and resource-demanding assessment process and for elimination of potential issues from the contrast effects which are "hard-wired" to longer protocols (Lim, 2011). Within the taste literature, this in a not a novel concept. In 1980, Lawless addressed the need to identify an efficient classification method that could be used to rapidly screen large cohorts in terms of bitter taste phenotypes for phenylthiocarbamide (PTC) and 6-n-propylthiouracil (PROP), i.e., thiourea tasters and nontasters (Lawless, 1980). After using multiple approaches within the same study cohort, he concluded intensity ratings (on a 7-point scale) for a single antimodal concentration of PTC or PROP presented in a two-series taste test allowed for a rapid and reliable separation of the tasters from the nontasters (Lawless, 1980).

Despite using a similar analysis to that of Asao et al. (2015), we concluded that approximately twice the concentration of sucrose, compared to the concentration they proposed, is required to deliver the highest sensitivity and specificity in the discrimination between distinct sweet-liking phenotypes. A small sample size, dichotomous grouping, and participants' pre-test fasting state in the earlier pilot experiment (Asao et al., 2015) raise questions about the broader applicability of the concentration (0.598 M sucrose) recommended in their study. Indeed, other studies

using multiple sweet taste stimuli identified concentrations ranging from 0.83 M (e.g. in Eiler et al., 2018; Garbutt et al., 2016; Kampov-Polevoy et al., 1998; Tremblay et al., 2009; Turner-McGrievy et al., 2013; Weafer et al., 2017) to 0.99 M (e.g. in Sienkiewicz-Jarosz et al., 2013; Swiecicki et al., 2009; Wronski et al., 2006). Moreover, the 0.6 M sucrose solution referred in Tuorila et al. (Tuorila et al., 2017) was actually shortlisted from their previous work where two additional lower concentrations were tested but not any higher (Keskitalo et al., 2007). Finally, the replication in our sample of the proposed by Asao and colleagues' U-shaped association between sucrose concentration and reproducibility of the liking ratings across the repeated blocks of the taste test (Asao et al., 2015) may also bear critically upon sweet-liking protocols based on intermediate concentrations. Indeed, taste measures for about 40% of the adult sample in Garneau et al. (2018) indicated indifferent responses to a range of stimuli between 0 M and 0.4 M sucrose.

Considering the comparatively less sophisticated and less restrictive concepts of the VAS compared to the labelled magnitude or Likert-type scales, the decision to record liking on an analogue scale further strengthens our classification criteria proposal. In particular, VAS-based ratings are independent of the range of prior sensory experiences and of the assumption that the same descriptors (labels) reflect equivalent meaning across different responders (Bartoshuk et al., 2003; Hayes et al., 2013). That said, in our lab, we have repeatedly observed that participants find VAS to be more straightforward than gLMS, although when we directly contrasted the two scales in a sample of young educated adults, VAS and gLMS yielded similar results (Yeomans et al., 2007). Additionally, VAS is appropriate for recording the multi-dimensional continuum of human responses that a fixed pre-coded format does not by principle permit (Ho, 2017). Clearly, no scaling approach is perfect: the "anchor effect" phenomenon (centering bias) characterized by less use of the extreme response has been associated with most rating scales, the VAS included (Lim, 2011). Overall, we propose that utilizing VAS for sweet-liking assessment when phenotyping protocols are applied to groups of diverse characteristics is likely to come with the least challenges.

3.4.5. Controlling for Protocol Conditions

Although previous research presents an inconclusive picture (Kim et al., 2014; Moskowitz et al., 1976; Thompson et al., 1976), some studies report an effect of hunger (Looy & Weingarten, 1991; Rolls et al., 1983; Yeomans & Mobini, 2006) and thirst (Winkielman et al., 2005) on liking for sweet taste stimuli. It was thereby critical to ensure that recorded sensory responses were not driven by participants' motivational state and that the motivational state did not differ between the contrasted sweet-liking phenotypes. Analysis of the pre- and post-test levels of hunger and thirst across our study sample and between-groups confirmed this was not so.

The nature of changes in levels of hunger and thirst over the test period (increased and decreased by 15.2% and 10.1%, respectively) also indicated little or no likely influence of post-ingestive effects of sucrose on the sensory-related measures (Sclafani, 2001), suggesting the "sip and spit" protocol worked as expected. Notably, Running and Hayes (2017) observed no significant differences in the rated intensity of a 0.5 M sucrose solution when "sip and spit" and "sip and swallow" protocols were contrasted. Nonetheless, the differences in the density of taste buds (Miller & Bartoshuk, 1991) and in the associated saliva (Schmale et al., 2007) across the different regions of the oral cavity and the known role of gastrointestinal tract's sweet taste receptors in metabolic regulation (Low et al., 2014; Sclafani, 2007), suggest a need for both explicit instructions and subsequent compliance checks in sensory evaluations, particularly when a wide range of concentrations or a relatively strong solution are being tested.

3.4.6. No Effect of Sweet-liking phenotype on Participant Characteristics

Analysis of this young healthy sample found no effect of sweet-liking phenotype on the few demographic, lifestyle, and anthropometric characteristics we examined. First, the frequency distribution of the SL phenotype did not differ between women and men. With the exception of the multi-ethnic cohort of Thai et al. (2011), lack of sex differences in sweet-liking is consistent with previous published work focusing on sweet-liking

phenotypes generated from simple sucrose solution-based taste tests and where women and men were represented equally (Asao et al., 2015; Coldwell et al., 2009; Kranzler et al., 2001; Oleson & Murphy, 2017; Tremblay et al., 2009; Weafer et al., 2017). In his recent review, Spence (2018) argues that individual differences rather than sex differences might be the most important influence on shaping our taste worlds, particularly when the hedonic aspects of taste are studied. Animal models provide equivocal results on sucrose sensory properties by sex (McCaughey, 2008). These findings fail to support Katz's theory of "gendered eating patterns" generated by either evolution or, according to others, by cultural norms (Bell & Hollows, 2005), as well as baseline reports from the NutriNet-Santé study where, remarkably, men and not women liked sweet tastes more (Lampuré et al., 2015). It is worth stressing though that sensory data in the French cohort were collected indirectly using "Pref-Quest," a proxy of laboratory-based taste tests that measures recalled liking for different taste modalities via asking questions on selective food items and eating habits (Deglaire et al., 2012). In the present work, we also failed to observe an effect of age on hedonic responses to sweet taste. This stands in direct contrast to the fairly consistent effect of age on sweet-liking whenever children or adolescents were compared with adult populations (Bobowski & Mennella, 2017; De Graaf & Zandstra, 1999; Desor & Beauchamp, 1987; Mennella & Bobowski, 2015), and may be due to the relatively restricted age range tested here. To note, in some (Garbutt et al., 2009, 2016; Garneau et al., 2018; Goodman et al., 2018; Kampov-Polevoy et al., 1998; Thompson et al., 1976; Travers et al., 1993; Turner-McGrievy et al., 2013, 2016) but not all (Bogucka-Bonikowska et al., 2001; Kampov-Polevoy et al., 1997; Swiecicki et al., 2015; Wronski et al., 2006) studies testing middle-aged or older adults, SDs and those with an inverted U-shaped response outnumbered SLs. Critically, methodological limitations that may lead to possible overestimation of the SD phenotype in prior studies cannot also be overlooked (Iatridi et al., 2019).

Other factors worth exploring with regard to humans' responses to sweet taste are dieting and BMI. Regarding attempts to investigate how being on a weight loss diet affects classification into the distinct sweet-liking phenotypes, evidence has been loose and is drawn on research on sweet-liking either as a continuous measure (e.g. in Asao et al., 2016; Burgess et al., 2016; Kleifield & Lowe, 1991) or assessed via questionnaires instead of laboratory-based taste tests (Lampuré et al., 2015). As discussed in a recent review, bariatric surgery is also likely to augment gustatory sensitivity to sweet taste and to attenuate relevant hedonic responses post-operatively (Ahmed et al., 2018). In our study, being a former dieter was more apparent in SDs. This may seem counterintuitive to the sensory specific satiety theory (decline in pleasantness for a food stimulus subsequent to consumption compared with the uneaten: Rolls et al., 1981), but could be backed up within the hedonic hunger context (motivation to consume palatable foods in the absence of food deprivation: Lowe & Butryn, 2007). Nonetheless, no explicit information on the timing, duration, or mode of the dietary regime or the extent of weight loss and weight regain was collected. Additionally, considering the small size of this particular subgroup and the subsequent lack of significance, caution is advised in interpreting this observation until replicated. BMI, on the other hand, did not differ across the three sweet-liking phenotypes. Although one can argue that this was due to the limited range of BMI in our sample, our finding was consistent with a sizable body of published evidence (Coldwell et al., 2009; Drewnowski, Henderson, Shore, et al., 1997; Drewnowski & Schwartz, 1990; Eikemo et al., 2016; Garneau et al., 2018; Goodman et al., 2018; Mennella et al., 2014; Methven et al., 2016; Thompson et al., 1977; Turner-McGrievy et al., 2013; Weafer et al., 2017; Yeomans et al., 2007; Yeomans & Prescott, 2016). It is also of note that some early reports testing individuals of greater BMIs showed that obese were more often classified into the SD phenotype than normal-weight participants (Grinker, 1977; Grinker & Hirsch, 1972; Johnson et al., 1979; Malcolm et al., 1980; Thompson et al., 1976).

3.4.7. Potential Mechanisms

Different mechanisms may account for the observed variations in affective responses to sweet taste, and fundamental biology likely plays a part. Sweet tasting substances activate various neural circuits including some associated with dopamine-linked reward centers in the prefrontal cortex (Berridge & Kringelbach, 2015; Fernstrom et al., 2012; Katz & Sadacca, 2011). This activation accommodates the urge to meet physiological needs such as the central nervous system's energy supply (e.g. in Mergenthaler et al., 2013). Internal state-specific factors ("homeostasis") have also been implicated in explaining the variation of hedonic responses to sweet taste as a function of deprivation state. In this context enhanced sweet-liking in fetuses (de Snoo, 1937; Liley, 1972) and infants (Desor et al., 1973; Steiner, 1979; Steiner et al., 2001) may relate to the increased needs for energy during the stages of rapid growth (Mennella et al., 2016). Likewise, Coldwell and colleagues reported that SL adolescents had higher levels of a bone growth factor compared with their SD peers (Coldwell et al., 2009). Similarly, negative gustatory alliesthesia, which refers to diminishing liking as a response to internal energy abundance (as in satiety or obesity) (Cabanac, 1971), has been proposed to contribute to the apparent inverse relationship between BMI and sweet-liking.

Later advances have implicated taste genetics with sweetness, both directly and indirectly. TAS1R2 and TAS1R3 taste receptor genes have directly been linked to sweet taste perception (Bachmanov et al., 2011; Chamoun et al., 2018; Dias et al., 2015). The heterodimeric protein encoded by these genes is expressed in taste receptor cells in the oral cavity, providing the mechanism by which sweet taste occurs (Nelson et al., 2001); subsequently, these receptors have also been found in extra oral tissues (Fernstrom et al., 2012). Salivary glucose levels and salivary protein profile have recently identified as additional potential determinants of sweet taste perception (Rodrigues et al., 2017). Finally, some reports suggest that differences in the density of structures that house taste cells (i.e., fungiform papillae) may explain differences in suprathreshold taste

intensity, including sweetness (Miller & Bartoshuk, 1991; Miller & Reedy, 1990), although others account conflict with this explanation (Dinnella et al., 2018; Feeney & Hayes, 2014; Fischer et al., 2013; Webb et al., 2015).

3.4.8. Limitations

The present study has some limitations that require further confirmatory analyses in different populations to allow the proposed method to be applied universally. First, we had a gender-imbalanced sample of young adults primarily from European Caucasian ancestry. Past literature has partly identified more SLs than SDs when direct contrasts between younger and older adults were performed (Enns et al., 1979; Grinker, 1977; Thompson et al., 1976; Tremblay et al., 2009). Whether sweet-liking phenotypes vary by ethnic group is, however, not yet well understood (Coldwell et al., 2009; Holt et al., 2000; Thai et al., 2011; Tuorila et al., 2017; Turner-McGrievy et al., 2013, 2016). Nevertheless, due to the higher risk of many non-Caucasian ethnic groups and of older versus much younger individuals in developed countries for non-communicable diseases (Bollyky et al., 2017), this research area is worthy of further investigation. Our findings may also not translate to populations with a different habitual intake of sugar. Studies in the U.S., for example, suggest a slightly higher daily intake of free sugars (Bowman, 2017) compared with U.K.-based cohorts (NDNS, 2018), whereas the recommended daily allowance (USDA, 2015) is also double the U.K. recommendations (SACN, 2015). On the basis of the conflicting evidence surrounding the influence of exposure in sweet-tasting foods on hedonic responses to sweetness (Appleton et al., 2018; Keast, 2016), this limitation may leave particular populations vulnerable to any possible interplay between sweet-liking patterns and eating patterns and therefore much still need to be learned. Moreover, women and men in our sample were not of a representative BMI for their age-matched group (Conolly & Davies, 2018). Whilst this is presumably a caveat for the generalizability of our results, the reader is advised to consider that, as noted earlier, both in our study and elsewhere, BMI did not differ by sweet-liking phenotype. Still, the fact that the observed proportion of SDs was relatively low, although it was expected from phenotyping results from prior studies using HCA (see 3.4.3 for details), it also means

that group contrasts need to be treated with some caution. Finally, no phenotyping method is beyond limitations. The one inherent in using HCA is the lack of a formal "stopping rule" in the clustering process; the researcher is called to indicate the number of stages displayed in the agglomeration schedule that need to be eliminated from further merging and then manually incorporate this decision on the generated dendogram (Yim & Ramdeen, 2015).

3.5 Conclusions

The present study confirms that the expression of sweet-liking is not universal but responses to sweet taste stimuli vary considerably across people. What is new is the statistical determination of some robust but concurrently usable classification criteria for the identification of the different sweet-liking phenotypes in a large-scale study. Despite limitations arising mainly from participant characteristics, there is good reason to believe that our approach might still be widely applicable as HCA-based liking patterns between our U.K. based study and those by American (Garneau et al., 2018) and Korean (Kim et al., 2017) researchers largely align. Conceivably, the potential of a broader use of the psychophysical comparisons we delivered herein in epidemiological studies and clinical trials could have a fruitful impact on research associated with health and wellbeing. Accordingly, we may now have appropriate tools to finally address a longstanding issue first Mattes noted over 30 years ago, that is: "The question remains whether individual responsiveness to sweet taste can tell us anything about the individual, his or her physiological or nutritional status, or the likely patterns of food selection." (Mattes, 1985).

Author Contributions

Conceptualization, V.I., M.R.Y., and J.E.H.; methodology, V.I., and M.R.Y.; software, V.I.; validation, V.I., and M.R.Y.; formal analysis, V.I; investigation, V.I.; resources, M.R.Y.; data curation, V.I.; writing—original draft preparation, V.I.; writing—review and editing, M.R.Y., and J.E.H.; visualization, V.I., and J.E.H.; supervision, M.R.Y.; project administration, V.I., and M.R.Y.; funding acquisition, M.R.Y.

Conflicts of Interests

V.I. declares no conflict of interest. J.E.H. has received speaker fees, travel reimbursements, and/or consulting fees from federal agencies, nonprofit organizations, trade/commodity groups, and corporate clients in the food industry. M.R.Y has received direct research funding from numerous sources including national and international companies, as well as speaker fees, travel reimbursements, and consultancy fees from various companies, none of which impact on the work reported here. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

Chapter 4 (Paper 3)

Effects of sweet liking on body composition depend on age and lifestyle: a challenge to the simple sweet-liker obesity hypothesis.

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Keywords

sweet taste, gustatory hedonics, sugar, body-composition, hedonic hunger

Significance Statement

Relationships between sweet-liking and obesity have been studied for decades, but this key issue remains unresolved as results are inconsistent. Here, we find that sweet-liking is related to either greater fat free mass or lower body fat, which implies sweet-liking may reflect an increased need for energy. Further, we demonstrate that associations between sweet-liking and adiposity are modified by age and environment.

Abstract

Taste hedonics drive food choices, and food choices affect weight maintenance. Despite this, the idea that hyper-palatability of sweet foods is linked to obesity development has been controversial for decades. Here, we investigate whether interpersonal differences in sweet-liking are related to body composition using a cross-sectional multi-country design. Healthy young adults from the UK (N = 148) and the US (N = 126) completed laboratory-based sensory tests (sucrose taste tests) and anthropometric measures (i.e., body mass index; BMI, body fat; fat-free mass; FFM, waist/hips circumferences). Habitual beverage intake and lifestyle and behavioural characteristics were also assessed. Using hierarchical cluster analysis, we classified participants into 3 phenotypes: sweet liker (SL), sweet disliker (SD), and inverted-U (liking for moderate sweetness). Effects of phenotype on anthropometry were observed, as well as a phenotype by age group interaction: being a SD was linked to higher body fat among those younger than 21 years old, while in the older group, SLs had the highest BMI and waist circumference; age groups reflected different levels of exposure to the obesogenic environment. FFM emerged as a better predictor of sweet taste hedonics than either BMI or body fat. Sweetened beverage intake partially explained phenotype-BMI and phenotype-adiposity associations, but only in the older group. Enhanced interoceptive abilities and reward sensitivity in SLs may provide some biological insight into the observed relationships. Collectively, our findings implicate sweet-liking as a potentially important consideration in obesity prevention strategies, but the moderating roles of age and obesogenic environment also require additional consideration.

4.1 Introduction

Obesity is a global public health concern. According to recent estimates, overweight and obesity affects one in two adults worldwide, and the incidence has tripled over the past 4 decades (WHO, 2018b). As excess body weight is the consequence of a long term positive energy balance (Spiegelman & Flier, 2001), food choices and intake play a central role in the multifactorial nature of obesity (Swinburn et al., 2011). Myriad factors influence what and how much people choose to consume, including biology, psychological factors, and the external environment (Mela, 1999). From a biological standpoint, taste has long been considered to have a powerful impact on eating behaviour (Clark, 1998). In that sense, humans preferentially eat what we like (Boesveldt et al., 2018), probably eat more of what we like (Yeomans, 1996), and definitely do not eat what we do not like (Hayes, 2020). This seemingly simple observation involves inputs from different systems, and the final hedonic decision integrates metabolic needs with activity in the brain's reward regions (Besnard, 2016).

The strong affective and rewarding appeal of sweet taste may be a primary reason why sweet-tasting foods and drinks are eaten in excess, independent of the body's need for energy. Specifically, tastants that are sweet initiate reflexes that project to brain areas stimulating specific dopamine- and perhaps opioid- based neural pathways (Wiss et al., 2018). These patterns of activity are thought to result in acceptance of the ingested sweet-tasting stimulus ('liking') followed by development of associative learning and positive memory ('reinforcement') for sweet sensations. New insights into gut-brain communication also suggest post oral detection of sugars may generate a positive feedback mechanism ('appetition') which potentially enhances the hedonic/rewarding value of the ingested stimulus (Shechter & Schwartz, 2018). This, in turn, may promote overconsumption of sweet tasting foods and drinks beyond energetic needs. These putative biological mechanisms are supported by epidemiological data showing that daily intake of sugars frequently exceeds recommendations (Newens & Walton, 2016). Elsewhere, a 2019 review on relationships between sweetness and dietary choices proposed that, unlike taste

sensitivity or perception, liking for ever higher sweetness may serve as a good predictor of intake of sweet-tasting foods and drinks (Tan & Tucker, 2019).

Collectively then, if food choices contribute to obesity, and affective taste responses govern dietary intake, liking for high levels of sweetness may be a potential driver for obesity. Despite a longstanding belief this is true by both researchers and the public, empirical evidence that intake of sugars or strong pleasure from sweetness contributes to obesity is lacking. Some have put forth the argument that use of sugars has noticeably increased since the 1970s alongside obesity rates (Popkin & Nielsen, 2003); further, given their association with unhealthy eating habits, simple/added sugars, along with fats and salt/sodium, are key dietary components targeted for reduction in the Western diet (WHO, 2018a). However, modern data indicate prevalence of obesity continues to rise despite a drop in intake of simple sugars and sugar-sweetened beverages in both the US (Welsh et al., 2011) and Australia (Brand-Miller & Barclay, 2017). Moreover, systematic reviews and meta-analyses of controlled trials have shown simple sugars do not behave any differently from other macronutrients in driving weight gain (Prinz, 2019). Still, in alignment with evidence that liquid calories are less filling and induce poor energy compensation compared to solid foods (Mattes, 2006), overconsumption of sugar sweetened beverages in specific has been associated with adverse effects of sugar intake beyond calories (e.g., Te Morenga et al., 2013).

Critically for the present context, data from studies on affective responses to sweetness have had inconsistent findings with regard to obesity. Some studies report no significant relationship (Asao et al., 2015a; Drewnowski et al., 1997; Garneau et al., 2018; Goodman et al., 2018; Methven et al., 2016; Turner-McGrievy et al., 2013; Weafer et al., 2017; Yeomans et al., 2007; Yeomans & Prescott, 2016) while others suggest individuals with overweight or obesity experience less pleasure from high sweetness compared to normal-weight individuals (Grinker, 1977; Grinker & Hirsch, 1972; Johnson et al., 1979; Malcolm et al., 1980; Thai et al., 2011; Thompson et al., 1976). To better understand reasons for these conflicting reports, a critical consideration is the classification methods used to identify distinct sweet-liking patterns (i.e., sweet-liker phenotypes). Research in the UK

(Iatridi et al., 2019a; Yang et al., 2019), the US (Garneau et al., 2018), and Korea (Kim et al., 2017) have all found evidence that liking for sweet taste can be separated into three distinct and definable phenotypes: those expressing strong liking to high levels of sweetness (sweet likers; SLs), those who have aversive responses to strong sweet tastes (sweet dislikers; SDs), and a third group exhibiting maximum liking for a moderate concentration of sucrose (Iatridi et al., 2019b). Prior to this emerging consensus, there was a major lack of agreement in criteria used to identify these patterns of hedonic responses across studies (Iatridi et al., 2019b), leading to an overly simplistic dichotic classification (SLs versus SDs) which failed to adequately describe the full range of human behavioural responses to sweetness. Further, earlier studies had strong potential for misclassification, as the same individual might have been identified as a SD by one method but not with another method. Consequently, it has been difficult to achieve consensus on whether individual differences in liking for sweetness are in fact a risk factor for overconsumption, weight gain, or obesity. These concerns were recently raised by Tan and Tucker (2019) in their review on the influence of sweet-liking on food choice and intake. They concluded the use of sweet-liker phenotypes, as opposed to treating affective responses as a continuous measure, will be central in elucidating effects of liking for intense sweetness (Tan & Tucker, 2019).

A separate limitation in evaluating the influence of individual differences in sweet-liking as potential drivers of obesity comes from an overreliance on BMI. As BMI fails to differentiate between body tissues, it is a crude estimate of body composition, particularly for values below 30 kg/m^2; indeed, half of individuals not labelled as overweight or obese may still have excess adiposity (Okorodudu et al., 2010). Notably, studies using BMI diverse samples identify participants with obesity more often as SDs compared to those with normal-weight (Grinker, 1977; Grinker & Hirsch, 1972; Johnson et al., 1979; Malcolm et al., 1980; Thompson et al., 1976). Conversely, datasets with truncated BMI ranges (mean BMI between 20.1 kg/m^2 and 27.2 kg/m^2) have either failed to find an effect of sweet-liker phenotype on BMI (Drewnowski et al., 1997; Drewnowski & Schwartz, 1990; Garneau et al., 2018; Goodman et al., 2018; Holt et al., 2000; Kim et al., 2014; Weafer et al., 2017) or differences in BMI between phenotypes which failed to reach statistical significance (Asao

et al., 2015; Methven et al., 2016; Yeomans et al., 2007; Yeomans & Prescott, 2016). To date, only one study in adults has investigated body composition as a function of sweet-liking, and they found no evidence of differences in body fat across liker phenotypes (Garneau et al., 2018).

Methodological inconsistencies not withstanding, psychological differences between sweet-liker phenotypes have also been understudied. To date, research has focused mainly on restrained eating (e.g., Drewnowski et al., 1997; Keskitalo et al., 2008; Yeomans & Prescott, 2016). However, strong liking for high sweetness might also reflect a variation in other personality traits like sensitivity to aspects of reward processing. Current understanding of the influence of impulsiveness in poor food choices (Stevenson, 2017) also suggest sweet-liker phenotypes might differ in impulsivity. For example, in a classic study by Kampov-Polevoy where the effect of individual sweet-liking patterns on alcohol addiction was the primary objective, impulsive behaviour was also assessed; alcoholism diagnosis, however, mediated the observed differences in impulsivity between SLs and SDs (Kampov-Polevoy et al., 1998). To complement our primary focus on body composition, we also included some common behavioural measures, of lifestyle and dietary characteristics to gain additional insight into differences in eating behaviour between sweet-liker phenotypes that may help explain potential differences in body composition.

In summary, given the widespread assumption that sugar intake is a driver of obesity, the lack of clarity in prior work suggests targeted data to clarify these issues are warranted. Specifically, two key issues need to be addressed. First, earlier studies most used overly-simplistic classification methods that lacked statistical validity and inflated the likelihood of misclassification: the emergence of a better defined method for defining phenotypes (Iatridi et al., 2019b) can be used toward more robust evaluation of these relationships. Second, most prior studies have focused on samples from a single country, thereby ignoring the importance of cross-cultural differences in obesity aetiology (Blüher, 2019). Here, we address this gap by testing our hypotheses in two countries with different levels of exposure to an obesogenic environment (the UK and the US).

4.2 Materials and Methods

4.2.1 Participants

Adults aged 18-34 years were locally recruited from the University of Sussex (UK cohort) from September to December 2017 and from the Pennsylvania State University (US Cohort) from October to November 2018, to take part in a two-session lab-based study advertised as a 'Taste and Body Metabolism' study. To qualify for the study, participants were required to be free of medication (other than oral contraceptives), non-smokers (less than five cigarettes a week), and without a history of diagnosed eating disorders, and to report a regular menstrual cycle if a woman. Individuals currently dieting or suffering from a respiratory illness, and who had undergone a dental procedure in the two weeks prior to testing were excluded. On arrival at the research facilities, written informed consent was obtained, but participants remained naive to the study's hypotheses until they completed all tasks. The University of Sussex Science and Technology Cross-Schools Research Ethics Committee in the UK (ER/VI40/1) and the Penn State Institutional Review Board in the US (STUDY00010753) approved all testing procedures. The study was conducted according to the guidelines of the Declaration of Helsinki.

4.2.2 Sensory measures

Participants evaluated liking and intensity for aqueous sucrose solutions ranging from 0 to 1 M. Detailed information about the sweet taste test can be found in Iatridi *et al*. (2019a). All ratings in the UK cohort were collected using the Sussex Ingestion Pattern Monitor (SIPM version 2.0.13, University of Sussex, Falmer, UK); all ratings for the US cohort were collected using Compusense Cloud, Academic Consortium (Guelph, Ontario, Canada).

4.2.3 Anthropometric measures

In both cohorts, all anthropometric assessments took place on a second visit, and were always conducted by the same trained researcher. Standing height to the nearest 0.1 cm using a wall stadiometer and body weight to the nearest 0.1 kg using the electrical weighing scales integrated into the bioelectrical impedance devices listed below were taken. Standard procedures were followed, including wearing light clothing but no shoes (WHO, 1995). Waist circumference (WC) and hip circumference (HC) were measured in duplicate to the nearest 0.5 cm with a stretch-resistant tape (WHO, 2011) and means were used for analysis. Total body fat (BodyFat) and fat-free mass (FFM) were evaluated from body composition measures assessed using a multi-frequency segmental bio-impedance device (MC-780MA P, TANITA, UK and BC-418, TANITA, US). Given that bioelectrical impedance analysis (BIA) relies on specific assumptions, including body hydration status, specific instructions were provided to all participants prior to the experimental day (Kyle et al., 2004). Specifically, participants were asked to refrain from consuming alcohol for 24 hours and from performing strenuous exercise for 12 hours before the anthropometry session. Appointments were scheduled at between 0700 and 1030 hours after an 8-hour fast and water abstinence; participants were also advised to avoid having a long shower or a bath on that morning. Body composition measures were taken whilst the participant had bare feet and carried no metal objects, were wearing light clothing, and after using the bathroom facilities in the laboratory.

4.2.4 Demographic, lifestyle, behavioural, and dietary[1] characteristics

Participants provided information about demographic characteristics (date of birth, sex, ethnicity), dieting (i.e., being a former, current, or never-dieter; losing or gaining 10% or more weight), breakfast habits, and sleeping routine (i.e., bedtime, wake-up time, and midday naps separately for weekdays and weekends). To assess physical activity level, the

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[1] The details (methodology, analysis, and interpretation) regarding the 24h dietary recalls were not part of the manuscript submitted to PNAS to be considered for publication.

short form of the International Physical Activity questionnaire was administered (Craig et al., 2003); based on its scoring algorithm (Patterson, 2015), this questionnaire allows participants to be classified into low, moderate, and high physical activity groups.

Standard questionnaires assessing personality traits related to eating behaviour were also administered. The behavioural questionnaires administered included the original 51-item Three Factor Eating Questionnaire (Stunkard & Messick, 1985) which presents questions about restrained eating, which is defined as the tendency to consciously restrict food intake in order to control body weight, disinhibition that concerns loss of control over eating in response to negative emotions or the presence of highly palatable foods, and trait hunger which is designed to measure the extent to which hunger feelings are perceived and drive food intake. From the Barratt Impulsiveness Scale (Patton et al., 1995) that assesses the predisposition to react to internal or external stimuli without adequate forethought about the consequences that are favouring immediate rewards over long-term goals, we examined the attentional, motor and non-planning impulsiveness subtypes. Participants were also asked to complete the English language version (O'Connor et al., 2004) of the Sensitivity to Punishment and Sensitivity to Reward Questionnaire (Torrubia et al., 2001). The Sensitivity to Punishment subscale refers to the behavioural inhibition under specific conditions of threat, punishment or non-reward, whereas the Sensitivity to Reward subscale reflects approach behaviour to specific conditioned and unconditioned rewards, appetitive stimuli included. Finally, responses on the Arnett's Inventory of Sensation Seeking questionnaire (Arnett, 1994) was obtained. Adapted from the original Zuckerman's Sensation Seeking Scale (Zuckerman et al., 1964), this questionnaire examines different constructs of sensation seeking (e.g. thrill, adventure, and experience seeking, boredom susceptibility etc.) that may be captured through two subscales: intensity seeking and novelty seeking. For all questionnaires listed above, higher scores indicated a more significant presence of the personality trait under investigation.

For the dietary assessment, the EPIC Norfolk Food Frequency Questionnaire (Bingham et al., 2001) adapted to incorporate a more extended list of beverages (energy drinks, sweetened canned tea, and concentrated juice drinks without added sugar), and the

15-item Beverage Intake Questionnaire (Hedrick et al., 2012) were completed by participants in the UK and the US, respectively. Dietary data were accordingly transformed to continuous measures prior to analysis (see 4.2.5 for details). In the UK cohort, 24h dietary recalls were also obtained. A 24h recall is a structured open-ended response interview intended to capture detailed information about all foods, beverages and possible dietary supplements consumed by the respondent in the past 24 hours, most commonly, from midnight to midnight the preceding day (Gibson, 2005). Three face-to-face 24h recalls were administered to each participant (Hoffmann et al., 2002) by the same trained interviewer across two weeks' time. Two of them referred to dietary intake during weekdays and one to a weekend day (Thompson & Byers, 1994; Willett, 2013). Due to possible non-independence of food and beverages intake on consecutive days and consequently less representativeness of the respondent's real diet (Thompson & Byers, 1994; Willett, 2013), 24h recalls from non-consecutive days were collected. To further enhance the consistency and accuracy of the recall process, the USDA multiple pass method was used (Conway et al., 2003, 2004). Pre-determined questions prompting the respondent to link eating, and drinking episodes to time periods and/or day time activities (Lam & Ravussin, 2016) were also applied.

4.2.5 Statistical analysis

Consistent with contemporary best practices, agglomerative hierarchical cluster analysis (HCA) with squared Euclidean distance and average linkage method was used for the identification of distinct patterns of liking for increasing sweetness (sweet-liker phenotypes). Clustering was performed on the mean liking ratings from the eight replicated stimuli concentrations, and the decision on the final number of clusters was informed by the magnitude of the difference between the coefficients of the agglomeration schedule and application of this information to the dendrogram produced as part of the statistical output (Yim & Ramdeen, 2015). To eliminate overfitting, two-by-two cross-tabulation were implemented aiming at reclassification of roughly 7% of each cohort's sample showing non-

erratic atypical hedonic responses through identifying the dyads of sucrose concentration and liking scores with the highest sensitivity and specificity in predicting the three sweet-liker phenotypes; more details on the clustering approach are found in Iatridi *et al*. (2019a).

Except for age and BMI, which are expressed as medians and 25th and 75th percentiles and later log-transformed to improve normality, means and standard errors of the means (SEMs) are used throughout; categorical variables are shown as percentages. One-way analysis of variance (ANOVA) or, when sex and/or age were included as covariate(s), one-way analysis of covariance (ANCOVA) were used. Fisher's least significant difference was used as the post hoc test and Welch tests and Games-Howell follow-up analysis were applied when equal variances assumptions were violated. Additionally, between subjects two-way (country or age group by phenotype) ANOVAs or ANCOVAs were carried out to determine if there were significant differences in the measured outcomes, while the interaction effect between sucrose concertation and phenotype or country was analysed with two-way Repeated Measures ANOVAs with Greenhouse-Geisser correction in cases of violation of assumption of sphericity. Eta squared values (ηp^2) are reported as the measure of effect sizes for the main analyses and was considered small when equal to 0.01, medium when equal to 0.06 and large when equal to 0.14. Finally, to quantify differences in each of the obesity-related anthropometric measures by phenotype when habitual intake of sweet-tasting beverages was accounted for, multiple linear regression models with dummy coding were employed. Variance inflation factors were used to check for multicollinearity in our models with more than one predictor; no evidence of multicollinearity was observed.

Student's t-tests (continues outcomes) and Pearson's chi-squares (categorical outcomes) were used to compare the various demographic, lifestyle, behavioural, and dietary data between cohorts and between age groups. Degrees of freedom were adjusted as appropriate when equal variances were not assumed. For the semi-quantified food frequency questionnaires, in order to facilitate direct comparisons of beverage use between cohorts and across taste phenotypes the 9- and 7-point frequency consumption scales in the UK- and the US-specific questionnaires, respectively, were transformed as an

annualised estimate of intake (e.g. 1/week = 52, 1-3/month = 104, etc.: Byrnes & Hayes, 2013). Additionally, to control for differences in portions between the two food frequency questionnaires, frequency x portion was calculated for the Beverage Questionnaire-15 and was further reduced to the portion reported on the EPIC Norfolk food frequency questionnaire (e.g. 1/day x 12 ounces of soft drink = 365 x 1.5 glasses of soft drink). To reduce skew in annualised intake data, values were log_e transformed. All 24h recall data were analysed using the Dietplan7 (Version 7.00.48), a nutritional analysis software based on the UK Nutrient Databank in terms of food and beverages composition (Finglas et al., 2015). Macronutrients (carbohydrates, fibre, fats, and proteins) and different subgroups of simple sugars (total sugars, non-milk sugars) were all expressed as absolute intakes in grams and as a percentage of total energy intake. Willet's sex-specific under-reporting (women: <500 kcal/day; men: <800 kcal/day) and over-reporting (women: >3,500 kcal/day; men: >4,000 kcal/day) energy range values were applied to each participant's average data (Willett, 2013).

Anthropometric data were not available for three participants (two women and one man) in the UK and ten participants (eight women and two men) in the US who failed to return for session 2. Also, four participants, two from each cohort, provided contradictory information about their dieting history at pre-screening and the first day of testing, so they were excluded from analyses related to anthropometrics, lifestyle and eating habits, and eating behaviour. Significance was set at $p < .05$. All statistical calculations were performed using IBM SPSS Statistics for Windows, version 25.2.

4.3 Results

A total of 148 participants in the UK (29.1% men; 75.7% Caucasians, *Mdn* = 20.2 years) and 126 in the US (32.5% men; 81.7% Caucasians; *Mdn* = 22.0 years) completed the taste test and the behavioural, lifestyle, and dietary questionnaires. The two cohorts did not differ in sex ($\chi^2(2, N = 274) = .389, p = .533$) or self-reported ethnicity ($\chi^2(3, N = 274) = 6.39, p = .094$). Despite recruitment in the same age range, participants in the UK were

slightly, but significantly, younger than those in the US (t(184.306) = -3.323, p = .001); accordingly, effects of age on between-country findings were considered in subsequent analyses.

4.3.1 Identification of distinct sweet-liker phenotypes[2]

As shown in Figure 4.1, hierarchical cluster analysis (HCA) revealed three distinct hedonic response patterns to sweet taste: a sweet-liker phenotype (SL) showing a rise in liking with increasing sucrose concentration, a sweet disliker phenotype (SD) characterised by a decline in liking as sucrose concentration increased, and an inverted-U group (IU) where participants expressed optimal sweetness at either 0.25 M or 0.5 M sucrose; liking ratings for the 0.25 M sucrose in the UK (M = 9.42, SEM = 1.172) and the 0.5 M sucrose in the US (M = 8.12, SEM = 1.377) did not significantly differ between cohorts (t(133) = 0.728, p = .468). Analysis of variance (ANOVA) confirmed the effect of phenotype on overall liking for each cohort (UK: F(2, 143) = 116.41, p < .001, ηp^2 = .619; US: F(2, 118) = 37.15, p < .001, ηp^2 = .386). Similarly, a sucrose concentration by phenotype interaction on liking was also observed (UK: F(8.884, 635.19) = 78.65, p < .001, ηp^2 = .524; US: F(8.340, 492.06) = 87.90, p < .001, ηp^2 = .598). Phenotypic differences in overall liking remained significant after controlling for pre-test levels of hunger and thirst.

To note, during the very last stages of the clustering process 8.1% participants in the UK cohort and 10.3% in the US cohort merged into six and seven one- to three-case (i.e. participant) clusters, respectively. Except for two UK and five US cases showed erratic responses to the taste stimuli and, hence, excluded from further analysis, the phenotype-specific classification criteria we have described elsewhere in detail (Iatridi et al., 2019a) and which embody the principles of sensitivity and specificity analysis for the identification of the dyads of sucrose concentration and cut-off liking scores that best discriminate between the three distinct sweet-liking phenotypes were used to re-classify the remainder

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[2] The details regarding the outcome of the HCA and the sensitivity/specificity analysis were not part of the manuscript submitted to PNAS to be considered for publication.

cases as either SLs, IU, or SDs. Indeed, plotting liking against sucrose concentration revealed that for participants whose hedonic responses were initially considered to be heterogeneous from those of the three main clusters, liking curves were either steeper or slightly shifted to the left or right compared to those of the three main sweet-liking phenotypes. The prediction value of the +15/-15 cut-off liking scores on the -50 to +50 VAS (SL: 97.7 percentage sensitivity and 93.5 percentage specificity for the +15 liking score; SD: 90.9 percentage sensitivity and 93.9 percentage specificity for the -15 liking score; interclass correlation coefficient: .763 95%CI [.662, .832]) alongside the good reproducibility of the 1 M sucrose reported in Iatridi et al. (2019a) for the UK cohort were confirmed in the US sample, too (SL: 96.3 percentage sensitivity and 95.3 percentage specificity for the +15 liking score; SD: 92.3 percentage sensitivity and 95.4 percentage specificity for the -15 liking score; interclass correlation coefficient: .881 95%CI [.820, .920]).

When each phenotype was examined separately, participants in the UK and in the US shared very similar hedonic response patterns. In particular, repeated measures ANOVA showed no interaction effect between sucrose concentration and country on liking (SL: $F(4.75, 341.74) = 2.060$, $p = .074$, $\eta p^2 = .028$; SD: $F(4.07, 228.01) = .900$, $p = .466$, $\eta p^2 = .016$; IU: $F(3.93, 522.45) = 1.869$, $p = .116$, $\eta p^2 = .014$); all within-phenotypes between-cohorts contrasts per sucrose concentration were non-significant save one: participants in the UK cohort who were classified into the inverted-U group liked 1 M sucrose solution more than the comparable sub-group in the US cohort (UK: $M = -1.74$, $SEM = 1.389$; US: $M = 2.60$, $SEM = 1.480$; $t(133) = -2.137$, $p = .034$). Water also tended to be rated as less unpleasant by SLs in the UK cohort compared to those in the US cohort (UK: $M = -4.08$, $SEM = 1.607$; US: $M = -9.99$, $SEM = 2.660$; $t(46.6) = 1.902$, $p = .063$).
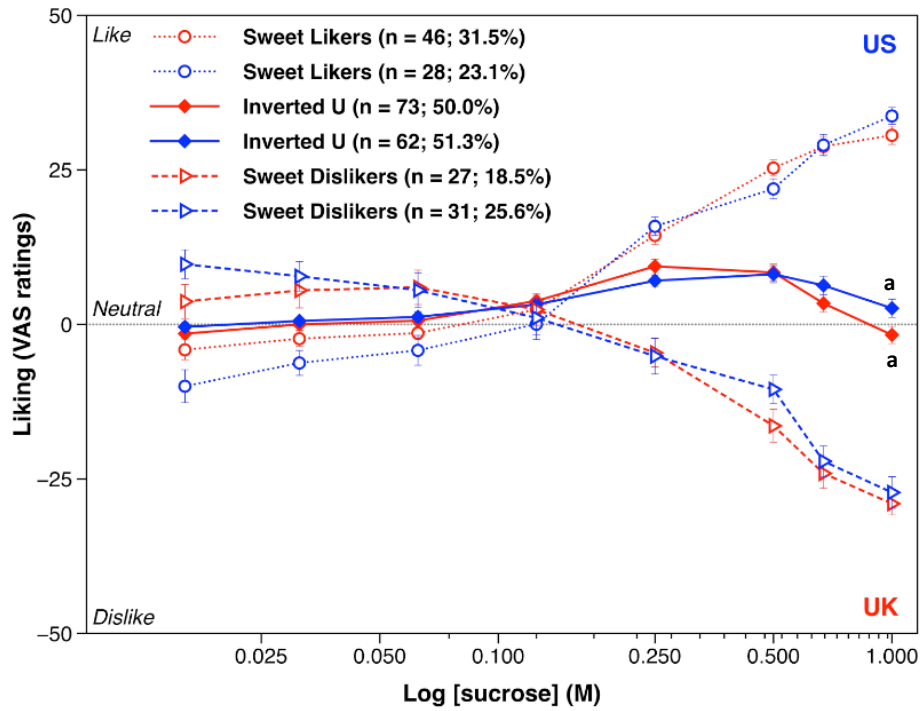
Fig. 4.1 Liking ratings (mean ± standard error of the mean) as a function of sucrose solutions by the three sweet-liker phenotypes by cohort.

Ratings were averaged across the two taste test blocks prior to clustering. Blue and red features represent ratings recorded in the US and the UK, respectively. The response pattern for the sweet-liker phenotype is displayed with a dotted line, the response pattern of inverted U-shaped phenotype with a solid line, and the response pattern of sweet disliker phenotype with a dashed line. Liking ratings within a sweet-liker phenotype that share a letter significantly differ.

4.3.2 Effect of phenotype and country on participant characteristics

4.3.2.1 Demographics

Across phenotypes, sex (χ^2(2, N = 267) = 6.541, p = .038) and ethnicity (χ^2(6, N = 267) = 14.050, p = .029) were significantly different. As shown in Figure 4.2, men were more often SLs than SDs, while participants self-identified as Asians were twice as likely to be SDs as SLs; for Caucasians, IU phenotype was the most prevalent, followed by the SL and the SD phenotype. ANOVA showed no effect of phenotype on age (F(2,264) = .863, p = .423).
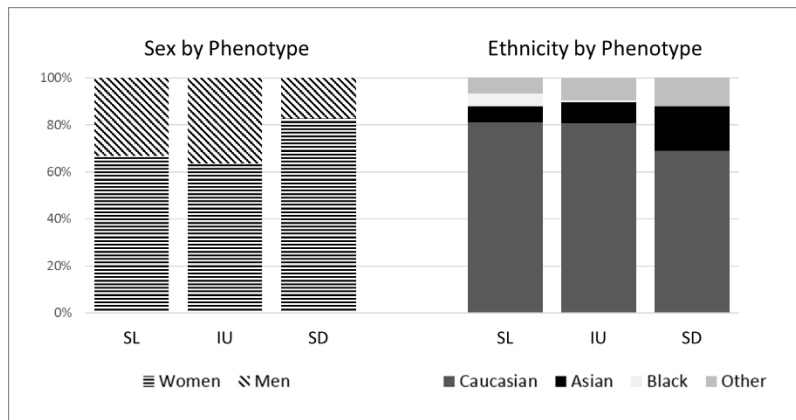
Fig. 4.2 Proportion (%) of sexes and ethnicities by phenotype

4.3.2.2 Anthropometry

Age was found to contribute significantly to the regression models predicting each anthropometric measure by phenotype with all associated changes in F-values being significant (Table 4.1). To further explore this moderating hypothesis, a median split on age was used to categorise participants into younger and older groups. A phenotype by age group interaction was found for BMI (F(2,244) = 3.034, p = .050, ηp^2 = .024), as well as for BodyFat (F(2,243) = 3.506, p = .032, ηp^2 = .028), FFM (F(2,243) = 4.315, p = .014, ηp^2 = .034), WC (F(2,243) = 3.413, p = .035, ηp^2 = .027), and waist to hip ratio (F(2,243) = 2.764, p = .065, ηp^2 = .022), in models adjusting for sex. In plotting these interactions, it was apparent the effect of sweet-liker phenotype on the anthropometric measures was in opposite directions for participants who were younger or older. In contrast, in phenotype by country models,

there was no evidence of interactions between country and phenotype for any of the anthropometric measures under investigation: BMI ($F(2,244) = 2.186$, $p = .115$), BodyFat ($F(2,243) = 2.340$, $p = .098$), FFM ($F(2,243) = 0.623$, $p = .537$), WC ($F(2,243) = 1.997$, $p = .138$), and waist to hip ratio ($F(2,243) = 1.087$, $p = .339$).

Table 4.1 Interaction effects of age on phenotypic differences in anthropometric measures

	B (SE)	β	95% CI (Lower Bound, Upper Bound)	t	p	R^2
log10BMI						
Step 1						.004
Constant	1.378 (.013)		(1.353, 1.403)	109.235	.000	
Phenotype	-.006 (.006)	-.060	(-.018, .006)	-.941	.348	
Step 2						.084
Constant	1.004 (.081)		(.8441, .164)	12.344	.000	
Phenotype	-.008 (.006)	-.084	(-.020, .003)	-1.379	.169	
log_{10}Age	**.282 (.061)**	**.284**	**(.162, .401)**	**4.648**	**.000**	
Total Body Fat						
Step 1						.377
Constant	16.674 (1.331)		(14.051, 19.296)	12.523	.000	
Phenotype	.137 (.605)	.011	(-1.055, 1.328)	.226	.821	
Sex	11.280 (.923)	.616	(9.461, 13.098	12.218	.000	
Step 2						.410
Constant	-15.671 (8.415)		(-32.246, .905)	-1.862	.064	
Phenotype	-.134 (.592)	-.011	(-1.301, 1.033)	-.226	.821	
Sex	12.090 (.922)	.661	(10.275, 13.906)	13.117	.000	
log_{10}Age	**24.069 (6.188)**	**.195**	**(11.881, 36.257)**	**3.890**	**.000**	
Fat Free Mass						
Step 1						.687
Constant	64.653 (1.130)		(62.426, 66.880)	57.190	.000	
Phenotype	-1.150 (.514)	-.080	(-2.161, -.138)	-2.238	.026	
Sex	-17.920 (.784)	-.817	(-19.464, -16.377)	-22.861	.000	

Step 2					.693
Constant	48.277 (7.286)		(33.927, 62.627)	6.626	.000
Phenotype	-1.287 (.513)	-.089	(-2.297, -.276)	-2.509	.013
Sex	-17.510 (.798)	-.798	(-19.082, -15.938)	-21.943	.000
log_{10}Age	**12.186 (5.357)**	**.082**	**(1.635, 22.738)**	**2.275**	**.024**

Waist Circumference

Step 1					.093
Constant	84.888 (2.190)		(80.575, 89.202)	38.765	.000
Phenotype	-.999 (.995)	-.061	(-2.958, .961)	-1.004	.316
Sex	-7.582 (1.518)	-.304	(-10.573, -4.592)	-4.994	.000
Step 2					.171
Constant	18.948 (13.611)		(-7.861, 45.757)	1.392	.165
Phenotype	-1.551 (.958)	-.095	(-3.438, .336)	-1.619	.107
Sex	-5.930 (1.491)	-.238	(-8.866, -2.994)	-3.978	.000
log_{10}Age	**49.070 (10.008)**	**.292**	**(29.358, 68.782)**	**4.903**	**.000**

Waist to Hip Ratio

Step 1					.149
Constant	.836 (.014)		(.809, .863)	60.172	.000
Phenotype	-.007 (.006)	-.066	(-.019, .005)	-1.114	.266
Sex	-.062 (.010)	-.381	(-.081, -.043)	-6.471	.000
Step 2					.178
Constant	.562 (.089)		(.387, .737)	6.335	.000
Phenotype	-.009 (.006)	-.087	(-.022, .003)	-1.493	.137
Sex	-.055 (.010)	-.339	(-.075, -.036)	-5.708	.000
log_{10}Age	**.204. (065)**	**.185**	**(.075, .332)**	**3.124**	**.002**

BMI, Body Mass Index; CI, Confidence Interval; SE, Standard Error

As shown in Figure 4.3c, in participants aged 21 years and older, post hoc analyses accounting for sex showed that, when compared to SDs (US: M = 49.76 kg, SEM = 1.48 kg; UK M = 51.84 kg, SEM = 1.79), SLs in the US had (M = 56.55 kg, SEM = 1.72 kg; p = .005) and those in the UK tended to have (M = 56.44 kg, SEM = 1.49 kg; p = .056) greater FFM. FFM was also greater in SLs relative to IUs, but significance was achieved only in the US cohort (p = .010). Critically, despite that, in the UK cohort, those 21 years old and older comprised only 33% of the sample, models for the effect of phenotype on FFM revealed medium to large effect sizes in both countries (UK: ηp^2 = .094; US: ηp^2 = .111; Table 4.2). Regarding phenotypic differences in obesity related measures (Figure 4.3a,b,d), in the US cohort, older SLs had higher BMIs by 4.3 kg/m^2, BodyFat by 7.0%, WC by 14.11 cm, and waist to hip ratio by 0.07 (BMI: p = .007; BodyFat: p = .010; WC: p = .003; waist to hip ratio: p = .025) when compared to the SDs. While older SLs in the UK cohort also appeared to have worse anthropometric profiles relative to SDs, this was not confirmed statistically for any obesity-related anthropometric measurements of interest.

As expected from the 2-way ANCOVAs that indicated an interaction effect of age group on the relationship between sweet-liker phenotypes and anthropometric measures, SDs younger than 21 years old recruited in the UK had significantly higher BodyFat (M = 27.9%, SEM = 1.3%) than those in the SL (M = 24.5%, SEM = .9%, p = .030) and the IU (M = 23.0%, SEM = .8%, p = .001) phenotypes; in fact, phenotype explained nearly 11% of the variance in BodyFat among participants less than 21 years after we partialled out sex effects (Table 4.2). In contrast, this was not seen for the younger US participants: despite SDs having higher BodyFat by 1.16 and 1.22 percentage units when compared with SL or IU phenotypes, respectively, the post hoc tests were not significant. However, the low representation of the younger age group in the US cohort (27.5%) may have reduced statistical power from 84% for the relevant ANCOVAs in the UK to 8% in the US. Indeed, when the effect of phenotype on BodyFat was examined in the two populations combined, a significant effect of phenotype was found ($F(2,121)$ = 3.062, p = .050, ηp^2 = .048).

Sweet Likers (SL)   Inverted-U (IU)   Sweet Dislikers (SD)

(a) BMI (kg/m²)

(c) Fat Free Mass (kg)

(b) Total Body Fat (%)

(d) Waist Circumference (cm)
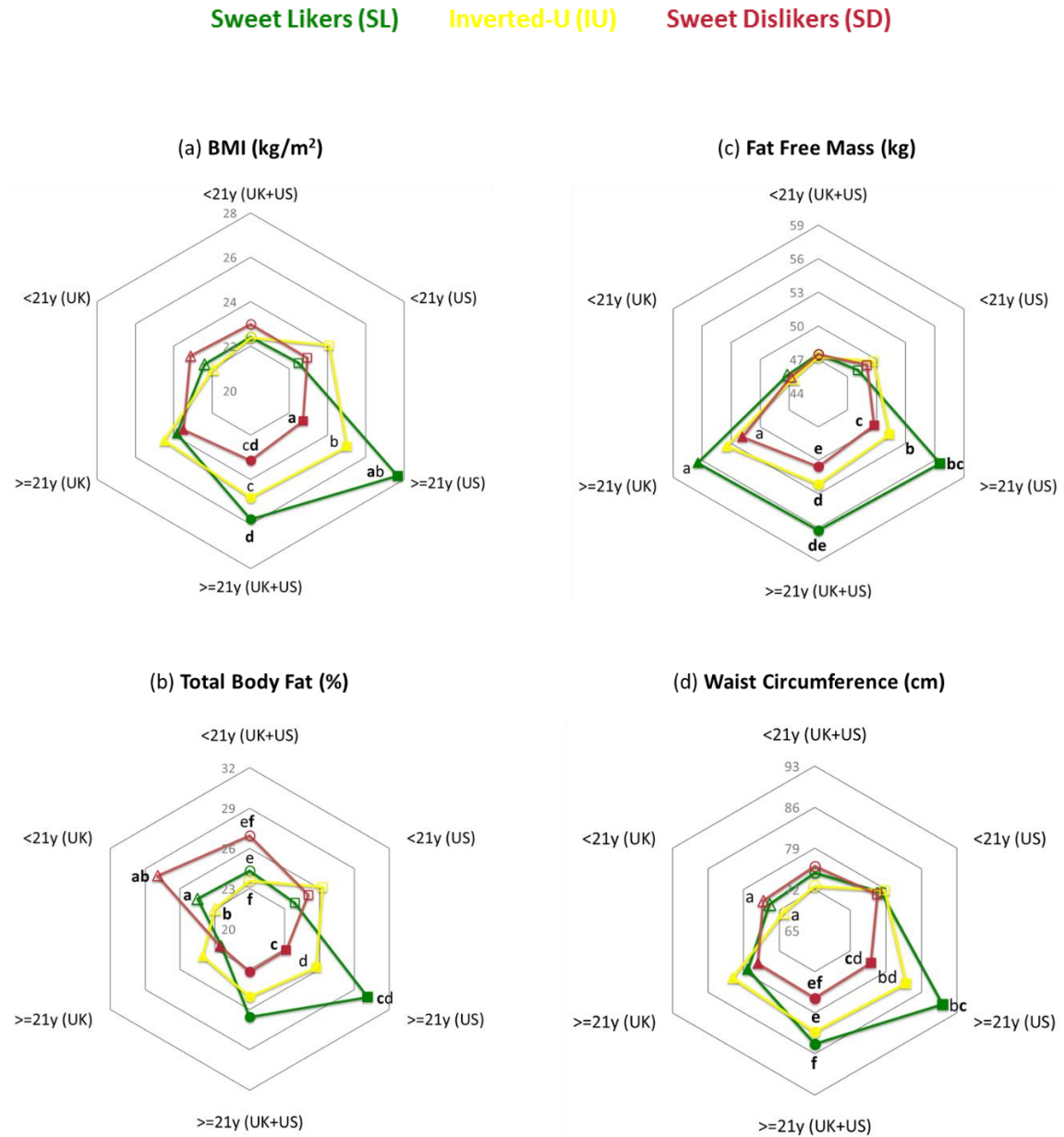
Fig. 4.3a-d A comparison of the follow-up effects of sweet-liker phenotype on the anthropometric profile for the two cohorts separately and for the sample as a whole (UK and US) plotted by age group.

Spider plots show the estimated marginal mean values of (a) BMI (kg/m2) and of (b) Total Body Fat (%), (c) Fat Free Mass (kg), and (d) Waist Circumference (cm) adjusted for sex. Examining each spider plot separately, same letters indicate significant differences (p < .05; bold) or tendencies (p < .075) in the paired post hoc comparisons. For BMI, highlighted p-values correspond to analysis of variance of BMI's natural logarithm; original BMI values are used for graphical representation only. BMI, body mass index.

Table 4.2 Adjusted main effects (one-way analysis of covariance) of sweet-liker phenotype on anthropometrics per age group per country and for the entire sample.

	< 21 y					≥ 21 y				
	F	*df*	*p*	*ηp²*	*n*	*F*	*df*	*p*	*ηp²*	*n*
log₁₀BMI										
Overall[1]	.427	2	.653	.007	125	*3.040*	2	*.051*	.047	125
UK	.987	2	.377	.021	95	.252	2	.778	.012	46
US[1]	.326	2	.725	.024	30	**3.820**	2	**.026**	**.091**	79
Total Body Fat										
Overall	**3.062**	2	**.050**	.048	125	1.521	2	.233	.025	125
UK	**5.502**	2	**.006**	**.108**	95	.375	2	.690	.018	46
US	.245	2	.784	.019	30	**3.557**	2	**.033**	**.087**	79
Fat Free Mass										
Overall	.044	2	.957	.001	125	**6.524**	2	**.002**	**.097**	125
UK	.165	2	.848	.004	95	2.176	2	.126	**.094**	46
US	.190	2	.828	.014	30	**4.679**	2	**.012**	**.111**	79
Waist Circumference										
Overall	1.612	2	.204	.026	125	**3.194**	2	**.044**	.050	125
UK	2.309	2	.105	.048	95	1.221	2	.305	.055	46
US	.037	2	.964	.003	30	**4.598**	2	**.013**	**.109**	79
Waist to Hip ratio										
Overall	1.080	2	.343	.018	125	*2.761*	2	*.067*	.044	125
UK	.717	2	.491	.016	95	1.438	2	.249	**.064**	46
US	.240	2	.788	.018	30	*2.983*	2	*.057*	**.074**	79

Statistically significant results (*p* > .05) and medium or large effect sizes ($ηp²$ > .06) are bolded.
[1]F statistics from analysis of variance (no adjustment for sex). BMI, body mass index.

Finally, as shown in Figure 4.3c, FFM was greater in older SLs (M = 54.9 kg, SEM = 1.1 kg) versus younger SLs (M = 50.4 kg, SEM = .9 kg, p = .004) across counties, with older SLs being also heavier for their height (M = 25.8 kg/m^2, SEM = 0. 8 kg/m^2 and M = 22.4 kg/m^2, SEM = 0.4 kg/m^2, p < .001 for older and younger SLs, respectively) and with higher BodyFat (M = 27.4%, SEM = 1.3% and M = 22.3%, SEM = 1.0%, p = .004 for older and younger SLs, respectively) than younger SLs. Relevant contrasts between older and younger SDs did not reveal significant differences either in FFM (p = .725), BMI (p = .876) or BodyFat (p = .671).

4.3.2.3 Behaviour, lifestyle, and diet

Analysis so far suggests hedonic responses to sweetness may reflect body composition and/or sizes, but this occurs in an age-specific manner. To interpret these observations, contributions of behaviour, lifestyle, and diet were considered.

First, the younger and older groups reflected shorter and longer periods of exposure to the obesogenic environment: participants younger than 21 years old scored lower in restraint eating (t(261) = -2.471, p = .014), whereas they reported sleeping 31 minutes more per day (t(216.84) = 3.643, p < .001) and being non-dieters more often (X^2 (1, N = 263) = 3.526, p = .060) relative to participants aged 21 years or older. Additionally, in the US cohort frequency of weight gain equal or greater than 10% among those 21 years old or older tended to correlate with phenotype (χ^2(4, N = 86) = 8.819, p = .066) with only 1 of 5 SLs never experienced such a change in their body weight as opposed to 2 of 3 SDs (data not available for the UK cohort). Due to the multifaceted role of restrained eating in food and weight regulation (Bryant et al., 2019), the dependence of restraint eating on disinhibition was also investigated. Unlike in the older subgroup (r = .308, p < .001), restraint scores did not correlate significantly with the disinhibition subscale of the TFEQ for participants younger than 21 years old (r = .142, p = .107). Similarly, a higher proportion of the US cohort regularly skipped breakfast (US: 14.5%; UK: 4.8%; χ^2(2, N = 270) = 7.622, p = .022) and reported a shorter sleep duration than the UK cohort (US: M = 8.29 hours/day, SEM = .075

hours/day; UK: M = 8.84 hours/day, SEM = .104 hours/day; $t(265)$ = -4.147, p < .001); differences remained significant after controlling for age. Specifically, the US cohort was characterised by higher dietary restraint ($F(1, 267)$ = 7.097, p = .008, ηp^2 = .026) and lower scores on the TFEQ-hunger scale ($F(1, 267)$ = 4.066, p = .045, ηp^2 = .015), lower attentional and non-planning impulsivity ($F(1, 267)$ = 4.973, p = .027, ηp^2 = .018 and $F(1, 267)$ = 19.847, p < .001, ηp^2 = .069 respectively) and weaker seeking for intensity and novelty in life experiences ($F(1, 267)$ = 3.810, p = .052, ηp^2 = .014 and $F(1, 267)$ = 12.078, p = .001, ηp^2 = .043, respectively), independently of age.

Regarding participant characteristics by phenotype across cohorts, no phenotypic differences in lifestyle habits were found (breakfast skipping: $\chi^2(4, N = 263)$ = 1.873, p = .759; sleeping duration: $F(1, 257)$ = .929, p = .396; dieting: $\chi^2(2, N = 263)$ = 2.338, p = .311; physical activity level: $\chi^2(4, N = 263)$ = 2.809, p = .590). Conversely, relevant ANOVAs for behavioural characteristics, revealed significant effects of phenotype on reward sensitivity ($F(2,260)$ = 5.616, p = .004, ηp^2 = .041), intensity seeking ($F(2,260)$ = 4.163, p = .017, ηp^2 = .031), and TFEQ-hunger ($F(2,260)$ = 11.705, p < .001, ηp^2 = .083). Results of ANCOVA on the effects of phenotype on trait hunger while controlling for effects of pre-test hunger, were also significant ($F(2,259)$ = 11.757, p < .001, ηp^2 = .083). Post hoc tests revealed that SLs scored higher on these three behavioural subscales than SDs did, whilst contrasts between SLs and IUs were only significant for TFEQ-hunger, i.e. trait hunger (Figure 4.4). Critically, SLs maintained these elevated values across age groups (TFEQ-hunger: $t(72)$ = .025, p = .980; intensity seeking: and $t(72)$ = .489, p = .627). Likewise, no interaction effect of age group neither of country on the differences of trait hunger (phenotype x age group: $F(2,257)$ = .850, p = .428; phenotype x country: $F(2,257)$ = .450, p = .638) and intensity seeking (phenotype x age group: $F(2,257)$ = .787, p = .457; phenotype x country: $F(2,257)$ = .810, p = .446) by phenotype were observed. For reward sensitivity, age group strongly interacted with phenotype for reward sensitivity ($F(2,257)$ = 8.562, p < .001, ηp^2 = .062) with higher values recorded in our older subgroup; a parallel interaction was not seen for country ($F(2,257)$ = .971, p = .380).
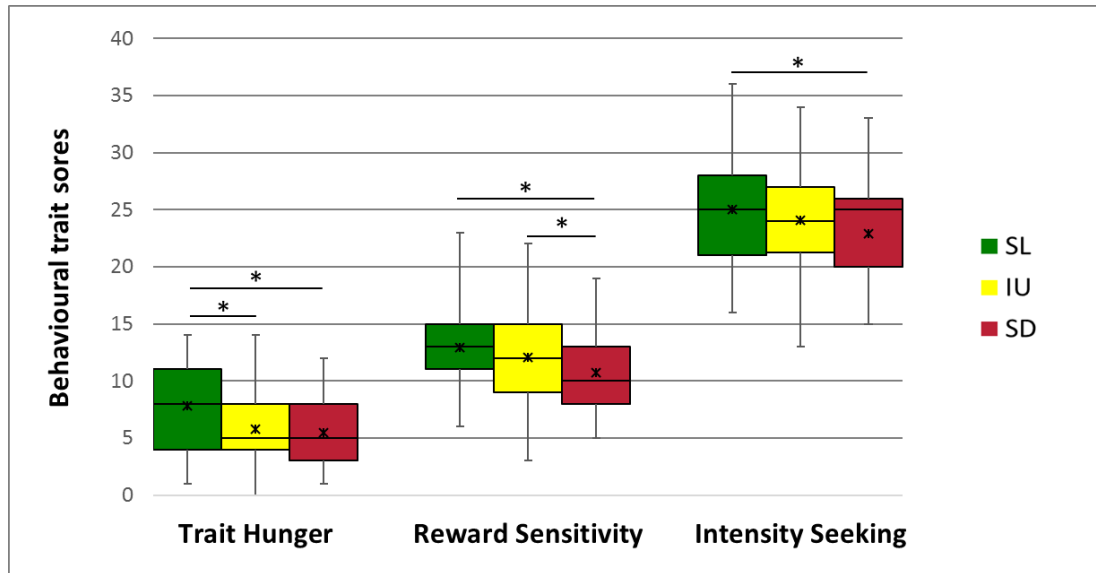
Figure 4.4 A comparison of selected behavioural traits across the three distinct sweet-liker phenotypes.

Boxplots compares the mean scores (✳ symbol in each box) of trait hunger, reward sensitivity, and intensity seeking by phenotype across the entire sample (UK and US cohort combined). Boxes are the interquartile ranges, whiskers represent the minimum and maximum score of each behavioural trait, and solid lines indicate the medians. Significant differences ($p < .05$) in the paired post hoc comparisons are denoted with an asterisk (*).

To test a possible role of diet on observed relationships between sweet-liking patterns and anthropometry, we examined self-reported use of beverages. Due to difference in the legal drinking age in the UK and the US, analyses related to habitual intake of alcoholic drinks were restricted to participants 21 years old and older. Country- and phenotypic differences in beverage habitual intake are shown in Table 4.3.

Table 4.3 Food frequency data by phenotype and by country.

	All[1]	SL	IU	SD
			Mean (SEM)	
Fruit juice (glasses/week)				
Overall	1.65 (0.16)	1.64 (0.21)	1.66 (0.27)	1.60 (0.38)
UK	2.04 (0.28)[†]	1.68 (0.28)	2.09 (0.45)	2.35 (0.77)
US	1.20 (0.14)	1.56 (0.33)	1.13 (0.21)	0.96 (0.22)
Concentrated juice drinks, or any juice drink with added sugar (glasses/week)				
Overall	1.35 (0.24)	1.57 (0.58)	1.25 (0.34)	1.36 (0.37)
UK	1.25 (0.33)	0.85 (0.19)	1.49 (0.61)	1.37 (0.69)
US	1.47 (0.36)[†]	2.75 (1.48)	0.97 (0.18)	1.35 (0.38)
Energy/Sports drinks or sweetened caffeinated drinks (glasses/week)				
Overall	0.61 (0.06)	0.65 (0.12)	0.51 (0.04)	0.82 (0.20)
UK	0.53 (0.06)	0.53 (0.10)	0.50 (0.07)	0.64 (0.22)
US	0.70 (0.11)[†]	0.84 (0.28)	0.52 (0.06)	0.96 (0.33)
Soft drinks (glasses/week)				
Overall	1.30 (0.12)	1.07 (0.14)	1.35 (0.19)	1.57 (0.31)
UK	1.24 (0.17)	0.94 (0.16)	1.39 (0.29)	1.41 (0.40)
US	1.37 (0.18)	1.29 (0.25)	1.29 (0.25)	1.71 (0.46)
Diet soft drinks (glasses/week)				
Overall	1.20 (0.20)	1.42 (0.57)	1.33 (0.25)	0.74 (0.14)
UK	1.10 (0.16)	1.05 (0.18)	1.26 (0.29)	0.83 (0.23)
US	1.33 (0.39)	2.02 (1.49)	1.42 (0.42)	0.67 (0.16)
Tea or coffee (cups/day)				
Overall	1.61 (0.09)	1.35 (0.15)	1.69 (0.14)	1.73 (0.18)
UK	1.90 (0.13)[†]	1.63 (0.21)	1.96 (0.20)	2.22 (0.24)
US	1.26 (0.11)	0.90 (0.17)	1.36 (0.18)	1.32 (0.25)
Wine (glasses/week)[2]				
Overall	1.98 (0.18)	1.95 (0.31)	1.85 (0.29)	1.89 (0.32)
UK	1.54 (0.41)	1.52 (0.45)	1.58 (0.74)	1.46 (0.56)
US	2.21 (0.18)[†]	2.27 (0.43)	1.99 (0.23)	2.10 (0.39)

Beer, cider, or cooler (half pints/week)[2]

Overall	2.62 (0.19)	2.52 (0.40)	2.81 (0.25)	2.34 (0.47)
UK	2.45 (0.33)	3.20 (0.73)	2.20 (0.42)	2.05 (0.66)
US	2.70 (0.23)	2.03 (0.43)	3.11 (0.31)*	2.49 (0.64)

Spirits/hard liquor (shots/week)[2]

Overall	1.30 (0.17)	2.00 (0.61)	1.25 (0.17)	0.83 (0.16)
UK	1.60 (0.43)	3.25 (1.33)*	1.18 (0.37)	0.47 (0.09)
US	1.14 (0.13)	1.10 (0.35)	1.29 (0.19)	1.01 (0.23)

The asterisk (*) indicates a significant effect ($p < .05$ for one-way ANOVAs) of phenotype on frequency of consumption of the item under investigation within each row. The dagger (†) denotes a cross country significant difference ($p < .05$ for Student t-tests) in the frequency of consumption of the relevant item under investigation.

To facilitate interpretation of the food frequency data, the non-log transformed values are displayed while they are coded as a weekly consumption of a standard portion; habitual intake of tea or coffee is expressed in daily units.

[1] Data presented refer to the study samples before the clustering process i.e. participants with erratic responses to the sweet taste test are included.

[2] Data presented are for the subgroup of participants aged 21 or older only.

To identify dietary predictors that significantly improved fit of anthropometry-specific regression models, multiple linear regression with forced entry was used for the anthropometric measures and in the sub-cohorts that phenotype-specific differences had emerged (Figure 4.3a-d, Table 4.2). After dummy variable transformations using SL phenotype as the baseline group against which IU and SD groups would be compared, adding the frequency of beverage intake of younger participants to prediction models of BodyFat resulted in an increase in F statistic by just .187 ($p = .992$) and .472 ($p = .796$) for the UK subgroup and the entire sample younger than 21 years old, respectively; no diet-related predictors emerged. From this, we can conclude relationships between sweet-liker phenotype and BodyFat for participants younger than 21 years old did not significantly change as a function of beverage intake. Conversely, among participants 21 years old and older tested in the US, sweetened fruit beverages (e.g. concentrated juice drinks, juice drinks with added sugar) were a significant predictor of BMI ($\beta = .248$, 95% CI [.000, .041], $t = 2.012$, $p = .048$, $R^2 = .325$) and WC ($\beta = .300$, 95% CI [.926, .7.571], $t = 2.552$, $p = .013$, $R^2 = $

.248) with the models including the dietary factors explaining 15.7% and 20.2% additional variance in BMI and WC between phenotypes; further, frequency of intake of soft drinks tended to predict BodyFat, (p = .057 and p = .054 for regular and diet soft drinks, respectively). For ease of interpretation, we discuss the relevant data without log-transformation: for older participants in the US, as intake of sweetened fruit beverages increased by one standard deviation (i.e. by 0.2 glasses per week, or 9.2 glasses per year), BMI increased by 0.25 and WC by 0.30 standard deviations or simply by 0.30 kg/m^2 and 4.1 cm, respectively. Examining the relevant prediction models among participants 21 years or older from both countries on BMI and WC, intake of sweetened fruit beverages (BMI: β = .182, 95% CI [.000, .030], t = 1.978, p = .050, R^2 = .172; WC: β = .239, 95% CI [.957, 5.838], t = 2.758, p = .007, R^2 = .278) and diet soft drinks (BMI: β = .188, 95% CI [.001, .028], t = 2.133, p = .035, R^2 = .172; WC: β = .178, 95% CI [.184, 4.534], t = 2.149, p = .034, R^2 = .278) all impacted the relationship between sweet-liking phenotypes and BMI and WC.

Regarding the real life intake of different macronutrients in the UK cohort, with the exception of fibre intake which was estimated to be highest among SDs (p = .52 and p = .43 for the post hoc comparisons between SDs and SLs and between SDs and IUs, respectively), analysis of 24h recalls failed to identify any other effect of phenotype on the diet (Table 4.4).

Table 4.4 Macronutrient data from 24h recalls by phenotype (UK only).

	All (N = 143)[1,2]	SL (n = 46)[2]	IU (n = 70)[2]	SD (n = 25)[2]
		Mean (SEM)		
Energy (kcal)	2133 (44)	2164 (79)	2146 (64)	2089 (104)
Carbohydrates (%EI)	45.2 (0.6)	46.9 (1.1)	44.4 (0.8)	44.3 (1.5)
Total sugars (%EI)	16.7 (0.4)	17.4 (0.9)	16.0 (0.5)	17.1 (0.9)
Total sugars (%CHO)	37.0 (0.8)	36.9 (1.5)	36.0 (1.1)	39.0 (1.9)
Non-milk sugars[3] (%EI)	13.5 (0.4)	14.0 (0.8)	12.9 (0.5)	13.8 (0.8)
Non-milk sugars[3] (%CHO)	29.8 (0.7)	29.5 (1.5)	29.1 (0.9)	31.3 (1.5)
Fibre (g/100 g product)	1.47 (0.22)	1.24 (0.39)	1.27 (0.25)	2.50 (0.70)*
Fats (%EI)	38.9 (0.5)	37.9 (0.9)	39.0 (0.8)	40.4 (1.4)
Proteins (%EI)	15.1 (0.3)	14.8 (0.5)	15.5 (0.4)	14.6 (0.7)

The asterisk (*) indicates a significant difference in post hoc comparisons ($p < .05$) in the intake of the relevant item under investigation.

[1] Data presented refer to the study samples before the clustering process i.e. participants with erratic responses to the sweet taste test are included.

[2] Data presented are for participants with available 24h recall data for all three days (two weekdays and one weekend day).

[3] Non-milk sugars constitute of all simple sugars but lactose.

CHO, Carbohydrates; EI, Energy Intake

4.4 Discussion

4.4.1 General findings

In both cohorts tested, we confirmed the existence of three distinct hedonic response patterns to stimuli of varied sweetness: the SL, inverted U, and SD phenotypes. Regarding the link between sweet-liking and weight status or body composition, our data fail to support a simple model where sweet-liking always leads to obesity. In fact, we provide novel evidence that FFM is potentially the main anthropometric measure involved in the pattern of hedonic response to sweetness. Further, our data suggest that the effect of phenotype on body composition varies with age. In the younger group, SDs presented with the highest BodyFat, whereas for the older subgroup, SLs had higher BMI, WC, and FFM. Here, increased age appeared to reflect behavioural and lifestyle indices typical of increased exposure to an obesogenic environment. Intake of sweet-tasting beverages partially mediated the phenotypic differences in obesity-related anthropometric measures, but only in the older subgroups (i.e., those with longer exposure to an obesogenic environment). Finally, we identified behavioural characteristics that may explain the phenotypic differences in anthropometrics: SLs had enhanced sensitivity to rewarding stimuli and characteristics analogous to those of high interoceptive performers.

4.4.2 What do sweet-liking patterns can tell us about individual variation in anthropometry?

To the best of our knowledge, this is the first study to consider a role of FFM in taste hedonics. Highlighting a potentially important determinant of the link between level of liking for sweet taste and anthropometry, here, we report a strong effect of sweet-liker phenotype on FFM in participants 21 years and older. Further, consistent results from both cohorts indicated that the greatest FFM was observed in participants classified as SLs.

Regarding the mechanisms underlying these effects, they might root in biology. For example, to maintain energy balance, FFM with its known contribution to daily energy requirements (Ravussin et al., 1986), exerts orexigenic effects and thus promotes energy

intake, as opposed to fat mass, which may have an inhibitory role in appetitive control (Stubbs et al., 2018). Specific adaptations in eating behaviour/patterns consistent with ensuring higher energy intake such as larger self-determined meal sizes (Blundell et al., 2012) or higher eating rate (Henry et al., 2018) have been positively associated with FFM; such links have been absent for BodyFat and/or BMI. Consistent with the idea that the body is tuned to prioritise signals deriving from FFM over those from fat mass, FFM has also been suggested to relate to neuronal density in brain areas involved in homeostatic regulation and eating behaviour independently of fat mass (Weise et al., 2013). The phenomenon of collateral adiposity or simply 'fat overshooting', where the potent internal signal for recovery of FFM after weight loss induces overeating and consequently a disproportional increase in fat mass, further emphasizes the critical importance of FFM over fat mass in regulating energy intake (Dulloo et al., 2018). Recently, disliking for low sweetness was proposed to be positively associated with habitual exercise levels (Feeney et al., 2019). Given that, in the absence of differences in BMI or age, active individuals are expected to have relatively higher FFM than those being more sedentary, so it could be theorised that the taste stimulus that signalled the poorest energy content (i.e. the stimulus of low sweetness) was likely to evoke lower liking among more active individuals. Staying with that idea, men have higher levels of FFM compared to women (Bredella, 2017), and strikingly, in our data, we find that, men were classified as SLs significantly more often than women. Similarly, the loss of FFM and relative increase in fat mass in the absence of changes in BMI that occurs with ageing (St-Onge, 2005) might offer an appealing explanation for the often reported inverse relationship between age and liking for sweetness (Deglaire et al., 2015; Garneau et al., 2018).

Here, we also observed significant effects of sweet-liking patterns on multiple obesity-related anthropometric measures. However, the direction of these relationships, was not straightforward. Interaction analysis suggested a dissociation of anthropometric measures by phenotype depending on age. That is, for participants younger than 21 years of age, being classified into the SD phenotype associated with the highest BodyFat percentage, whilst SLs 21 years old and older had significantly higher BMI and WC relative

to SDs (Figure 4.3a-d). Also, the IU phenotype had an equally good anthropometric profile to SLs when younger, and only differed from SLs when older, although they were still presented with anthropometric profiles closer to those of SLs than of SDs. It is tempting to speculate that the interaction between age and phenotype found here may provide an explanation as to why a considerable number of studies seeking to describe how sweet-liking patterns relate to obesity have failed to show consistent results.

Before exploring this hypothesis further, we also note many previous attempts to explore influences of individual differences in sweet-liking on obesity have been marred by discrepancies in classification methods, as recently reviewed (Iatridi et al., 2019b). Similarly, the singular focus of previous studies on BMI – which is now recognised as a poor predictor of adiposity (Okorodudu et al., 2010) – may have further obscured potential relationships between phenotype and adiposity; this view is supported by our finding that the effect of phenotype in our lean young group was seen in differences in BodyFat, but not in BMI. Recently, Garneau et al (2018) also used bioelectrical impedance to assess body composition, and they failed to find any effect of sweet-liker phenotype on BodyFat. However, it is unclear whether their analyses controlled for participant sex, and under what testing conditions they performed bioelectrical impedance analysis; their data came from a community based sample where hydration status was presumably not controlled, which may have added substantial noise to their estimates of the body composition.

Regarding the role of age in the relation between sweet-liking patterns and obesity, other researchers have also found some age-dependent variation in BMI, although these differences failed to reach significance. For example, in Methven *et al*. (Methven et al., 2016) and Asao *et al*. (Asao et al., 2015), SLs had ~3 units greater BMI than SDs, with participants of a median and mean age of 26 and 32 years, respectively. Presumably, such magnitude of difference in BMI would be clinically meaningful. Yeomans and colleagues (Yeomans et al., 2007) analysed a younger cohort and found that SDs were heavier than SLs by 1.4 units. Notably, all of these studies only divided participants into two sweet-liking hedonic response groups. In the NutriNet-Santé cohort, one of the largest ongoing web-based chemosensory studies, liking for natural sweetness expressed as a continuous

variable and assessed via an online questionnaire was negatively associated with self-reported BMI in a sample of over 45k French adults (Deglaire et al., 2015). Consistent with our age-related observation, those authors noticed that in women, the association between liking scores for all factors composing the sweet sensation and BMI differed by age category: in women 18-34 years old, the higher the liking, the lower the BMI whereas the inverse relationship was proposed for those in the 35-54 and >55 years age groups. However, since liking ratings were not inferred from analyses of lab-based sensory tests and even natural sweetness was referred to food entities of enhanced sweetness (e.g. added jam, honey, gingerbread), some caution should be exercised in interpreting these data. In summary, a close inspection of past research suggests sweet-liking may only drive overconsumption in relatively older adults, while in younger individuals, SL is associated with reduced risk of less healthy anthropometric characteristics.

4.4.3 The obesogenic environment approach

How might age modulate the influence of phenotypic differences in sweet-liking on body composition? One possibility relates to increased exposure to an obesogenic environment over time. Here, the older group scored higher in TFEQ restrained eating subscale, and they also reported being on a weight loss diet more frequently and sleeping less. These differences in behaviour and lifestyle are likely associated with the obesogenic environment. Restrained eating is thought to be an adaptive behaviour to an environment of oversupply of easily accessible hyper-palatable foods and of the associated cues that amplify temptation in an obesogenic environment (Bryant et al., 2019). Here, a strong correlation between restrained and disinhibited eating among our older group, alongside their higher rates in dieting frequency compared to younger participants, is consistent with weaker internal regulation of appetite control, which has been hypothesised as a key consequence of the obesogenic environment (Bilman et al., 2017; Sample et al., 2016). Repetitive dieting is also likely to further contribute to the aforementioned paradigm of disordered eating through predisposing weight gain (Pietiläinen et al., 2012) particularly

among normal-weight individuals (Lowe, 2015). That considered, the pro-dieting messages overwhelming Western and Westernised societies may demonstrate an additional link between obesogenic environment and frequency of dieting. Regarding poor sleeping habits, inadequate sleep has been identified as a key feature of modern obesogenic societies (Grandner, 2018). Our finding that older participants had poorer sleeping habits again suggests this age group may be more exposed to multiple aspects of an obesogenic environment.

Considering the central role of exposure to an obesogenic environment in our hypothesis, another finding worth highlighting is the age-specific mediating effect of habitual intake of liquid calories and sweetened non-caloric drinks and beverages. Our analysis suggests that with longer exposure to an obesogenic environment, dietary choices are more likely to contribute to a relationship between sweet-liking and anthropometric outcomes. Furthermore, more subtle anthropometric advantages were observed in younger SLs of the US cohort and diminished disadvantages in older SLs of the UK cohort, pointing to possible involvement of the different effects of the obesogenic environment in the two countries. Indeed, between-country differences in restrained eating, sleeping habits, breakfast consumption, WC, and intensity and novelty seeking were found here. Notably, breakfast skipping is often cited as a component of the modern obesogenic world that may contribute to poor energy regulation (Dhurandhar, 2016), and disproportionate abdominal fat is also believed to be a downstream effect of Western lifestyle (Li & Qi, 2019). If one considers the evidence about the inverse relationship between food neophobia and the personality trait of sensation seeking (Alley & Potter, 2011), lower sensation seeking scores in the US cohort as opposed to the UK cohort might also be a marker of food choices and/or diet quality characteristic of a Western Diet. As such, it may be that alongside age-related duration of exposure, the degree of exposure to the obesogenic environment that is linked to cultural-specific factors may also be important.

Critically, studies dating back more than four decades (i.e., to a time when the obesogenic environment was not cast as a public health issue) have found a significant effect of sweet-liker phenotype on obesity-related characteristics that are consistent with

our data in younger participants (Grinker, 1977; Grinker & Hirsch, 1972; Johnson et al., 1979; Malcolm et al., 1980; Thompson et al., 1976). That is, individuals of normal weight experienced stronger pleasure from high sweetness relative to those with overweight or obesity. In contrast, more recent literature has failed to show any significant relationships (Asao et al., 2015b; Drewnowski et al., 1997; Garneau et al., 2018; Goodman et al., 2018; Methven et al., 2016; Turner-McGrievy et al., 2013; Weafer et al., 2017; Yeomans et al., 2007; Yeomans & Prescott, 2016). Accordingly, we might speculate that recruiting participants of a broad range of ages (i.e. 18-65 years) without accounting for the effect of the exposure to the obesogenic environment may have attenuated links between hedonic responses to sweetness and anthropometric outcomes. For example, in the NutriNet-Santé cohort in France (a country lacking the obesogenic profile of the US and the UK where most previous investigations took place: WHO, 2017), the direction of the relationship between sweet-liking and obesity differ by age group (Deglaire et al., 2015). Collectively, these data suggest the importance of cross-cultural differences must be considered, as they modify the contribution of the external environment to health-related behaviours and outcomes. Clare Llewellyn, the director of the largest twin birth cohort in the UK recently noted: "Somewhat ironically, research into the genetic basis of obesity has revealed more than anything the urgent need for environmental modification." (Llewellyn, 2018).

4.4.4 The alliesthesia and hedonic (non-homeostatic) approach

Above, we provided a framework to show how the obesogenic environment may account for the age-specific effects of sweet-liking on adiposity. However, a conceptual model which can explain observed associations between the distinct sweet-liker phenotypes and anthropometry needs to be elucidated. Our data suggest the answer may lay within SL's distinctive behavioural profiles, a pattern which is characterised by relatively high values of TFEQ-hunger, intensity seeking, and reward sensitivity (Figure 4.4). TFEQ-hunger as a proxy of hunger-driven eating and accordingly of better interoceptive abilities was enhanced in our SLs compared to IU and SD phenotypes, and was unaffected by age.

Previous studies that examined eating behaviour in relation to sweet-liking only reported non-significant results for restrained and/or disinhibited eating (Drewnowski et al., 1997; Drewnowski & Schwartz, 1990; Yeomans et al., 2007; Yeomans & Prescott, 2016). Meanwhile, SLs here scored higher on the intensity subscale of Arnett's Inventory of Sensation Seeking (AISS), which could be interpreted as an indirect measure of behavioural adaptation to internal body signals (Roberti, 2004). Robust empirical data linking sensation seeking and hedonics have only recently become available (Byrnes & Hayes, 2013, 2016) and experiments have focused on oral burn from capsaicin. Consistent with our observation of higher intensity seeking in SLs, a rise in liking for a range of spicy foods as a function of AISS total score has been reported (Byrnes & Hayes, 2013, 2016). Thus, it is possible to explain this pattern of differences by considering the expression of sweet-liking in relation to homeostasis, as classically suggested by Cabanac's work on alliesthesia, which describes a dependent relationship between the need state of the internal body and the perceived pleasure of a stimulus (Cabanac, 1979). Specifically, the relatively low levels of BodyFat in younger SLs may trigger liking for readily available sources of energy, which include sweet-tasting stimuli, whereas the increased FFM in older SLs with its well-established link to increased energy requirements (Ravussin et al., 1986) may overrule the negative feedback from the relatively high fat mass and, hence, formulate positive hedonic responses to high level of sweetness.

Notably, Cabanac did not consider individual sweet-liking patterns when explaining his data on changes in pleasantness as a response to the usefulness of a stimulus (Cabanac, 1979), but his basic principle may be relevant if sweet-liker phenotypes express liking as a function of differences in need-state. That is, those in a high need state would be more likely to be SLs, while those in a low need state would be more likely to be SDs. This would be entirely consistent with early reports that prevalence of the SD phenotype was greater in those who were obese than in those being normal-weight (Johnson et al., 1979; Thompson et al., 1976). More recently, Coldwell and colleagues proposed a similar relationship between sweet-liking and biological/internal needs in adolescents: those classified into the high sucrose preference phenotype showed stronger signs of active

growth, as assessed by a bone-growth biomarker (Coldwell et al., 2009). These findings were later replicated in a cohort of 5-10 year old children (Mennella et al., 2014). Critically, for hedonic responses to sweetness to represent the internal need state of the body, efficient interoceptive mechanisms need to be in place. Growing evidence suggests an association between Western lifestyle and poor interoceptive abilities (Bilman et al., 2017; Sample et al., 2016). While we did not obtain any objective measure of interoception here, in those with shorter exposure to the obesogenic environment (i.e. our younger group), positive hedonic responses to high sweetness (as alliesthesia would dictate) could be interpreted as a reflection of the internal state of the body. Our data may then suggest longer exposure to an obesogenic environment undermines a role for sweetness as an expression of homeostatic state. However, it was notable that the SLs retained relatively high interoceptive abilities, even in the older group. If this holds true, one would expect these presumably intact interoceptive abilities to balance signals from increased FFM against homeostatic mechanisms responding to fat tissue, thereby preventing weight gain.

Our findings suggest a factor that might make SLs less resilient to the temptation of highly liked sweet-tasting foods and drinks is their enhanced reward sensitivity. A conceptual model that distinguishes between the homeostatic and hedonic drives of consumption is the hedonic hunger model; this model posits that desire to eat is expressed in response to seek for pleasure in the absence of physical hunger (Lowe & Butryn, 2007). Thus, higher sensitivity to reward in our SLs may be explained by an underlying stronger pleasure-seeking trait. Indeed, in the current dataset, while heightened reward sensitivity was found in SLs of both age groups, relatively higher scores were observed in the older group who had been exposed to an obesogenic environment for longer. Further, a positive feedback loop between repeated consumption of palatable foods and hedonic hunger through effects on incentive salience (i.e. desire for a rewarding stimulus) has been suggested (Espel-Huynh et al., 2018). Given that sweetened beverages partially explained the relationship between phenotype and anthropometrics among our older participants, but failed to do so in the younger groups, confirm that this might be the case. Essentially, when the obesogenic environment drives food choices, liking for sweetness is likely to be a

stronger determinant of dietary intake, and this might be why SLs end up being heavier while SDs are leaner, at least in older individuals. In other words, hedonic responses to sweetness seem to be driven by the relative balance of two factors: need-state and desire for pleasure as alliesthesia and hedonic hunger would suggest, respectively.

4.4.5 Strength and limitations

Here, we used a statistically robust method to classify participants into groups of distinct sweet-liking patterns. Further, we collected multiple obesity-related anthropometric measures with sensory and anthropometric measures obtained on separate lab visits to ensure all measures were made under optimal testing conditions that is control for extreme hunger or thirst at the time of the taste test and overnight fast and water abstinence for accurate body composition measures. Acknowledging the need for direct between country contrasts to delineate better the effect of different geographical regions on the drivers of obesity (Blüher, 2019), the experimental protocol that was initially designed for the UK was then replicated in a similar population in the US. Some limitations of this study should be noted. While the two cohorts were matched in proportions of women and men, and we controlled for sex in analyses when appropriate, more women than men were recruited. In terms of ethnicity, Caucasians dominated both cohorts and therefore, our findings may not generalise to other ethnic groups. Finally, our exploration of dietary correlates was limited to using FFQs for beverages only, and in the absence of a standardised FFQ suitable for both UK and US populations, relied on the comparability of different FFQs in the two cohorts. Still, since most convincing evidence of sugars' involvement in obesity derives from research on simple sugars consumed in the form of beverages (e.g., Te Morenga et al., 2013), we were able to generate clear and relevant findings from the FFQ data which can extended in the future by more detailed dietary analysis for the different phenotypes.

4.5 Conclusion and future directions

Here, we propose individual variation in liking for sweetness might be a potent candidate towards improved understanding of obesity aetiology. To that end, our findings may be of use in adapting tailored health messaging and promotion to each sweet-liker phenotype. That is, developing behavioural techniques to regulate reward sensitivity in SLs and resetting homeostatic eating in SDs. The observed differential effects of sweet-liking patterns on anthropometry that depend on age or more broadly on the level of exposure to the obesogenic environment (i.e. worse anthropometric measures in younger SDs and older SLs) alongside our novel finding that FFM is the body composition compartment most strongly linked to sweet-liking patterns, should be a focus of attention by future studies.

Author Contributions

V.I. conceptualised and designed the study; M.R.Y., and J.E.H. assisted in study design; V.I. collected the data; V.I. analysed the data and wrote the original draft of the paper; and M.R.Y. and J.E.H. reviewed and edited the paper.

Chapter 5 (Paper 4)

Sweet-likers have enhanced cross-modal interoceptive abilities

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Abstract

There are well known phenotypic differences in sweet-liking across individuals, but it remains unknown whether these are related to broader underlying differences in interoceptive abilities (abilities to sense the internal state of the body). Here, healthy women (N = 64) classified as sweet likers (SLs) or sweet dislikers (SDs) completed a bimodal interoception protocol. A heartbeat tracking and a heartbeat discrimination task determined cardiac interoception; both were accompanied by confidence ratings. A water load task, where participants consumed water to satiation and then to maximum fullness was used to assess gastric interoceptive abilities. Motivational state, psychometric characteristics and eating behaviour were also assessed. SLs performed significantly better than SDs on both heartbeat tasks, independently of impulsivity, anxiety, depression, and alexithymia. No differences in metacognitive awareness and subjective interoceptive measures were found. With gastric interoception, SLs were more sensitive to stomach distention, and they ingested less water than SDs to reach satiety when accounting for stomach capacity. SLs also scored higher on mindful and intuitive eating scales and on emotional eating particularly in response to negative stimuli; emotional overeating was fully mediated via interoceptive performance. Overall, our data suggest the SL phenotype may reflect enhanced responsiveness to internal cues more broadly.

5.1 Introduction

Food choice and intake typically occur in response to need for energy and pleasure seeking, although other factors also play a role (Berthoud et al., 2017). Specifically, bottom-up processes activate positive and negative feedback loops which trigger satiety and hunger cues until energy equilibrium is achieved (Fantino, 1984). From the intake-promoting aspects of homeostatic eating, internal energy reserves such as the amount of fat tissue, as the lipostatic model proposed (Kennedy, 1953), and acute metabolic requirements communicated through peripheral hormones and metabolites (e.g. glucagon-like-peptide-1, peptide YY, cholecystokinin, glucose, amino acids, insulin, ghrelin, leptin) dominate (Williams & Elmquist, 2012). Pleasure seeking, on the other hand, elicits enhanced appetitive responsiveness to highly palatable foods – i.e. foods being rewarding for the hedonic system in the brain, often beyond homeostatic needs (Lowe & Butryn, 2007). While some have argued that the obesity epidemic has occurred among increased availability of highly palatable foods in Western and Westernising societies, suggesting an increasing role for hedonic drive in the control of food intake (Yeomans et al., 2004), need-state still remains a critical aspect of human feeding behaviour (Berthoud et al., 2017). Moreover, the obesogenic environment puts pressure on the homoeostatic regulatory system: we misinterpret or confound internally generated nutritional and metabolic signals being unable to monitor food choice and intake in accordance to need state (Bilman et al., 2017; Sample et al., 2016). However, some individuals appear to be less responsive to influences of the modern environment. Some researchers have focused on understanding individual differences in the susceptibility to the maladaptive effects of obesogenic environment on mechanisms involved in decision-making around food. Interpersonal variation in interoceptive ability, which is defined as one's ability to perceive their internal bodily state (Craig, 2002), may be especially relevant.

Historically, interoception has referred to sensing the state of various inner systems such as the viscera, skin, chemical/osmotic homeostatic systems, and emotions (Schleip & Jäger, 2012). Here, we focus more narrowly on the cardiac and gastric modes of interoception. To help address inconsistencies in the prior literature, we also adopt the following definitions to quantify distinct dimensions in interoception: *interoceptive*

accuracy (i.e. interoceptive performance), which is an objective index of interoceptive ability and assessed using tests such as the heartbeat detection (Garfinkel et al., 2015; Garfinkel & Critchley, 2013) and voluntary water ingestion (i.e., water load: van Dyck et al., 2016) tasks; (2) *interoceptive sensibility*, which is a subjective measure of interoceptive ability as it represents the self-reported tendency to focus on signals of the inner body, assessed using questionnaires (Garfinkel et al., 2015; Garfinkel & Critchley, 2013); (3) *interoceptive awareness* that reflects the metacognitive awareness of interoceptive accuracy and calculated by combining the mathematical results of different accuracy and sensibility measures (Garfinkel et al., 2015; Garfinkel & Critchley, 2013); and (4) *trait prediction error,* which quantifies the discrepancy between objective assessments of *interoceptive accuracy* and *interoceptive sensibility* for a range of sensations (Garfinkel et al., 2016).

Although putative relationships between reduced sensitivity to homeostatic signals and energy intake and body weight have been suggested for decades (Berthoud et al., 2017), only recently have researchers begun exploring whether variation in the ability to sense the state of the internal body – that is, interoception – might be associated with disordered eating behaviour and obesity development in healthy individuals. Specifically, only two reports have directly examined the relationship between cardioceptive accuracy and intuitive eating (a homeostasis-driven eating style); positive correlations were revealed in both cohorts (Herbert et al., 2013; Richard et al., 2019). The altered interoception seen in those with eating and feeding disorders may further support this rationale (reviewed in Quadt et al., 2018). The mechanisms related to interoception have also been proposed to explain the benefits of practising mindful eating vis-à-vis weight control (Warren et al., 2017). However, direct evidence of a relationship between objectively measured interoceptive accuracy and compliance to the principles of mindful eating is lacking. Elsewhere, being overweight or obese has been associated with attenuated interoceptive abilities among children (Koch & Pollatos, 2014) and young adults (Herbert & Pollatos, 2014); a study in an age-diverse adult group confirmed that this was also true for interoceptive sensibility (Murphy, Geary, et al., 2018). As the traditional homeostatic models suggest, responsiveness to and processing of internal signals of hunger and satiety, and internal signals elicited from

energy reserves, have been proposed to underlie these findings (Herbert & Pollatos, 2018; Simmons & DeVille, 2017). Other data consistent with the role of interoceptive abilities on obesity development comes from neuroimaging data of the insular cortex, which is regarded as the primary cortical substrate involved in interoception: a negative correlation between BMI and adiposity and insular cortex's grey matter volume has been observed (Rasmussen et al., 2017; Smucny et al., 2012). Brain areas known to mediate interoceptive processes also receive afferents from the gustatory system (Avery et al., 2015; Kurth et al., 2010), whilst homeostatic signals that serve the gut-brain communication also project to regions where interoception and gustation appear to be co-located (Simmons & DeVille, 2017). Can, then, individual differences in interoceptive abilities and variation in taste responses be linked as this shared neural representation of interoception and gustation suggests?

Alliesthesia, a classical phenomenon whereby experienced pleasure for a given sensory stimulus changes depending on the internal state of the body (Cabanac, 1979), may provide some support for the hypothesized convergence of interoceptive and gustatory information. Further, as detailed above, interoception has a role in human feeding behaviour and consequent weight regulation, as enhanced interoceptive abilities signify a more efficient body-to-brain axis of sensation. Taste is classically considered an exteroceptive sense, and taste hedonics are also key features in food choice and intake (Boesveldt & de Graaf, 2017; Hayes, 2020). While studies reporting distinct hedonic responses to sweetness (sweet taste phenotypes) date back a half century, recent data have emphasized the importance of accounting for individual variation in sweet-liking (Iatridi et al., 2019b; Tan & Tucker, 2019). Despite some inconsistencies in methods used to identify distinct sweet taste phenotypes, when effects of these phenotypes on weight status were examined, some researchers (Grinker, 1977; Grinker & Hirsch, 1972; Johnson et al., 1979; Malcolm et al., 1980; Thai et al., 2011) have reported those liking ever-higher sweetness (i.e. sweet likers; SLs), were more often of normal weight compared to sweet dislikers (i.e. individuals expressing aversive responses to high sweetness; SDs). In a multi-country study, we recently found that SLs had either lower fat mass or greater fat free mass than SDs (Iatridi et al., 2020). We concluded that, for SLs, hedonic response to sweetness matched

their bodily needs, either in respect to energy stores or energy requirements. Conversely, SDs seemed to be less responsive to the internal state of their body, especially for the subgroup of SDs who were more exposed to an obesogenic environment. This aligns with a model arguing that the human body has drifted evolutionary in its responsiveness to positive feedback loops that relate to surplus in internal energy stores, i.e. it is less effective in resisting to weight increases (Speakman et al., 2011). Conversely, human body primarily defends undersupply in order to prevent or reverse body mass loss (Speakman et al., 2011). Further, SLs also exhibited behavioural characteristics analogous to those of high interoceptive performers, such as enhanced trait-hunger, intensity seeking, and reward sensitivity (Iatridi et al., 2020). Collectively then, interoception appears to be a good candidate to explain the observed effects of sweet taste phenotype on body composition and psychometric profiles.

To date, most research on interoceptive processes has focused on sensitivity to cardiac signals. While cardiac interoception has been associated with experienced hunger (Herbert et al., 2012), whether cardiac and gastric interoception can be used interchangeably has not been resolved thus far. Still, experimental data from objective interoceptive measures suggests some degree of overlap in perceiving these discrete visceral events. For example, Whitehead and Drescher showed accuracy in detecting stomach contractions and heartbeats were significantly correlated (Whitehead & Drescher, 1980). Using more modern techniques, other groups have confirmed this association, with cardiac accuracy predicting the amount of water volume required for fullness to be sensed (Garfinkel, Manassei, et al., 2017; Herbert et al., 2012). However, Herbert and colleagues also noted there were no differences in subjective fullness ratings between high and low cardiac perceivers (Herbert et al., 2012). Discrepancies in interoceptive accuracy across senses have also been reported (Ferentzi et al., 2018) including a study where, unlike in previous investigations, a water load task accounting for individual differences in stomach capacity was used (van Dyck et al., 2016). To the best of our knowledge, no subsequent study has tested putative associations between the ability to sense gastric and cardiac signals while accounting for stomach capacity; we address this knowledge gap here. Given that the primary aim of the present study was to investigate the phenotype-specific differences in interoceptive abilities within an

ingestive behaviour context, inclusion of a bimodal interoception task was deemed essential.

In summary, except for one study on multimodal interoception that found no correlation between bitterness liking and interoceptive accuracy operationalized via cardiac and gastric measures (Ferentzi et al., 2018), this is the first systematic attempt to link interoceptive abilities and distinct gustatory hedonic patterns for sweetness. To do so, we contrasted two extreme hedonic patterns for sweet taste: SL and SD phenotypes. From a public health perspective, sweetness appears to be the taste modality of the most interest. By signifying nutritious and safe food sources (Drewnowski et al., 2012) and activating reward circuits in the brain (Wiss et al., 2018), sweetness uniquely forms food preferences. Moreover, high-sugar consumption has been a common target of healthy eating campaigns (WHO, 2015) due to its contribution to obesity (Hu, 2013) and modern diseases (Stanhope, 2016). Based on research work from our research group (Iatridi et al., 2020), we hypothesized SLs would exhibit better interoceptive performance than SDs. A bimodal interoception protocol incorporating state of the art cardiac (Garfinkel et al., 2015) and gastric (van Dyck et al., 2016) interoception tasks was used; both objective and subjective measures of interoception were included. Also, the predictive utility of sweet taste phenotype for a broad range of eating, lifestyle, and psychometric measures believed to relate to homeostatic or hedonic eating was assessed. The mediating role of interoceptive performance in the phenotype-specific differences in eating habits and behaviours of interest was also determined. Because interoception mechanisms have been shown to relate to emotions (Critchley & Garfinkel, 2017), we also explored the possible dissociable effect of positive versus negative emotions on gustatory decision making (Macht, 2008) between sweet taste phenotypes.

5.2 Methods

5.2.1 Participants

Sixty-four women aged 18-34 years old were recruited from students and staff at the University of Sussex. Sample size was determined from earlier studies in women where associations between interoceptive abilities and eating habits and behaviours such as intuitive eating (Richard et al., 2019) and emotional eating (Young et al., 2017), as well as the association between interoceptive performance across senses had been considered (Herbert et al., 2012). Given that men and women differ in both objective and subjective measures of interoception (Grabauskaitė et al., 2017) and in many eating behaviours (Rolls et al., 1991), as well as sex influencing food-related activation of brain areas closely related to interoceptive processes (Chao et al., 2017), a decision was made to only recruit women for the study. As part of the recruitment process, potential participants were screened for their sweet taste phenotype: only those classified as SLs or SDs were allowed to participate (see 2.2. for details). During screening, all but four participants (one SL and three SDs) attended a separate early morning session to obtain anthropometry; BMI and body composition were measured using bio-impedance (MC-780MA P, TANITA, UK). Before anthropometry, participants were asked to abstain from food and water for 8 hours, to not exercise for 12 hours, and to avoid consuming alcohol for 24 hours (Kyle et al., 2004).

In addition to exclusion criteria related to the taste test (i.e., diabetes, prescription medication other than oral contraception, irregular menstrual cycle, smoking 5+ cigarettes per week, being on a weight loss regimen and/or on a special diet for medical reasons, current respiratory illness, history of a dental procedure within the past two weeks), potential participants were also screened for a current diagnosis of mental and psychiatric disorders, past or current diagnosis of gastro-oesophageal reflux disease and/or hiatal hernia, a current diagnosis of diabetes insipidus, and a current or past diagnosis of cardiac arrhythmias and/or any other cardiovascular and/or heart disease. All study procedures (Figure 5.1) were carried out in accordance with the Declaration of Helsinki, and written informed consent was obtained at enrolment. The protocol was approved by the Science and Technology Cross-Schools Research Ethics Committee of the University of Sussex (ER/VI40/2).

5.2.2 Sweet taste test

Participants rated liking for a 1 M sucrose solution on a visual analogue scale (VAS) ranging from -50 to +50; liking scores above +15 and below -15 were used to define participants as SL or SD, respectively. These criteria were recently proposed by our lab (Iatridi et al., 2019a) and further validated in a multi-country study (Iatridi et al., 2020). During screening, potential participants rated two series of 0 M and 1 M sucrose solutions presented using a 'sip and spit' protocol with a rinsing step between the stimuli and a 2-minute break between the two sets of stimuli. Participants were asked to refrain from consuming foods and flavored drinks, smoking, chewing gum, and tooth brushing for the two hours prior screening. Sucrose solutions were prepared weekly at room temperature (22 °C) by dissolving food-grade sugar in mineral water. All taste stimuli were stored at 4 °C and brought back to room temperature before tasting. Perceived liking ('How much did you like Sample X?') and intensity ('How sweet was Sample X?') were recorded on a visual analogue scale (VAS) anchored as 'Dislike Extremely' (-50) and 'Like Extremely' (+50) and a generalized labelled magnitude scale (gLMS) ranging from 'No Sensation' (0) to 'Strongest Sensation of any Kind' (100), respectively; training for scales was provided, presented using Sussex Ingestion Pattern Monitor (SIPM, University of Sussex, UK). Both 1 M replicates had to be rated higher than +15 or below -15 for the classification into the SL and SD phenotype, respectively (Mobini et al., 2007).

5.2.3 Interoception (objective measures) – Interoceptive accuracy

5.2.3.1 Cardiac interoception

To determine interoceptive accuracy across different cardiac interoceptive processes, a heartbeat tracking (Schandry, 1981) and a heartbeat discrimination task (Whitehead et al., 1977) using electrocardiography were employed; they were programmed in Psychtoolbox-3 for MATLAB (MathWorks Inc., Natick, MA) executed on a laptop computer running Microsoft Windows. The same researcher who was present during both tasks tested all participants. The researcher was blind to each trial's characteristics and accuracy of recorded responses. The researcher provided instructions, coordinated tasks, and made electronic records of participants' responses

immediately after the end of each trial. A pulse oximeter (Xpod, Nonin, Medical Inc.) connected through a USB port to the laptop was attached to the participants' non-dominant index finger to record their actual heart rate. During both cardiac tasks, participants remained seated, relatively still, and with their arm comfortably rested on a pillow placed on a flat surface in front of them. They were also instructed to breathe at a regular pace.

Upon completion of the heartbeat tasks, participants completed a series of mood questionnaires to assess known confounders of interoceptive performance. Specifically, anxiety (Domschke et al., 2010), depression (Paulus & Stein, 2010), alexithymia (Brewer et al., 2016), and impulsivity (Chen et al., 2018) have all been associated with altered interoception, so the General Anxiety Disorder-7 (Spitzer et al., 2006), Patient Health Questionnaire-9 (Spitzer et al., 1999), Toronto Alexithymia Scale (Bagby et al., 1994), and Barratt Impulsiveness Scale (Patton et al., 1995) were administered. Participants' beliefs about heart rate ('Do you know what a heart rate is?', 'Do you know what your heart is?') were also obtained (Murphy, Millgate, et al., 2018).

5.2.3.1.1 Heartbeat tracking task

For the heartbeat tracking task (Schandry, 1981), participants were asked to internally count their heartbeats across six trials varying in duration (25, 30, 35, 40, 40, 45 and 50 seconds in a randomized order). The start and end of each interval was signaled by an auditory cue ("start" and "stop") delivered via software. The instructions were: "Without manually taking your pulse, please count each heartbeat you feel from the time you hear "start" to when you hear "stop'' as it will be prompted by the computer."

Heartbeat tracking accuracy score (IAcHTr; Interoception Accuracy from the Heartbeat Tracking task) was calculated by averaging relevant accuracy scores across the six trials. The latter was computed from the following formula:

$$1 - \frac{|n\text{beatsreal} - n\text{beatsreported}|}{(n\text{beatsreal} + n\text{beatsreported})/2}$$ per trial (Hart et al., 2013).

5.2.3.1.2 Heartbeat discrimination task

The heartbeat discrimination task comprised of 26 blocks of auditory tones played for 100 seconds at 440 Hz; half of the blocks were synchronized with the participant's heartbeat and half were presented with a 300 milliseconds delay in a randomized order (Garfinkel et al., 2015). Participants were asked to indicate synchronicity between the auditory stimuli and their own heartbeats. The specific instructions were: "The computer will play your heartbeat back to you in real time. Whenever the computer detects a heartbeat, it will play a tone. Without manually taking your pulse, you have to decide whether the tones you hear are synchronous or asynchronous with your heartbeat.".

A heartbeat discrimination accuracy score (IAcHDi; Interoception Accuracy from the Heartbeat Discrimination task) was calculated as the percentage of correct answers (i.e., affirmative responses under synchronous conditions or negative responses under asynchronous conditions) across the total number of trials.

5.2.3.1.3 Time tracking task

To control for guessing of the number of heartbeats and monitor participants' engagement, a time tracking task analogous to the 'heartbeat counting paradigm' was introduced between the two cardiac interoception tasks: participants were instructed to count number of seconds over six predetermined time-windows without using any help or receiving any feedback upon completion of each trial.

5.2.3.2 Gastric interoception

The gastric channel of interoception was tested by performing a modified water load test (WLT) protocol developed by van Dyck and colleagues (2016). To eliminate carry-over effects of a possible discomfort associated with ingestion of large amounts of water and to ensure a relatively empty stomach, the gastric interoception task was performed last and after approximately a 3-hour abstinence from eating and drinking (water included). As the researcher was not allowed into the testing room other than to serve the water, written instructions guided participants through the steps, including

advice to discontinue water ingestion if they felt unwell. Over two successive 5-minute periods, participants drank from a hidden 5 L flask containing 1.5 L of commercial table water (ASDA, UK), served at room temperature, with an integrated tubing system which ended in a long (30 mm) wide (8 mm) flexible straw; the flask was weighed between the two periods and refilled. During the first period, ad libitum water ingestion was required until the point of perceived satiation, which was explained as 'the comfortable sensation you perceive when you have eaten a meal and you have eaten enough, but not too much'. Participants were then asked to continue ingesting water until fullness, i.e. 'sensation of stomach being entirely filled with water' was reached. Appetite ratings (hunger, satiety, fullness, thirst) and ratings about abdominal feelings (stomach tension, immobility, discomfort, guilt, sluggishness, nausea, arousal) were obtained before the first and after both the first and the second drinking tasks on computerized visual analogue scales (van Dyck et al., 2016). Participants remained seated in a half-supine position (i.e., leaning back at a 45 degree angle) during the entire test.

By weighing the flasks before and after each ingestion period, the water volume needed for satiation the additional volume required for fullness and the total stomach capacity (i.e., total volume ingested) were estimated. Gastric interoception was defined as the volume needed for satiation expressed as a percentage of total stomach capacity; lower values were interpreted as better gastric interoceptive ability (van Dyck et al., 2016).

5.2.4 Interoception (subjective measures) – Interoceptive sensibility

5.2.4.1 Confidence ratings

Using a computerized VAS anchored as 'Total Guess/No heartbeat awareness' (0) and 'Complete Confidence/Full perception of heartbeat' (100), participants were asked to rate their confidence in the accuracy of their responses regarding the perceived number of heartbeats of the heartbeat tracking task (IS_HTr; Interoceptive Sensibility from the Heartbeat Tracking task) and perceived synchronicity with their heartbeats of the heartbeat discrimination task (IS_HDi; Interoceptive Sensibility from the Heartbeat Discrimination task) immediately after each trial.

5.2.4.2 Body Perception Questionnaire

The awareness subscale of the Porges Body Perception Questionnaire (BPQ: Porges, 1993) that measures one's beliefs about own sensitivity to a spectrum of bodily processes such as breathing, itching, sweating, swelling, digestion's noises, muscle tension, was administered after completion of the cardiac interoception tasks. The original subscale consists of 45 items rated on a five-point Likert scale ranging from 'Never' (1) to 'Always' (5). Here, we used the scoring protocol whereby full responses are summed to a total raw score (BPQ Manual, version 2); higher values represented higher levels of interoceptive sensibility.

5.2.5. Metacognitive Interoceptive Awareness

Metacognitive interoceptive awareness (IAw) was calculated separately for each heartbeat detection task based on the correspondence between accuracy and confidence (Garfinkel et al., 2015). As such, it illustrated how well one's confidence matched the correctness of their responses. For the heartbeat tracking task, we correlated accuracy (continuous responses) and confidence scores (Pearson r) on a within-subject trial-by-trial basis. To determine the heartbeat discrimination task-specific interoceptive awareness, the diagnostic value of the reported trial-by-trial confidence for accuracy (binary responses) was calculated from the area under the receiver operating characteristic (ROC) curve as described in Garfinkel et al. (2015). High metacognitive ability was yielded when correct trials (synchronicity or asynchrony judged correctly) were accompanied by high confidence or incorrect trials (synchronicity or asynchrony judged incorrectly) by low confidence (Garfinkel et al., 2015).

5.2.6 Trait Prediction Error

Interoceptive Trait Prediction Error (ITPE) quantifies the discrepancy between objectively assessed interoceptive performance measured during heartbeat detection tasks and interoceptive sensibility, i.e. one's beliefs about own sensitivity to interoceptive signals (Garfinkel et al., 2016). As described in Garfinkel et al. (2016), ITPE was computed separately for the heartbeat tracking and the heartbeat discrimination

tasks as the difference between the awareness subscale of the BPQ and interoceptive accuracy. Prior to calculations, BPQ and accuracy scores were converted to standardised Z-values. Positive and negative values of ITPE indicate overestimation and underestimation of own interoceptive abilities, respectively.

5.2.7 Behavioural measures

Participants were asked to complete questionnaires on eating styles that encompass the principles of interoception, i.e. mindful eating and intuitive eating styles (Palascha et al., 2020). Mindful eating, which is conceptualised as being aware of physical versus emotional hunger and satiety cues and of associated effects of food choices on both the body and psychological state, was assessed through the Mindful Eating Questionnaire (MEQ: Framson et al., 2009). MEQ measures five distinct eating behaviour-related factors for a total of 28 items: (1) disinhibition (e.g. 'I stop eating when I'm full even when eating something I love'); (2) awareness (e.g.' I notice when there are subtle flavours in the foods I eat'); (3) external cues (e.g. 'I recognize when food advertisements make me want to eat'); (4) emotional response (e.g. 'When I'm sad I eat to feel better'); (5) distraction (e.g. 'My thoughts tend to wander while I am eating'). For intuitive eating which also concentrates on internally focused eating, the 23-item Intuitive Eating Scale (IES: Tylka, 2006) was administered. Items targeted four facets: (1) unconditional permission to eat (e.g. 'If I am craving a certain food, I allow myself to have it'); (2) eating for physical rather than emotional reasons (e.g. 'I stop eating when I feel full'); (3) reliance on internal hunger and satiety cues (e.g. 'I trust my body to tell me when to eat'); (4) body-food choice congruence (e.g. 'I mostly eat foods that give my body energy and stamina').

Whether the differential role played by external cues versus emotions in the control of food intake was reflected in the behavioural profile of SLs and SDs was also tested. Susceptibility to external food cues was quantified through the external eating subscale of the Dutch Eating Behaviour Questionnaire (DEBQ: Strien et al., 1986). For emotional eating, the relevant subscale of DEBQ was analysed alongside the Emotional Appetite Questionnaire (EMAQ: Geliebter & Aversa, 2003) which explicitly separates effects of positive (e.g. confident, relaxed, falling in love) from effects of negative (e.g.

sad, angry, when under pressure) emotions and emotional situations on eating behaviour, as well as considering the direction of disrupted food intake: that is whether a given emotion or emotional situation drives intake up or down. The effect of each emotion or emotional situation was rated on a 9-point Likert scale ('As compared to usual, do you eat…') ranging from 'much less' to 'much more' including a middle point labelled 'the same', as well as a 'not applicable' and 'don't know' options. If any of the two latter options was selected, then this response was omitted from the analysis.

Finally, participants answered questions related to their dieting and body weight history. Behaviours akin to dietary restraint and overeating which are considered to underlie repetitive dieting and/or significant changes in body weight across the lifespan may also reflect attenuated interoceptive abilities (Bryant et al., 2019; Speakman et al., 2011). Indeed, higher neural density in the insula for the obesity resistant phenotype as opposed to individuals prone to obesity has been reported (Smucny et al., 2012). Here, participants were prompted to make a series of choice from the following list of dichotomous responses, characteristic of an obesity resistant versus an obesity prone phenotype (Schmidt et al., 2012): (1) 'I am constitutionally thin, i.e. I believe it is difficult for me to gain weight and/or I expend little effort to maintain my weight' *vs*. 'I am chronically struggling with body weight control'; (2) 'I experience weight stability despite few to no attempts to lose weight' *vs*. 'I have a history of weight fluctuations despite putting effort into not gaining weight'; (3) 'I do not have any first degree relative (parents or siblings) who is obese' *vs*. 'I have at least one first degree relative (parents or siblings) who is obese'; (4) 'I have never been overweight or obese' *vs*. 'I have been at least one time or I am currently overweight or obese'. Responses for an obesity resistant phenotype were scored as 0 versus 1 for the alternatives, so the lower the total score, the more resistant they were to obesity.
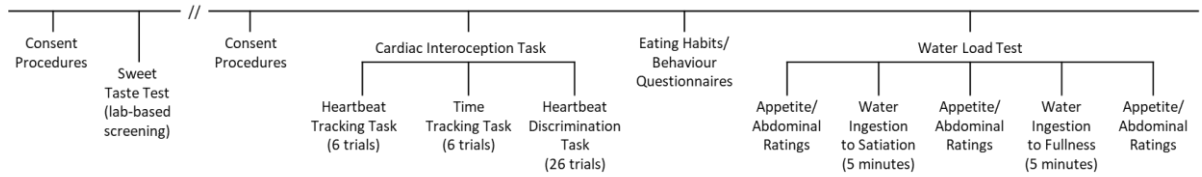
Fig. **5.1** Schematic representation of the study's testing procedures.

The lab-based sweet taste test, as well as the analysis of participants' body composition (optional session; not shown) took place a few days before the interoception tasks.

5.2.8 Statistical analysis

First, basic descriptive statistics (i.e., percentages and means and standard errors of the means) were computed. Group differences (SLs versus SDs) in continuous and categorical variables were tested with independent t- and χ^2-tests, as appropriate. Due to the novelty of our research hypothesis multiple comparisons (not corrected) were performed, and therefore, finding should be treated with caution (preliminary findings). Regression analyses entering all confounders simultaneously were conducted to test the predictive utility of phenotype for each interoceptive accuracy score (heartbeat tracking, heartbeat discriminating, gastric) accounting for known confounders. To explore whether interoceptive accuracy in either heartbeat tasks related to gastric interoception independent of the sweet taste phenotype, additional regression models were employed. Pearson correlations of scores on emotional eating scales with interoceptive abilities and of cardiac with gastric interoception measures were also calculated.

The extent to which differences in participants' characteristics by phenotype were mediated by individual differences in interoceptive performance was tested using Hayes PROCESS macro v3.4 (Model 4: Hayes, 2013) with 5000 bootstrapped bias corrected resamples. Direct and indirect effects of sweet taste phenotype separately on each participants' characteristic of interest were estimated with interoceptive performance accuracy as the mediating variable; separate mediation analysis was carried out for each objective measure of interoception (i.e., interoceptive accuracy derived from the heartbeat tracking task, the heartbeat discrimination task, and WLT).

As illustrated on Figure 5.2, the direct effect, path c', represents the effect of the predictor (i.e., sweet taste phenotype) on the outcome (i.e., participant characteristics) while accounting for the effect of the mediator (i.e., interoceptive performance). Path a shows the strength of the influence of predictor on the mediator and path b denotes the effect of mediator on the outcome when the predictor is statistically controlled. This type of mediation analysis determines whether the effect of the predictor on the outcome is fully explained by the mediator. For significant results 95% bias corrected confidence interval (CI) should not have included the zero value.
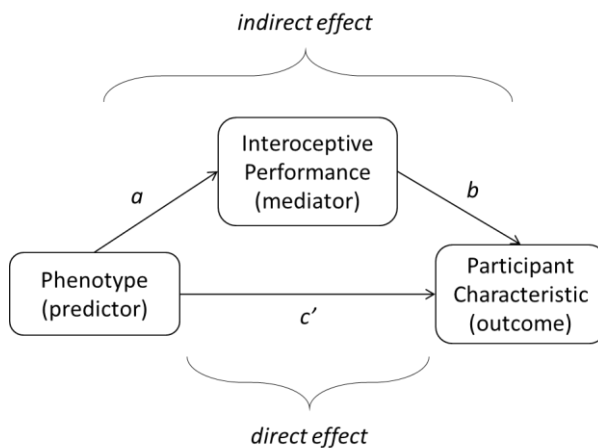
Fig. **5.2** The path model for mediation analysis (Hayes, 2013)

Cohen's *d* and f squared (f^2) were used as the effect size measures for pairwise comparisons and analyses of variance, respectively. Cohen's *d* was considered small when equal to 0.20, medium when equal to 0.50 and large when equal to 0.80. For f^2, 0.2, 0.15, and 0.35 were the thresholds for a small, medium and large effect size. (Cohen, 2013). The level of significance was set to α = .05. Data were analysed using SPSS v25.0 and the MATLAB (R2019b) software package. All tested hypotheses and the main analysis plan were specified prior to data collection.

5.3 Results

The study sample comprised of 64 women, 31 SLs and 33 SDs with an age and BMI range of 18.8 to 33.8 years and 17.19 to 32.23 kg/m^2, respectively. 67.2% were self-identified as Caucasians and 21.9% were of Asian ancestry. SDs were older than SLs

(24.3±0.08 SEM vs. 22.4±0.05 SEM; t(55.207)= -2.083, p = .042), whereas individuals of Asian ancestry were classified into the SD phenotype (92.9%) more often than participants of Caucasian ancestry (39.5%) or participants from other ethnicities (42.9%; χ^2(1,N=64) = 12.262, p = .002). Conversely, comparisons of sweet liker phenotypes by BMI (SLs: M = 22.03, SEM = .42; SDs: M = 22.87, SEM = .60), total body fat (SLs: M = 25.2, SEM = 1.1; SDs: M = 26.1, SEM = 1.2), and fat free mass (SLs: M = 45.3, SEM = .7; SDs: M = 44.9, SEM = 1.4) were not significant (all ps > .05).

Regarding interoception-specific measures, due to technical problems, cardiac and gastric interoception data were missing from two and one participant, respectively. Across participants, cardioceptive performance in the heartbeat tracking (M = .600, SEM = .035) and the heartbeat discriminating (M = .576, SEM = .017) tasks were comparable to recent work in non-clinical subgroups (Critchley et al., 2019). For the WLT, mean gastric interoceptive performance was .588 (SEM = .018), similar to values from van Dyck et al. (2016).

5.3.1 Interoceptive abilities by sweet taste phenotype

The different interoception constructs (i.e., accuracy, awareness, sensibility) across interoception modalities (i.e., cardiac, gastric) by sweet taste phenotype are shown in Figure 5.3. SLs obtained higher accuracy scores than SDs in the heartbeat tracking (t(61) = 2.538, p = .014, d = .64) and the heartbeat discrimination (t(60) = 2.785, p = .007, d = .71) tasks (Figure 5.3a-b). Notably, the observed patterns persisted even after accounting for known confounders of interoceptive performance (Table 5.1) that is alexithymia, anxiety, depression, and impulsivity (IAcHTr: $β$ = - .286 $95\%CI$ (-.150, -.006), t = -2.157, p = .035, f^2 = .12; IAcHDi: $β$ = - .404 $95\%CI$ (-.091, -.019), t = -3.086, p = .006, f^2 = .19). Analysis of participants' performance in the time tracking task showed no differences between SLs (M = .784, SEM = .026) and SDs (M = .769, SEM = .030) in their overall engagement in the experimental procedures (t(62) = .370, p = .713; d = .09). SLs and SDs did also not differ in their knowledge of own heartbeats (41.9% SLs vs. 27.3% SDs reported knowledge of own heartbeat; χ^2(1,N=64) = 1.523, p = .217, V = .02).

SLs also exhibited enhanced gastric interoceptive abilities, as they ingested less water to sense satiety in relation to their stomach capacity when compared to SDs (t(61) = -2.722, p = .008, d = .69: Figure 5.3c); notably, this was independent of their pre-test levels of satiety and thirst ($β$ = .333 *95%CI* (.013, .082), t = 2.758, p = .008, f^2 = .16). The low pre-test levels of satiety (SLs: M = 31.2, *SEM* = 3.8; SDs: M = 33.4, *SEM* = 4.0; t(61) = -.395, p = .694) and relatively high levels of thirst (SLs: M = 66.3, *SEM* = 4.1; SDs: M = 67.0, *SEM* = 4.3; t(61) = -.107, p = .916) seen here were unsurprising given the 3-hour food and water abstinence protocol. The importance of accounting for stomach capacity in assessing gastric interoception also deserves note: if absolute ingested water volume had been used as a measure of gastric interoception, no phenotype-specific difference in gastric interoception would have been observed (t(61) = .003, p = .998: Figure 5.3c). Likewise, adding total stomach capacity to the multivariate regression model that tested the effect of phenotype on gastric interoception improved the model's predictive ability at a larger degree (R^2 = .141), compared to using the absolute ingested water volume (R^2 = .029).

Table 1. Trait mood and behaviour characteristics by sweet taste phenotype

	Sweet Likers (n = 31)	Sweet Dislikers (n = 33)
	Mean (SEM)	
GAD-7 (anxiety)	8.4 (0.9)	8.8 (1.0)
PHQ-9 (depression)	7.2 (0.8)	9.0 (1.1)
TAS-20 (alexithymia)	46.6 (2.1)	50.2 (2.1)
BIS (impulsivity)	57.9 (1.8)	62.1 (1.6)

BIS, Barratt Impulsiveness Scale; GAD-7, General Anxiety Disorder-7; PHQ-9, Patient Health Questionnaire-9; TAS, SEM, Standard Error of the Mean; Toronto Alexithymia Scale

All group comparisons were non-significant (p > .05)

Here, an effect of phenotype on objectively measured sensitivity to internal signals was not confirmed for constructs entailing subjective assessment of

interoceptive abilities. Mean confidence from the heartbeat tracking task ($t(61) = .558$, $p = .579$; $d = .14$) and the heartbeat discrimination task ($t(60) = -1.335$, $p = .187$; $d = .34$) each failed in distinguishing SLs from SDs (Figure 5.3a-b); this failure was also seen for interoceptive awareness (IAwHTr: $t(61) = .763$, $p = .448$; $d = .19$; IAwHDi: $t(60) = .625$, $p = .534$; $d = .16$: Figure 5.3a-b). Although the mean scores for the SLs on the BPQ were slightly higher than for the SDs, this apparent difference was not significant (SLs: $M = 75.4$, $SEM = 3.3$; SDs: $M = 68.7$, $SEM = 2.9$; $t(62) = 1.547$, $p = .127$; $d = .39$). Finally, while there were no phenotype-specific differences in interoceptive trait prediction error as assessed using either the heartbeat tracking task (SLs: $M = -.114$, $SEM = .263$; SDs: $M = .144$, $SEM = .291$; $t(61) = -.657$, $p = .514$; $d = .17$) or the heartbeat discrimination task (SLs: $M = -.138$, $SEM = .267$; SDs: $M = .143$, $SEM = .225$; $t(60) = -.807$, $p = .323$; $d = .21$), SLs were prone towards underestimating their interoceptive abilities as opposed to SDs who tended to overestimate their abilities to sense the internal state of their body accurately.

(b) Heartbeat Discriminating Task
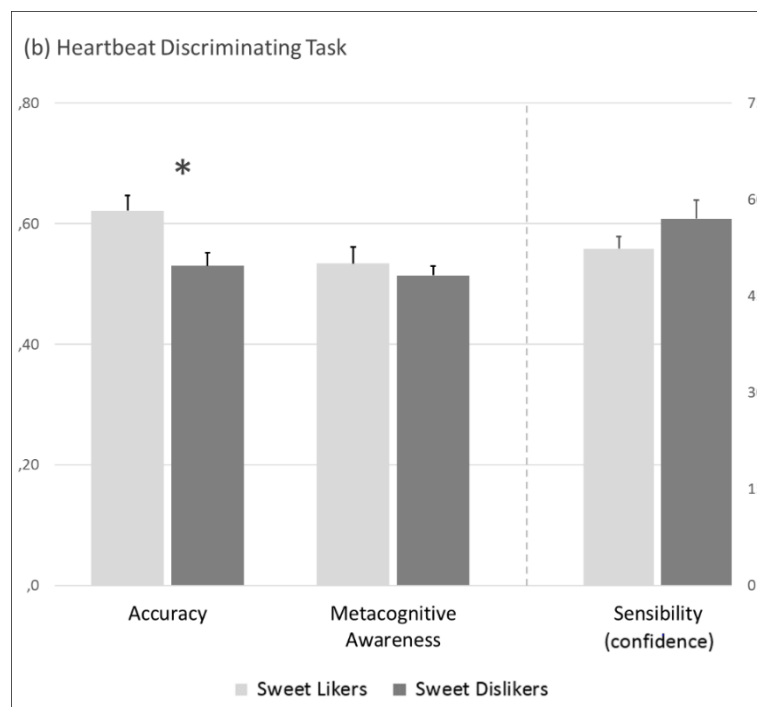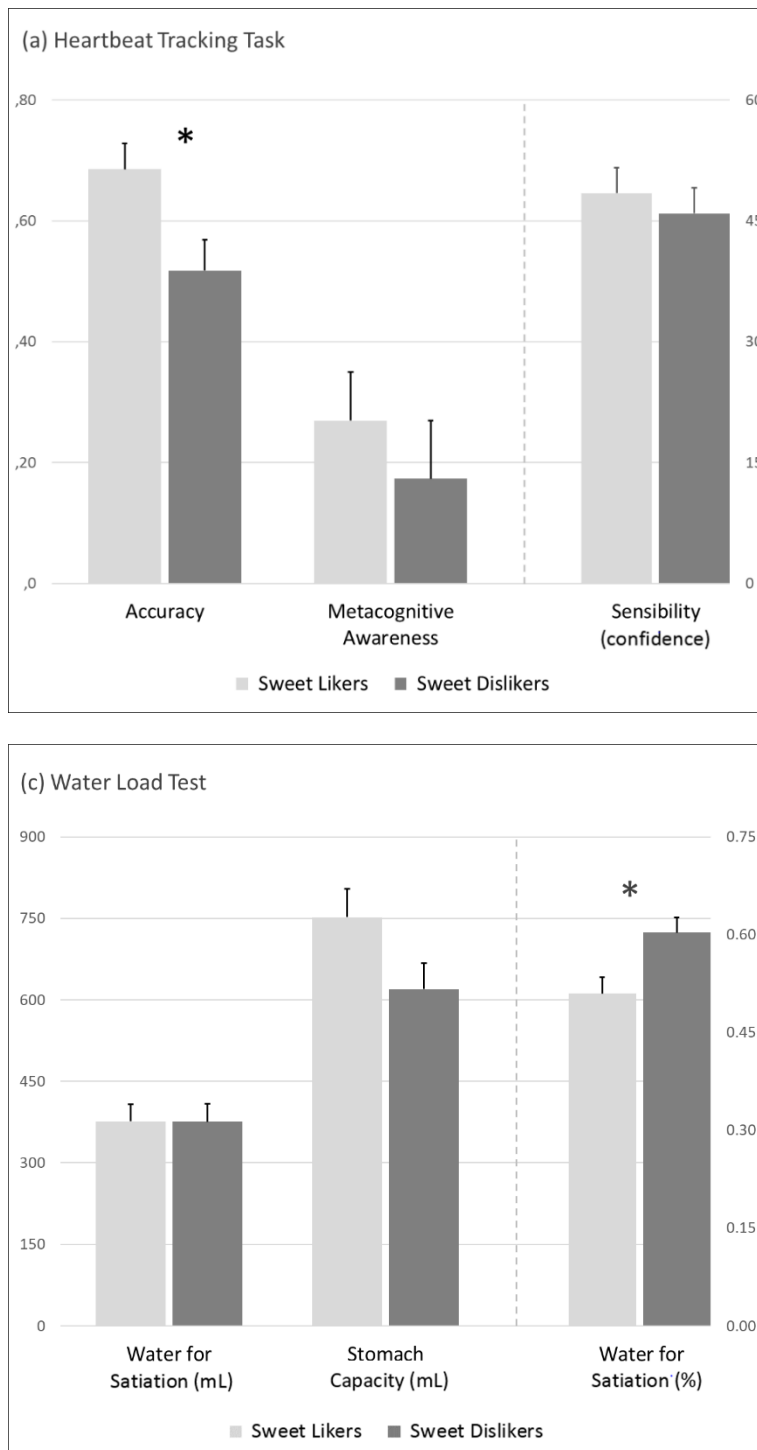
Fig. 5.3a-c. Interoceptive dimensions by phenotype and task (a: heartbeat tracking task; b: heartbeat discrimination task; c: water load test).

An asterisk (*) denotes statistically significant differences ($p < .05$) between the sweet taste phenotypes for each interoceptive measure. Error bars indicate standard errors of the mean. Notably, scores for the satiation measure are reversed relative to the cardioceptive accuracy scores; that is, higher values indicate lower gastric interoceptive abilities.

5.3.2 Eating habits and behaviours by sweet liker phenotype

In relation to our main hypothesis – those classified into the SL phenotype would have enhanced interoceptive abilities – eating habits and behaviours associated with responsiveness to internal signals and bodily needs were analyzed by phenotype (Table 5.2). Overall, SLs scored higher than SDs in mindful eating (t(62) = 3.060, p = .003, d = .76) and intuitive eating (t(62) = 4.321, p < .001, d = 1.09). From the different subscales under investigation, phenotype-specific differences were significant for awareness of feeding-specific internal states of the body (t(62) = 2.620, p = .011, d = .65) and of external feeding cues (t(62) = 2.682, p = .009, d = .67) of the mindful eating questionnaire, as well as eating to meet physical rather than externally-generated needs (t(62) = 2.795, p = .007, d = .70), favoring food choices that benefit the body (t(62) = 4.286, p < .001, d = 1.08), or tending to refrain from placing external restrictions on eating (t(62) = 1.872, p = .066, d = .47) as derived from the intuitive eating questionnaire. SLs were also more likely than SDs to have an obesity resistant profile (t(62) = 2.151, p = .035, d = .54).

SLs also scored higher on the DEBQ emotional eating scale (t(62) = 2.153, p = .035, d = .54). Examining the positive and negative scales of the Emotional Appetite Questionnaire (EMAQ), SLs reported to increase their food intake at a significantly lower degree than SDs for positive emotions (t(62) = -2.245, p = .028, d = .56) but more in response to negative emotional stimuli (t(62) = 1.651, p = .104, d = .41). To note, in the total sample, positive emotional stimuli triggered significantly greater increases in food intake than negative emotions or emotional situations (t(63) = 2.968, p = .009, d = .52). In fact, only a third of our study sample (39.1%) reported eating more than usual (i.e. mean score > 5) when experiencing negative emotions compared to 51.6% who increased their food intake in response to positive emotions or emotional situations. Emotional eating in response to positive stimuli was also negatively associated with heartbeat accuracy scores across tasks (HTr: r(63) = -.294, p = .019; HDi: r(62) = -.302, p = .017), while the higher the increase in food intake in response to negative emotions, the better the measured cardioceptive performance (HTr: r(63) = -.290, p = .021; HDi: r(62) = -.262, p = .040). When the link between interoceptive abilities and emotional eating captured by the more generic subscale of the DEBQ was tested, weaker

correlations emerged (IAcHTr: $r(63) = .242$, $p = .056$; IAcHDi: $r(62) = .245$, $p = .055$). No differences between phenotypes were observed for DEBQ-external eating or frequency of dieting (all $ps > .05$).

Table 5.2 Eating habits and behaviours by sweet taste phenotype

|	Sweet Likers (n = 31)	Sweet Dislikers (n = 33)
	Mean (SEM)	
Intuitive Eating Scale		
Total score	3.506 (.040)*	3.204 (.056)
Unconditional eating	3.371 (.081)	3.172 (.069)
Physical eating	3.323 (.060)*	3.030 (.084)
Hunger-driven eating	3.586 (.119)	3.424 (.118)
Body-food convergence	4.108 (.110)*	3.293 (.153)
Mindful Eating Scale		
Total score	2.489 (.048)*	2.291 (.044)
Awareness	2.805 (.082)*	2.516 (.075)
External cues	2.955 (.093)*	2.616 (.086)
Emotional response	1.989 (.097)	1.861 (.108)
Distraction	2.258 (.117)	2.132 (.082)
Dutch Eating Behavioural Questionnaire		
Restrained eating	22.9 (1.3)	24.2 (1.7)
Emotional eating	36.8 (2.1)*	30.6 (1.9)
External eating	31.6 (.9)	32.1 (1.2)
Emotional Appetite Questionnaire		
Positive	5.0 (.1)*	5.4 (.1)
Negative	4.9 (.2)	4.5 (.2)
Resistant obesity (%)	52.4 (2.9)*	43.2 (3.1)

SEM, Standard Error of the Mean

An asterisk (*) denotes statistically significant differences between phenotypes.

5.3.3 Mediation effect of interoception on phenotype-specific differences in eating habits and behaviour

To test whether the observed phenotypic differences in characteristics related to eating habits and behaviour might be explained by individual differences in interoceptive abilities, mediation analyses were used. Specifically, we treated sweet taste phenotype as the categorical predictor, different eating habits and behaviours as outcomes and objective measures of interoception separately as mediators. Mediation, i.e., the indirect effect shown in Figure 5.2 where the moderator mediates the relationship between the predictor and the outcome) was present only for the positive and negative scales of the Emotional Appetite Questionnaire (EMAQ). In particular, the effect of sweet-liking phenotype on eating in response to positive or negative emotions and emotional situations was fully explained by the relationship of the phenotype, i.e., the predictor, and EMAQ-scales scores, i.e. the outcome, with the interoceptive performance (accuracy) across in the heartbeat tracking task (Figure 5.4).
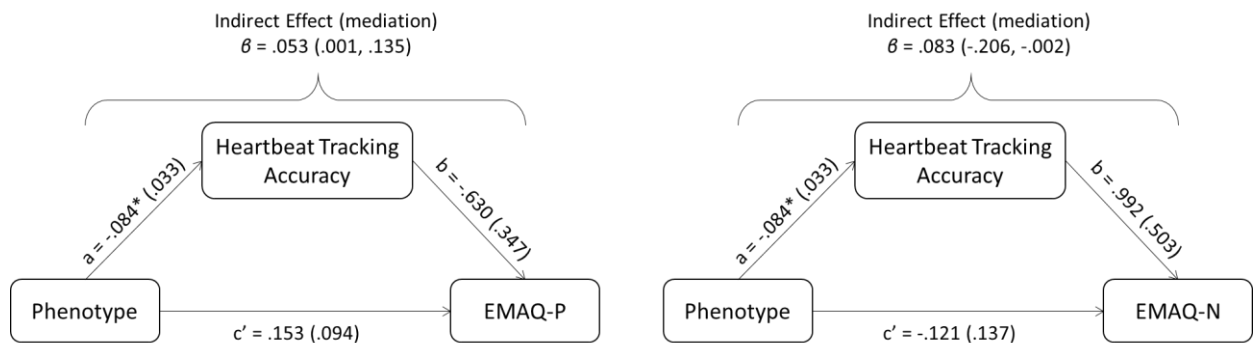
Fig. 5.4 Mediation model illustrating that the effect of phenotype on both EMAQ subscales was fully explained by participants' performance in the heartbeat tracking task. Path c' represents the effect of phenotype on the EMAQ subscales while accounting for the effect of the interoceptive performance, path a shows the strength of the influence of phenotype on interoceptive performance, and path b denotes the effect of interoceptive performance on the EMAQ subscales controlling for sweet-liking phenotype.

EMAQ-N, Emotional Appetite Questionnaire-Negative subscale; EMAQ-P, Emotional Appetite Questionnaire-Positive subscale. *$p < .05$

Besides these indirect effects, Hayes PROCESS macro v3.4 also revealed that phenotype predicted intuitive and mindful eating (total scores) independent of interoceptive performance across both heartbeat tasks and the water load task (c', i.e., direct, path in Figure 5.2; Table 5.3), further supporting our earlier finding about enhanced intuitive and mindful eating in SLs.

Table 5.3. Results of mediation analysis for the independent effect of predictors on outcomes

	Mediation by Heartbeat Tracking Accuracy	Mediation by Heartbeat Discriminating Accuracy	Mediation by %Water for Satiation
	Direct effect *b* (*SEM*)		
	c' path		
Intuitive eating (total score)	-.132 (.036) $p = .001$	-.148 (.038) $p < .001$	-.137 (.037) $p < .001$
Mindful eating (total score)	-.087 (.034) $p = .014$	-.091 (.035) $p = .013$	-.094 (.035) $p = .009$

SEM, Standard Error of the Mean

5.3.4 Effect of sweet liker phenotype on the relationship between cardiac and gastric axes of interoception

Across participants, we observed a significant inverse relationship between accuracy scores from both the heartbeat tracking and discrimination tasks, and the percentage amount of ingested water volume from the WLT (HTr: $r(61) = -.298$, $p = .019$; HDi: $r(60) = -.244$, $p = .058$), suggesting that ability to sense one's own heartbeats was linked to sensitivity for gastric functions. Cardiac interoceptive performance from both heartbeat tasks was also correlated with total stomach capacity (HTr: $r(62) = .410$, $p = .001$; HDi: $r(61) = .283$, $p = .027$), but not absolute ingested water volume for satiation (HTr: $r(62) = -.196$, $p = .126$; HDi: $r(61) = .110$, $p = .398$). Regression analysis accounting for pre-test level of satiety and thirst provide similar results (all $ps < .05$ for stomach capacity and $> .05$ for absolute ingested water volume).

Adding sweet taste phenotype as a factor to the regression model testing the relationship between heartbeat tracking performance and gastric interoception significantly improved the variance explained by the model (ΔR^2 = .063, $p_{\Delta F}$ = .041). The contribution of sweet taste phenotype to the model remained significant even after controlling for known confounders of cardiac and gastric interoception, i.e. alexithymia, anxiety, depression, impulsivity and pretest levels of satiety and thirst (β = .284 *95%CI* (.004, .078), *t* = 2.197, *p* = .032); heartbeat tracking performance did not significantly predict gastric performance in the fully adjusted model (β = -.182 *95%CI* (-.229, .037), *t* = -1.451, *p* = .153). Additional regression analysis demonstrated similar results regarding the effect of sweet liker phenotype on the relationship between interoceptive accuracy scores obtained during the heartbeat discrimination task and percentage amount of ingested water volume from the WLT (phenotype: β = .316 *95%CI* (.006, .085), *t* = 2.292, *p* = .026; f^2 = .36; IAcHDi: β = -.111 *95%CI* (-.393, .159), *t* = -.851, *p* = .399; f^2 = .35).

5.4 Discussion

This is the first study to report a link between objectively assessed accuracy in detecting internal bodily sensations and hedonic responses to concentrated sweet stimuli. By employing two distinct heartbeat detection tasks alongside a gastric interoception task in the same sample of healthy adults, we also avoid limitations that arise from focusing too narrowly on individual measures of interoceptive accuracy. Notwithstanding the exploratory nature of these findings, the phenotypic differences in interoceptive abilities across all three interoceptive tasks coupled with medium to large effect sizes highlight the potential robustness of the observed differences. Specifically, participants who expressed heightened liking for strong sweetness (that is, SLs), performed better than SDs in detecting their heartbeats accurately despite being similarly confident about their responses. For the gastric mode of interoception, SLs reported to feel satiated after they ingested a lower amount of water in relation to their total stomach capacity compared to SDs.

To our knowledge, only one research group has examined potential links between interoception and taste hedonics. In those studies, participants were asked to taste and rate a single concentration of a bitter herbal extract; neither pleasantness nor

intensity ratings were correlated with accuracy scores from the heartbeat tracking task (Ferentzi et al., 2017). Subsequently, Ferentzi and colleagues extended their finding by proposing a dissociation between bitterness pleasantness and gastric interoception, as measured by a WLT (Ferentzi et al., 2018). Interestingly, an inverse relationship between bitterness pleasantness and sensitivity to the internal sensation of pain was reported in the first study (Ferentzi et al., 2017), which might be of relevance to the current dataset as sweetness has also been proposed to have implications in mechanisms of pain (Fantino et al., 1986; Yeomans & Wright, 1991). On the other hand, given that, unlike most bitter taste stimuli, the oft-used sweet tastants contain some energy, closer links between hedonic responses to sweetness than bitterness and the homeostatic system, which is centre to feeding-related interoceptive abilities, could be expected. Indeed, additional to the role of sweetness in signposting safe sources of energy (Steiner et al., 2001), animal research recently identified taste receptors in the hypothalamus, a brain structure directly associated with body's homeostatic control (Kohno et al., 2016).

Consistent with the common neural site that monitors interoception and taste perception, Frank and colleagues, who served 1 M sucrose solution while participants were undergoing functional magnetic resonance imaging, reported a positive correlation between accuracy in identifying sweetness and activation of the insular cortex in their healthy subgroup, as well as a tendency towards a relationship between accuracy in identifying sweetness and interoceptive deficits assessed by an eating-disorder questionnaire (Frank et al., 2016). Our finding of a novel link between hedonic responses to sweetness and interoception may, then, have support in insula's connectivity with higher order brain structures including the orbitofrontal cortex, which is known to respond to taste affective valence (Small, 2010). Notably, insular activation has been related both to cardiac (Schulz, 2016) and gastric cues (e.g., stomach distention, subjective satiety/fullness; see: Wang et al., 2008). Therefore, it seems reasonable to speculate that if a broader relationship between affective valence of external stimuli and ability to sense the internal state of the body was suggested, this may have implications in the level of pleasure one seeks from a given stimulus to match their homeostatic or emotional internal needs. Considering the vulnerable interoceptive sensitivity to insults from the obesogenic environment (Bilman et al., 2017; Sample et

al., 2016), such a relationship could point to additional mechanisms underlying obesity epidemic and illustrate how attenuated interoceptive abilities may confer elevated risk of obesity susceptibility.

In contrast to our observation that SLs outperformed SDs in objective interoceptive measures, when participants self-reported their beliefs about their capacity in detecting and self-focusing on internal bodily sensations, there were no phenotypic differences across either measure of interoceptive sensibility. Regarding confidence scores, they were averaged around the middle point (i.e., neither guess nor complete confidence), while relatively small variances were calculated indicating that, overall, participants did not provide guess responses neither were they familiarized with the tasks. The results from the BPQ (which provides a measure of interoceptive sensibility across a range of internal bodily sensations) further confirmed the divergence between interoceptive performance and sensibility (i.e., true ability versus confidence in one's ability). We also examined the phenotypic differences in metacognitive interoceptive awareness derived from each of the heartbeat detection tasks, and found that SLs and SDs did not differ in their metacognitive insight into own interoceptive abilities. That is, their ability to know when their responses did or did not correspond to their actual heartbeat data.

The distinct effect of phenotype on interoceptive performance versus sensibility, metacognitive awareness, or trait prediction error is not entirely surprising given the clear dissociation between the different constructs of interoception in the framework proposed by Garfinkel and Critchley (2013). As detailed by Garfinkel et al. (2015), an individual's belief in their own interoceptive aptitudes should not necessarily be taken as an accurate predictor of the their ability in detecting interoceptive signals; this idea is further supported by the notion that top down and bottom up processes are rather distinguishable. It has also been argued by others that – unlike with one's broader psychological state – experiencing significant changes in emotions and perceptions requires one to be consciously aware of their internal signals (Gibson, 2019). Considering the metacognitive aspects of self-regulation (Whitebread & Pino-Pasternak, 2010) and the consequences of self-dysregulation (Vainik et al., 2013) and particularly impaired emotional regulation (Fernandes et al., 2018) in eating behaviour, attenuated ability to

mentally represent internal body state may leave one more vulnerable to influences of the modern affluent food environment. Recently, Willem and colleagues demonstrated a link between obesity and both interoceptive sensibility deficits and self-dysregulation (Willem et al., 2019). In similar work, enhanced awareness of internal state of the body has been theoretically (Calì et al., 2015) and empirically (Willem et al., 2020) suggested to compensate for the positive association between different interoceptive facets and emotional eating. Our data showing that SLs were more prone to emotional eating than SDs supports this premise; similar observations have also been made elsewhere for high interoceptive performers (Koch & Pollatos, 2014; Young et al., 2017). Notably, although acute changes in interoceptive performance have been achieved at experimental settings (Ainley et al., 2012, 2013; Filippetti & Tsakiris, 2017), interoceptive performance is regarded as a relatively stable trait (e.g. Bornemann et al., 2014; Melloni et al., 2013). Conversely, interoceptive sensibility and awareness have been reported to improve subsequent to interventions targeting the brain-to-body axis such as meditation or contemplative practice (e.g. Garfinkel, Mclanachan, et al., 2017; Khalsa et al., 2008; Parkin et al., 2014).

In line with their enhanced abilities to detect internal body sensations more accurately, SLs in our study were both more mindful and intuitive eaters than SDs. Our data align with previous research showing positive correlations between interoceptive accuracy scores derived from heartbeat tracking tasks and intuitive eating (Herbert et al., 2013; Richard et al., 2019). In support to the genetic basis of obesity development and either the setting or settling point theories (reviewed in Speakman et al., 2011), SLs also appeared to be better at 'resisting to obesity'. Resistant obesity profile is a assumed to reflect a weaker inherent predisposition to obesity development along with a better ability to maintain a healthy body weight more effortlessly. Smucny and colleagues (2012) have linked increased grey matter volume in the insula, which is known to be important in interoceptive processes in the brain, with this 'obesity resistant' profile.

Regarding our mediation analyses, only the relationship between sweet liker phenotype and emotional eating in response to positive and negative stimuli was fully explained by interoceptive performance. This supports the increasingly recognized relationship between sensing the internal body and emotional experiences (Critchley &

Garfinkel, 2017). Further, it highlights a closer relevance of sweet-liking to the homeostatic aspect of interoception. By illustrating such independence from interoceptive performance of the relationship between sweet liker phenotype and eating habits and behaviours that rely on internal cues to monitor feeding behaviour, it also seems reasonable to conclude that being a SL may reflect a better attuned sense of bodily state. Following this reasoning, the present data suggests the sweet liker phenotype classification we recently put forward (Iatridi et al., 2019a) could be conceived as a means to operationally characterize a profile that links exteroceptive and interoceptive information. For instance, considering the argument that ingestion of sugars may facilitate synthesis of neurotransmitters that elicit positive emotional cues (Gibson, 2012), our preliminary evidence that SLs recruited more coping mechanisms such as increases in food intake in response to negative compared to positive emotions, may further support SLs' enhanced sensitivity to interoceptive signals.

From an evolutionary standpoint, it is believed that taste systems were initially evolved to inform us about the nutritional value or toxicity of food stimuli and therefore, we developed mechanisms that facilitated the intake of calorically dense foods to cope with food scarcity (Drewnowski et al., 2012). A classic demonstration of this phenomenon is featured by sensory experiments in human and non-human neonates whereby sweetness, as opposed to bitter and sour tastes, elicited positive facial expressions and matching sucking responses (Desor et al., 1973; Maone et al., 1990; Rosenstein & Oster, 1988; Steiner et al., 2001); both behaviors may resonate an inherent drive towards foods providing a safe and useful source of energy and rejection of those being potentially poisonous. Such typical sensory reactions have also been linked to biological indices of growth in children and adolescents (Coldwell et al., 2009; Mennella et al., 2014). Although the cross sectional nature of the present dataset does not allow for cause-effect relationships to be inferred that is to conclude whether enhanced interoceptive abilities result from the enhanced liking for sweetness or whether enhanced interoceptive abilities form an enhanced liking for sweetness, the above evolutionary/biological basis of sweet-liking considered, being classified into the SL phenotype may constitute a physiological mechanism that contributes to the feedback loops generated as a response to the internal state of the body.

In addition to our novel finding that sweet-liking associates with interoceptive performance, we also provided evidence about a potential general body control system that monitors one's ability to sense cardiac and gastric signals. To interpret these data, two issues require consideration. First, the observed correlations of interoceptive performance during heartbeat and gastric tasks reached significance only when the accuracy scores from the heartbeat tracking task were analysed. Taking into consideration that the pattern of correlation was the same across heartbeat tasks, that is, independent of the heartbeat task, cardioceptive accuracy was negatively associated to percentage ingested volume of water required to produce satiation, the difference in statistical significance may be attributed to characteristics inherent to the distinct heartbeat detection tasks (Garfinkel et al., 2015). Presently, there is very little information regarding correlations of heartbeat discriminating ability with gastric interoception. An early report by Whitehead and Drescher (1980) is the only one we can find that tested the relationship between interoceptive performance in a heartbeat discrimination task and gastric sensitivity. In that study, participants were instructed to indicate possible synchronicity between a visual stimulus (i.e. flashing light) and their gastric contractions evoked through an inflating balloon within participants' stomach, as well as their heartbeats (Whitehead & Drescher, 1980).

The second issue of note concerns the gastric interoception protocol. Although the WLT introduced in the field eliminated methodological constraints attached to measuring gastric sensitivity by producing mechanical distention through barostats (e.g. gastric balloons filled with water: Geliebter & Hashim, 2001), a serious confounding variable remains underconsidered: individual differences in stomach capacity. As shown here, if absolute ingested water volume had been the gastric sensitivity measure of choice, we would have failed to observe phenotypic differences in interoceptive performance. Our findings agree with those of Herbert et al. (2012) where, besides controlling for substantial variations in stomach capacity by recruiting only normal weight women, they measured changes in gastric movements via electrical sensors, which further reduced potential noise from subjectivity in participants' responses regarding sensed satiety. Following a different approach where participants ingested a predetermined water volume adjusted for their body size, Ferentzi and colleagues

(2018) proposed a divergence of gastric and cardiac interoceptive axes. Critically, van Dyck and colleagues who put forward the water load protocol used here, reported a non-significant (p = .107) correlation between cardiac and gastric interoceptive abilities; the extent to which an interoception task that exclusively relies on eating-related stimuli/memory could match interoceptive performance across discrete visceral events was questioned (van Dyck et al., 2016). Further research to disentangle these issues is needed. Notably, the overlap between the two modes of interoception measured here was partially dependent on the sweet liker phenotype, with SLs (who showed enhanced interoceptive abilities) showing a stronger cross-modal relationship. Indeed, in prior reports where the two interoceptive axes were not associated, checks for interactions of groups differing in interoceptive performance on correlations under investigation were not reported (Ferentzi et al., 2018; Keenan, 2015; van Dyck et al., 2016). Further, sex-mixed cohorts (Keenan, 2015) are expected to suffer more from limitations such as not accounting for differences in stomach capacity unless a measure of body size is considered (discussed in Monrroy et al., 2019).

Our study has several strengths and weaknesses that should be noted. Strengths include the examination of interoceptive processes across constructs and senses, as well as consistent testing conditions across participants using specific wording in instructions (Desmedt et al., 2018; van Dyck et al., 2016) and the same equipment throughout (Murphy et al., 2019), as well as not providing feedback on the participants' performance (Ring et al., 2015). In addition, comparison of the present dataset with similar reports in literature suggests that the magnitude of phenotypic differences in interoceptive accuracy across all three objective interoceptive tasks (heartbeat tracking: $\Delta Mean$ = .168; heartbeat discrimination: $\Delta Mean$ = .092; WLT: $\Delta Mean$ = .093) is of both statistical and clinical significance. For example, in a 2016 study, anorexic patients were presented with significantly lower heartbeat tracking-specific interoceptive accuracy than their matched healthy controls ($\Delta Mean$ = .017: Fischer et al., 2016). Likewise, Critchley and colleagues reported nearly half, yet significant (p = .03), difference in interoceptive accuracy derived from the heartbeat discrimination task between psychiatric outpatients and healthy controls (Critchley et al., 2019). For the WLT, in van Dyck et al. (2020) where the same experimental protocol was used, water needed for

satiation as a percentage of total stomach capacity was calculated at 0.620 and 0.565 in patients with eating disorders and their healthy counterparts, respectively (higher values indicate lower gastric interoceptive abilities).

Some limitations of the present study call, however, for caution. First, due to time constraints, our measurements of anxiety and depression were based on widely used but brief assessment tools (i.e., the General Anxiety Disorder-7 and Patient Health Questionnaire-9) rather than more exhaustive psychometric tests such as the State-Trait Anxiety Inventory and the Beck Depression Inventory. However, this limitation is tempered somewhat in that we recruited participants from a non-clinical population, and also excluded participants with known mental disorders from participation, so we believe use of a brief assessment tool is justified. We should also note that the participants were young, educated women of mostly normal weight, so these data may not generalize to men, older individuals, or individuals with obesity, especially since sex (Grabauskaitė et al., 2017), age (Murphy, Geary, et al., 2018), and BMI (Herbert & Pollatos, 2014) have also shown to influence interoception measures.

5.5 Conclusion

Consistent with the literature on newborns (Steiner et al., 2001) and children in acute developmental stages (Coldwell et al., 2009; Mennella et al., 2014) where signals for strong liking for high sweetness are generated internally, our preliminary data here suggest a connection between sweet-liking and interoceptive abilities in adults: individuals with strong liking for high sweetness had enhanced interoceptive performance and were more mindful and intuitive eaters than those who exhibited aversive responses to high sweetness. We also noted interesting parallels between cardiac and gastric interoception, suggesting a possible generalized precision in sensing visceral events. Overall, measurement of individual variation in sweet-liking may prove useful to identify those predisposed to poorer interoceptive abilities and, hence, to food choices beyond internal needs, as well as to adjust healthy eating advise and obesity interventions that target highly interoceptive individuals towards addressing their elevated sensitivity to emotional eating (Chen et al., 2018). Whether this will be confirmed by clinical trials, it remains to be seen.

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Authors' contribution

VI conceptualized this study, developed study's protocol, collected and analysed the data, interpreted the results, and drafted the manuscript. LQ contributed to development of study's protocol and data analysis, and critically reviewed the manuscript. JEH and SNG critically reviewed the manuscript. MRY contributed to development of study's protocol and interpretation of the results, and critically reviewed the manuscript. All authors approved the final version of the manuscript.

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Declaration of interest

The authors have no declarations of interest.

Chapter 6 (Paper 5)

Does the effect of an 8-day exposure to a diet high in simple sugars on liking for sweetness and highly palatable foods and beverages differ by sweet-liking phenotype?

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Abstract

Within the 'food addiction' framework, overconsumption of sugars has been theorised to increase liking for sweetness perpetuating intake of sweet-tasting foods. Empirical evidence of the above narrative has primarily focused on the effect of repeated exposure to a single sweet-tasting product on subsequent liking and eating behaviour with mixed findings. Here, we tested whether exposure to a whole diet high in sugars influences overall sweet-liking and liking and desire-to-eat for palatable snacks. We also posed the question of whether individual variation in hedonic response patterns to sweetness alters susceptibility to the effects of the high-sugar diet. Under laboratory conditions, 93 young non-restraint eaters (31 sweet likers, 31 inverted-U responders, 31 sweet dislikers) rated 1 M sucrose (overall sweet-liking) and snacks typical of a Westernised diet before and after an 8-day exposure to a diet providing at least 10% of energy from sugars (exposure condition) or their usual diet (control group). For the exposure diet, tailored amounts of high-sugar/low-fat breakfast items and snacks were provided. Condition had a direct effect on overall sweet-liking with participants who received the high-sugar diet decreasing their liking. Sweet-liking remained stable in the control group. No interaction between condition and baseline classification into sweet-liking phenotypes was calculated. For the palatable snacks, findings about liking were fully dependent on phenotype: sweet dislikers (SDs) in the exposure condition experienced a small rise in liking relative to a significant decline among SDs in the control group. There was no significant change in desire-to-eat ratings for the palatable snacks. Although sensory fatigue was evident for overall sweetness, a preliminary role of repeated exposure and overconsumption of sugars in directing food preferences towards highly palatable options was suggested with SDs affected the most. Future research is required to confirm a simultaneous alteration in voluntary intake of palatable foods as a result of exposure to diets that exceed the recommended intake for sugars.

6.1 Introduction

Although food environments have the potential to support human health and wellbeing, they are currently threatening both. For decades public health initiatives have failed to effectively remove the 'obesogenic' factors from our environments (Livingston, 2018); these 'obesogenic' factors are known to promote overconsumption which, if coupled with sedentarity, could lead to positive energy balance and subsequent weight gain (Spiegelman & Flier, 2001). Lately, more concerted efforts to address obesity epidemic have also included relevant legislative interventions such as taxation of free sugars in food products (Redondo et al., 2018). Free sugars, defined as the monosaccharides and disaccharides added to foods and beverages and the naturally occurring sugars (milk extrinsic sugars excluded) in honey, syrups, and fruit and vegetables juices of all kinds, constitute a major component of the westernisation of the food environments (Popkin & Nielsen, 2003). For simplicity, we henceforth refer to free sugars as sugars.

WHO recommends intake of less than 10% of dietary energy as sugars (WHO, 2015). The 10% threshold was also highlighted in the 2015 Dietary Guidelines for Americans (USDA, 2015) and the Nordic Nutrition Recommendations (Becker et al., 2004). Since 2015, the UK has adopted an even more demanding limit, recommending a reduction in intake of sugars to less than 5% of total energy intake (SACN, 2015) that is a roughly 50% reduction compared to latest estimation of sugar intakes for UK adults (NDNS, 2018). Such recommendations were initially based on the relationship between patterns of consumption of foods rich in sugars and dental caries (WHO, 2017), but it also finds support in evidence for benefits for weight management and beyond. Reviews and meta-analyses report moderate to strong relationships between high intake of sugars and particularly overconsumption of sugar-sweetened beverages and adverse health outcomes, such as obesity (Hu, 2013; Malik et al., 2013; Te Morenga et al., 2013) and metabolic diseases. Follow-up data from prospective cohorts also indicate that high intake of total sugars (Anderson et al., 2020) or systematic high consumption of sugar-sweetened soft drinks (Mullee et al., 2019) increase all-cause mortality independent of known confounders. To date, comprehensive empirical confirmation for the proposed

threshold in intake of sugars or the direct effect on food choice and intake of sustaining a diet that exceeds the recommended threshold for sugars is lacking.

Besides the profound direct benefits from the above policies and recommendations in reducing total energy intake and/or improving diet quality, there is this longstanding belief that if decreased exposure to sugars or sweetness was achieved, it would promote lower preferences for sweet-tasting foods and beverages, and such generalised reduced desire for sweet-tasting foods and beverages would affect consumption alike (e.g., PAHO, 2016; WHO, 2019). A variant of this belief has been evidenced for dietary sodium intake and preferred saltiness: individuals who adhered to reduced-sodium diets experienced reductions to their preferred level of saltiness (Beauchamp et al., 1983; Bertino et al., 1982, 1986) which, over time, may facilitate voluntary reductions in their salt intake (CDC, 2018). However, there is only very little empirical evaluation as to whether such parallel adjustments with sodium and saltiness also occur for sugars and sweetness. Wise and colleagues showed that a 3-month exposure to a diet low in sugars increased perception of sweet intensity, but did not alter sweetness preference (Wise et al., 2016). Elsewhere, substitution of SBBs with either water or beverages with non-nutritive sweeteners significantly reduced intake of sweet tasting desserts only in the group which sustained exposure to sweetness (Piernas et al., 2013).

The rationale for the proposed causal chain linking sugars' exposure to sweetness liking and sweetness liking to sugars' overconsumption is largely based on the innately rewarding (Olszewski et al., 2019) and self-reinforcing (Berridge et al., 2010; Sclafani, 2018) properties of sugars and sweetness. In brief, once a sweet tastant is detected, reward- (Wise, 2006) and hedonic-specific (Yeomans & Gray, 2002) brain regions are activated. In turn, neural cascades that promote both explicit liking and implicit wanting are triggered (Finlayson & Dalton, 2012), often in a manner that overrides neuroendocrine signals typically protecting the internal milieu, which may subsequently promote addiction-like behaviours (Olszewski et al., 2019). 'Sugar addiction' theory has been developed to bridge the above mechanisms with the notion that the highly palatable foods of the modern environments hijack physiological reward processes in the brain leading to impairments in the decision-making processes similar

to those documented for drugs of abuse (Wiss et al., 2018). Indeed, 'food addiction' has been reported to non-linearly increase with BMI (Meule & Gearhardt, 2019). Nevertheless, there need to be efforts to document these presumed addiction-like effects of exposure to high-sugar diets to support relevant evidence-based recommendations.

Thus far, existent empirical evidence has provided no consistent support for a relationship between increased exposure to sugars and preference for or intake of sweet tasting foods and beverages (reviewed in Appleton et al., 2018). To understand inconsistencies in the relevant published data and better address gaps in knowledge, a few issues require consideration. The first issue concerns the ecological validity of exposure protocols: most clinical trials in adults employed approaches which provided for repeated exposure to a predetermined fixed amount of a single food product rich in sugars (Burger, 2017; Hetherington et al., 2000, 2002; Liem & De Graaf, 2004; Tey et al., 2012) and less often attempted to modulate the whole diet (Griffioen-Roose et al., 2012). An additional limitation relates to the use of some foods high in both sugars and fats as proxies for exposure to sweetness (Hetherington et al., 2000, 2002; Tey et al., 2012); concerns in regards to what nutrient and/or taste quality mediated the observed effects are raised. Finally, it could be assumed that efforts to conclude about putative effects of exposure to sugars on sweetness preference by interpreting changes in liking for the exposure product alone or a product of similar sensory characteristics miss a critical point: the well-established confounding effects of sensory specific satiety (i.e., decline in pleasantness associated with a food that is eaten relative to a food that has not been eaten: Rolls et al., 1981). Although a better understanding of the effects of repeated exposure over multiple days to a particular food product on its sensory evaluation could be of interest, careful experimentation of the dynamic role of sugar overconsumption in altering broader food preferences and associated intake may contribute to elucidating the underpinnings of human ingestive behaviour in the current obesogenic environments.

Current views highlight that, due to the obesogenic environment which variously highjacks homeostatic control of eating, an increasing part of human ingestive behaviour is driven by pleasure (Bilman et al., 2017; Sample et al., 2016). For example,

emerging empirical evidence from human studies indicates effects of exposure to high-fat/high-sugar diets on aspects of homeostatic control of eating in favour of intake beyond needs (Attuquayefio et al., 2017; Stevenson et al., 2020). A question arises: do whole diets high in sugars also directly affect food choice and intake through influences in pleasure? Likewise, it would also be of interest to examine whether the proposed addiction-like eating behaviours associated with exposure to high-sugar diets promote enhanced liking for and desire to consume a range of foods and beverages typical of a Westernised diet which are believed to elicit equivocal palatability without regards to their taste qualities. If such a generalised effect of exposure to sugars on preferences for highly palatable less nutritious foods is confirmed, informed decisions about policies aiming to reduce sugar overconsumption would be facilitated.

Sensory properties of foods are only one contributor among many (e.g., cultural environment, personal experiences) to direct food choice and intake (Mela, 2001). Still a convincing argument can be made that individual variation in taste hedonics may explain why 'obesogenic' factors of modern food environments affect some but not others. In prior work from our lab, we confirmed distinct anthropometric and eating behaviour-related profiles for individuals who exhibit different hedonic response patterns to varying sweetness (Papers 3 and 4). Hence, investigating whether one's sweet-liking phenotype interacts with the effect of exposure to sugars on sweetness liking might be important for providing relevant conceptual insights.

Collectively, more methodologically robust research that probes causal relationships is warranted before conclusions on the underpinnings of the role of sugar overconsumption in perpetuating intake of highly palatable energy dense foods can be drawn. To our knowledge, no data exist that test the effects of sugar overconsumption on alterations in liking for sweetness and broader preferences for sweet and non-sweet snack foods typical of a Westernised diet under the same design and through targeting one's whole diet over multiple days. To address this gap, a randomised controlled trial was performed consisted of measuring the effects of exposure to a high-sugar diet versus a group that continued with their usual diets on liking for sweetness, and liking for and desire to eat a range of highly palatable foods and beverages without regard to their predominant taste quality. To examine whether participants who differed in their

hedonic response pattern to sweetness also differed in their susceptibility to the effects of a high-sugar diet, we recruited people varying on this sensory dimension. This is the first time that individual variation in sweet liking is accounted for the study of the effects of repeated exposure to sugars.

6.2 Methods

6.2.1 Study design

Here, we designed a randomised controlled trial examining how repeated consumption of food products high in sugars alters generalised sweet liking and broader preferences for sweet and non-sweet food products typical of a Westernised diet. All investigations were also performed by sweet-liking phenotype to elucidate whether the above effect of repeated exposure to sugars depends on one's baseline hedonic response pattern to sweetness. To do so, we contrasted taste and related evaluations of simple sucrose solutions and a number of commercial foods and beverages before and after an 8-day exposure to the same breakfast and snacks which together provided 10% of each participant's daily energy needs from sugars. A control group completed the pre- and post-exposure evaluations but was not offered the breakfast items and the snack high in sugars.

6.2.2 Participants

Participants were students at the University of Sussex recruited to take part in a study described as investigating the effect of consumption of breakfast and snacks on one's mood; thus all participants would be naive of the experimental hypothesis until completing all tasks. Inclusion criteria were: aged 18-34 years; stable body weight (less than 10% change) in the last six months; and able to take breakfast in the lab in morning hours. Exclusion criteria were: lactose or gluten intolerant or a vegan; known food allergies or aversions to the products used in the study; be on a weight loss diet or a special diet for medical reasons; smoke regularly (> 5 cigarettes per week); medicated (excl. contraceptives); confounding health problems (diabetes, hypertriglyceridemia, abnormal oral glucose tolerance test, polycystic ovary syndrome); current diagnosis or

history of eating/feeding disorders; and, if a woman, have an irregular menstrual cycle or be pregnant or lactating.

To ensure that compliance to the protocol would not be hindered by restrained eating behaviours, infrequent breakfast consumption, or products considered unpleasant, prior to taking part, potential participants completed online the restrained scale of the Three Factor Eating Questionnaire (TFEQ: Stunkard & Messick, 1985), answered a question related to their breakfast routine, and reported liking for the exposure products; a number of foods and beverages similar to those used in the exposure condition were also rated to direct participants' attention away from the foods and drinks of interest (e.g., porridge and frosties, orange juice and apple juice, etc.). A score of 12 or higher on the TFEQ-restraint scale (4th quartile of TFEQ-restraint scores from a previous study in our lab targeting young, healthy adults of all three sweet-liking phenotypes: Chapter 4), breakfast consumption less than three times a week, or liking ratings for any of the exposure products lower than 40 on a 100pt visual analogue scale (VAS) ranging from 'Dislike extremely' and 'Like extremely', were indicative of eating behaviours, habits, or preferences incompatible with the study's eligibility criteria.

Participants qualified for the main study were further selected based on their hedonic response to sweetness to achieve an equal number of participants per sweet-liking phenotype per condition. As previously described (Iatridi et al., 2019), distinct hedonic responses to sweetness were defined as rating liking for 1 M sucrose solution higher than +15, lower than -15, or anywhere in-between on a -50/+50 VAS for the sweet liker (SL), sweet disliker (SD), and inverted-U (IU) phenotype, respectively. Due to the known low representation of the SD phenotype in the study's targeted age group/recruitment pool (Armitage et al., 2021; Iatridi et al., 2019a) and time and resources constraints that would not allow for a washout period, a parallel over a cross-over study design was decided. In addition and beyond the aforementioned practical constraints, as the magnitude, direction, and duration of the effect of exposure to a diet relatively high in sugars on liking for highly palatable snack foods and potentially their consumption were yet to be determined, a cross-over design is likely to be unsuitable to serve our study's objectives. Likewise, in a cross over design we would be unable to account for possible variations from participants' usual dietary intake due to short-term

but significant influences from the external environment (e.g., national celebrations, time-limited product promotions, etc.). Therefore, allocation to experimental conditions (exposure condition vs control group) was based on a pre-determined random schedule stratified by sweet-liking phenotype aiming at a 2:1 ratio between the exposure condition and the control group.

On the basis of prior work (Liem & De Graaf, 2004), a borderline large effect size to detect a significant change in liking for sweet-tasting food products following repeated exposure to sugars relative to non-exposure was expected. Using an a-priori sample size calculation with G-Power software (Faul et al., 2007), we estimated that a power of 80% and Cohen's d of 0.8 (minimum large effect size) with a sample size of 58 participants of a 2:1 ratio between exposure condition (n = 39) and control group (n = 19) would be sufficient to give >95% probability of detecting significant differences in changes in liking for sweet tastants/stimuli between the two conditions. However, if the effect of phenotype on post-exposure liking scores accounting for pre-exposure liking and experimental condition was considered, to achieve an 80% chance of rejecting the null hypothesis, with f set at 0.4 (minimum large effect size) and alpha at 0.05, a sample size of 92 participants would be required. Due to the short duration of the exposure period, the attrition rate was not expected to be higher than 10% (Liem & De Graaf, 2004), and therefore, we aimed to recruit between 95 and 100 participants. Towards the end of the study, further targeted recruitment was performed to obtain groups that were more balanced for their sweet-liking phenotype. The final study sample comprised of 97 participants: 65 participants in the IG group (23 SLs, 20 IUs, 22 SDs) and 32 participants in the CG group (11 SLs, 11 IUs, 10 SDs). Failure to attend the day/time-specific sessions prevented four participants (two SLs and one SD from the IG and one SL from the CG) from completing the study.

The study complied with the Declaration of Helsinki. Participants gave consent both at screening and, if qualifying, at enrolment and received £50 for their time or a combination of credits towards their courses' modules and momentary compensation. Given that minor deception was used during recruitment, full disclosure of the study's objectives was provided on a debriefing upon completion of study's last session. Ethical

approval for the study was granted by the Science and Technology Cross-Schools Research Ethics Committee of the University of Sussex (ER/VI40/4).

6.2.3 Exposure condition

Exposure products (breakfast items and a snack/dessert) aimed to contribute to 10% (9-11%) of each participant's estimated daily energy needs from sugars. This level of intake is double the recommendation by the Scientific Advisory Committee on Nutrition (SACN, 2015). Still, it matches the reported average sugars intake of the same age group in the UK (NDNS, 2018). As such, even if participants added this extra 10% to the existing average sugars intake, the sum would not exceed the 25% of their daily energy requirements which is the recommended upper limit for added sugars according to the Institute of Medicine (Trumbo et al., 2002).

The age- and sex-specific Henry equations (Henry, 2005) and the physical activity level estimated through the International Physical Activity Questionnaire (IPAQ: Craig et al., 2003) were used to estimate the individual energy requirements. Unless being overweight (body mass index between 25 and 29.9 kg/m^2) or obese (body mass index $\geq$ 30 kg/m^2) whereby the ideal (body weight for body mass index of 25 kg/m^2) or corrected (average of present and ideal body weight) body weight was used, respectively, the present body weight was entered in the energy calculation formulas. The physical activity level factors of 1.49, 1.63, and 1.78 (Henry, 2005) were matched to the low, moderate, and high activity categories as defined by the IPAQ (Patterson, 2015). Considering the dietary reference values for energy for women and men 19-34 years old (women: 2175 kcal; men: 2775 kcal; SACN, 2011), participants were then allocated to 1 of 8 energy bands ranging from 1175 to 3375 kcal in 200 kcal intervals and received a corresponding portion size of the exposure products (Table 6.3).

Commercially available foods and drinks that allowed for portion and sugar content customisation to achieve the desired level of exposure to sugars across participants of varied energy needs were chosen as the exposure food products. For breakfast, meals consisted of: flavoured instant porridge (Quaker Oatmeal So Simple pot) to be prepared with boiling water with the addition of brown sugar; orange juice

without added sugars or non-nutritive sweeteners (Tesco 150mL or ASDA 200mL own label packs of orange juice from concentrate); and cereal bars with jam filling (Go Ahead biscuit-style bars). A caramel-flavoured milk-based dessert low in fats was selected as the exposure snack/dessert (Tesco own label crème caramel pot). Exposure items and their nutritional information are presented in Table 6.2. During the 8-day exposure period, breakfast was served in the lab on Exposure Days 1, 3, and 7, whereas on Exposure Days 2, 4-6, and 8 participants consumed the breakfast items at home; the snack/dessert was provided exclusively for consumption outside the lab. All exposure products were required to be eaten to entirety.

6.2.4 Sensory Measures

6.2.4.1 Sweet Taste Test

The lab based sweet taste test described in Chapter 5 was employed to classify participants into the SL, IU, or SD phenotypes. For the majority of the study participants, it took place during the pre-exposure session on Day 0 (see 6.2.6 for details). However, as explained in 6.2.2, towards the end of the study, targeted recruitment was performed to ensure the required number of SLs, IUs, and SDs per study group, and therefore, the aforementioned sweet taste test took place in a separate lab session a few days prior to Day 0 (Figure 6.1). Average liking scores for the 1 M sucrose solution at pro- and post-exposure were also used as a measure of the effect on overall hedonic response to sweetness of repeated consumption of food products high in simple sugar in the within- and between-subjects comparisons.

6.2.4.2 Food Taste Test

A taste test that involved ingestion (3-5 g/solid item or 10 mL/liquid item) was used to measure participants' broader preferences for snack foods and beverages typical of a Westernised diet. Test foods and drinks were chosen to provide a range of snacks from both sweet, sour, salty, and fatty categories to account for different preferences (Table 6.1).

Table 6.1. Sensory and nutritional characteristics of foods and beverages comprising the food taste test

	Taste				Nutritional Information (per 100 g or 100 mL		
	Sweet	**Sour**	**Salty**	**Fatty**	**Energy (kcal)**	**Total Sugars (g)**	**Total Fats (g)**
Fizzy lemonade with 2% lemon juice (Schweppes)	�				18	4.2	0
Fizzy lemonade with 16% lemon juice (San Pelegrino)	▢	▢			22	4.7	0
Milk chocolate (Tesco)	▢			▢	547	45	32.1
Dark chocolate 85% cocoa (Tesco)				(+bitter)	585	15	47
Sweets (Marks & Spencer)	▢				324	54.2	0
Fizzy sweets (Marks & Spencer)	▢	▢			313	56.4	0
Sweet popcorn (Tesco)	▢			▢	482	16.7	23
Salty popcorn (Tesco)			▢		522	0.5	31.3
Crisps ready salted (Pringles)			▢		514	1.2	33
Crisps sweet chilli (Pringles)				(+spicy)	506	4.7	31

The test foods were presented on a tray in 6 cm diameter serving bowls and the test drinks in transparent 60 mL glasses. All items were labeled with a 3-digit code. Presentation order was randomised and counterbalanced across participants based on a 120-food taste test schedule, while the same presentation order per participant was followed during the pre- and post-exposure sessions. To avoid possible influences of the

test drinks on test foods, the two samples of lemonade were always tested first; still, test drinks' presentation order was randomised across participants. After ingestion, participants rated the associated food or drink on liking and desire-to-eat/drink. Responses were collected with VASs delivered through a computer software (SIPM). Rinsing with commercial bottled water (ASDA) followed each trial; rinsing water was expectorated. Rating for subjective sensations of hunger and thirst were obtained immediately before and after the food taste test. The use of VASs to measure subjective appetite has been widely accepted as valid and reliable (Yeomans, 2018).

6.2.5 Anthropometry

Height and weight of all participants were measured at the closest 0.1 kg and 0.1 cm using a stadiometer-digital scale (SECA) without shoes and with heavy clothing removed.

6.2.6 Study Procedures

Day 0 (Session 1 - pre-exposure)

Following the online screening procedures, participants qualified for the main study attended Session 1. Standardised instructions to refrain from consuming any food or drinks (excluding water), smoking, chewing gum, and brushing their teeth for the two hours before the sensory tests were given beforehand. Upon completion of the sweet taste test, participants' sweet-liking phenotype was identified, and those selected to continue were randomly allocated to the two conditions based on the schedule described above. After a 15-minute break to reduce carryover effects from tasting the sucrose solutions, the food taste test took place. Finally, participants answered questions about their usual engagement in physical activities (IPAQ), provided their demographic data, and the researcher took their weight and height; the following sessions were also scheduled. To prevent influences of current weight status on later dietary choices and intake, the results of the anthropometric assessment were not shared with participants.

Days 1, 3, and 7 (Sessions 2, 3, and 4 – exposure)

Only participants allocated to the exposure condition attended Sessions 2, 3, and 4, which took place on Exposure Days 1, 3, and 7, respectively. Sessions 1 and 2 were separated by 4-6 calendar days. Depending on their usual breakfast routine, participants arrived at the lab in morning hours (0815h to 1100h) having skipped breakfast and also refrained from drinking flavoured beverages (e.g. coffee or tea) the two hours before their appointment. First, participants tested (ingestion involved) and rated all breakfast items for liking, sweetness, and desire-to-eat/drink on a computerised 100pt VAS anchored at two extreme points ('Like extremely' and 'Dislike extremely', 'Not sweet at all' and 'Extremely sweet', and, 'No desire to eat/drink the [*name of breakfast item*]' and 'Strong desire to eat/drink the [*name of breakfast item*]', respectively). Them, they were asked to finish the served breakfast at their own pace. Subjective appetite (hunger, fullness, thirst) and mood states (happy, angry, anxious, and tired) were measured at two time points during each breakfast session (pre-consumption and post-consumption).

Before leaving the lab, participants were provided with take-home food boxes that would cover the breakfast meals and desserts/snacks until the next lab visit. Take-home boxes contained the same products served in the lab-based breakfast pre-packed into sealed plastic bags labelled with the relevant consumption day and clear preparation/consumption details available in hard copies and online. Paper spoons for the porridge and the snack/dessert were also supplied to promote compliance to the protocol. All food items were prepared in our facilities following standard operating and hygiene protocols (foods sourced from Tesco's and ASDA).

A two-level approach to monitor compliance to the exposure protocol was employed. First, in line with relevant practices from previous studies (e.g., Arciero et al., 2016; Krishnan et al., 2020), participants were instructed to return all used food packages within the day-specific plastic bag to receive new supplies. Secondly, on the home consumption days, participants were asked to record their perceived hunger (pre- and post-consumption), as well as their liking, intensity, and desire to eat for the freshly prepared porridge on a day-specific rating sheet provided by us or by visiting an associated online survey. As with the lab-based breakfast days, a mood question ('How

happy are you right now?') was integrated into the main ratings so that the cover story, i.e. how consumption of breakfast and snacks alters mood, to be adequately supported. To eliminate discrepancies between a pen-and-paper and electronic VAS, home-based ratings were collected using a 9-point Likert scale.

Day 8 (Session 5 – post-exposure)

The sensory tests and weighing protocol of Session 1 were repeated in Session 5. Upon completion of all tasks, participants were debriefed and compensated for their time. To minimise any interference between participants allocated to the two conditions, pre- (Session 1) and post-exposure (Session 5) took place at different times than sessions when breakfast was served (Session 2, 3, and 4).

6.2.7 Statistical analysis

Baseline characteristics between the two groups (exposure, control) and across sweet-liking phenotypes (sweet liker, moderate liker/inverted-U, sweet disliker) were compared using independent T-tests, Pearson chi squares, and one-way analyses of variance (ANOVAs) as appropriate. To test whether ratings for liking and intensity of the sucrose solutions and liking and desire-to-eat of the snack foods and beverages were modulated by condition, analyses of covariance (ANCOVAs) were conducted, contrasting condition (exposure, control) separately with the post-exposure ratings for liking, intensity, and desire-to-eat correcting for the relevant pre-exposure (baseline) values. Two-way ANCOVAs were employed to test for possible interaction of sweet-liking phenotype with condition on the above sensory and prospective consumption measures. Finally, to investigate overtime changes in ratings for liking, intensity, and desire-to-eat of the exposure products, within-subjects repeated measures ANOVAs were performed. The significance level was set at $p < .05$. All analyses were conducted using IBM SPSS Statistics 25.
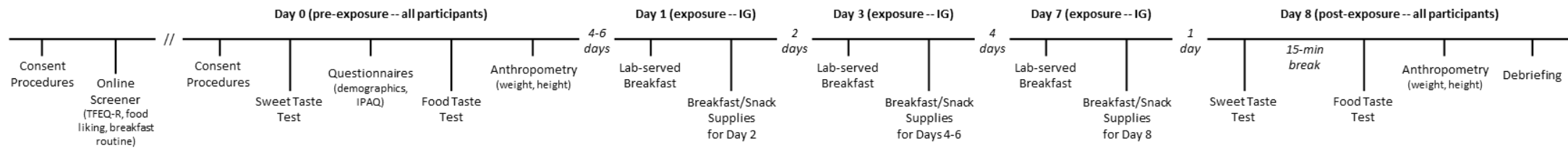
Fig. 6.1 Schematic representation of the study's testing procedures.

The online screener related to restrained eating, food likings, and breakfast routine took place a few days before the main exposure study and was accompanied by separate informed consent procedures.

IG, Intervention Group; IPAQ, International Physical Activity Questionnaire; TFEQ-R, Three Factor Eating Questionnaire;

Table 6.2. Nutritional information of exposure products

Product Name (Brand)		Portion Size	Nutritional information per typical portion					
			Energy (kcal)	CHO (g)	Sugars (g)*	Fibre (g)	Fats (g)	Proteins (g)
Instant porridge with apple-blueberries flavour (Quaker)		1 pot (57 g)	207	37.0	8.0	3.1	2.9	8.1
Brown sugar (Tesco)		1 tsp (5 g)	20	4.9	4.9	0.0	0.0	0.0
Orange juice	(Tesco)	1 carton (150 mL)	67	15.8	15.8	0.0	< 0.1	0.8
	(ASDA)	1 carton (200 mL)	90	21.0	21.0	0.0	< 0.5	1.0
Cereal bars with forest fruits flavour (Go Ahead)		1 slice (14.5 g)	56	10.9	4.6	0.5	1.0	0.8
Crème caramel (Tesco)		1 pot (100 g)	110	21.8	16.0	0.0	1.6	2.2

CHO, Carbohydrates

*Excluding milk sugars

Table 6.3. Serving size, simple sugar content, and contribution to estimated energy requirements of exposure products

Energy Band (EER range)	%EER from Sugars in Exposure Products (g of Sugars)		%EER (kcal) from Exposure Products	Breakfast					Snack/Dessert	%EAR from Breakfast	%Energy in Breakfast from Sugars	Fiber (g) to Total CHO (g) ratio in Breakfast
	Goal	Achieved		Instant Porridge (1 pot)	Brown Sugar (g)	Orange Juice (mL)	Cereal Slices (1 slice)		Crème Caramel (1 pot)			
1775 kcal (1675-1875)	10.0% (44.4 g)	10.0% (44.4 g)	23.5% (418 kcal)	1	8	150	1		0.5	20.4%	40.1%	0.050
1975 kcal (1875-2075)	10.0% (49.4 g)	10.6% (52.4 g)	23.9% (473 kcal)	1	8	150	1		1	18.4%	40.1%	0.050
2175 kcal (2075-2275)	10.0% (54.4 g)	10.5% (57.0 g)	24.3% (529 kcal)	1	8	150	2		1	19.2%	39.1%	0.050
2375 kcal (2275-2475)	10.0% (59.4 g)	10.4% (61.6 g)	24.6% (585 kcal)	1	8	150	3		1	20.0%	38.4%	0.049
2575 kcal (2475-2675)	10.0% (64.4 g)	10.4% (66.8 g)	23.6% (607 kcal)	1	8	200	3		1	19.3%	40.9%	0.047
2775 kcal (2675-2875)	10.0% (69.4 g)	10.5% (73.0 g)	25.3% (703 kcal)	1.5	12	150	2		1.5	19.4%	36.4%	0.054
2975 kcal (2875-3075)	10.0% (74.4 g)	10.5% (78.2 g)	24.4% (726 kcal)	1.5	12	200	2		1.5	18.8%	38.7%	0.051
3175 kcal (3075-3275)	10.0% (79.4 g)	10.4% (82.8 g)	24.6% (782 kcal)	1.5	12	200	3		1.5	19.7%	38.2%	0.051

Calculations were based on the manufacturers' nutritional information displayed on the product packaging and the assumption that 1 g of sugars provides 4 kcal. CHO, Carbohydrates; EER, Estimated Energy Requirements

6.3 Results

6.3.1 Participant characteristics

Included participants (*N* = 93) were primarily women (81%), Caucasians (62%), and with a mean age of 21.3 ± 0.3 years (range: 18.1 – 34.2 years). The majority of participants were normal weight (77%) with a mean BMI of 22.4 ± .3 kg/m^2 (range: 17.6 – 32.9 kg/m^2). There were no significant differences in baseline characteristics between participants assigned to the exposure condition and those in control group (Table 6.4); this was also confirmed when we tested for effects of condition by sweet-liking phenotype (data not shown).

Table 6.4 Baseline participant characteristics by condition

	Control Condition (*n* = 31)	Exposure Condition (*n* = 62)
	n (%)	
Sex (woman)	27 (87)	48 (77)
	Mean (SEM)	
Age (years)	21.9 (.6)	21.0 (.4)
BMI (kg/m^2)	22.7 (.6)	22.3 (.3)
EER (kcal/day)	2314 (52)	2384 (43)
TFEQ-Restraint[1]	7.2 (.6)	6.3 (.4)
Exposure products liking[1]		
Porridge	72.0 (3.1)	72.0 (2.0)
Orange juice	75.4 (3.1)	77.4 (2.1)
Cereal/Biscuit bars	73.4 (2.2)	73.9 (1.8)
Milk-based dessert	70.7 (3.5)	71.6 (2.4)
Sweetness liking (1 M)	51.3 (5.1)	54.0 (3.7)
Sweetness intensity (1 M)	54.8 (4.8)	55.9 (2.1)
Snacks average liking	68.9 (2.1)	64.9 (1.5)
Snacks average desire-to-eat	56.7 (2.5)	51.2 (2.0)

All *p*s > .05 for the comparisons between conditions

[1] Online screening questionnaire; EER, Estimated Energy Requirements (Henry equations adjusted for level of physical activity); SEM, Standard Error of the Mean; TFEQ, Three Factor Eating Questionnaire

To note, there was a main effect of phenotype on liking (F(2,89) = 3.584, p = .032, ηp^2 = .075) and desire-to-eat/-drink (F(2,89) = 6.116, p = .003, ηp^2 = .121) for the highly palatable snack foods and beverages; differences were more evident when our exploratory analyses were focused on phenotypic differences in sweet-tasting high-sugars snacks, i.e. sweetened lemonade with 2% lemon juice, regular sweets, milk chocolate, and sweet popcorn (liking: F(2,89) = 5.934, p = .004, ηp^2 = .118; desire-to-eat/-drink: F(2,89) = 6.131, p = .003, ηp^2 = .121). Post-hoc analysis revealed that, independent of condition, SDs liked the relevant products less and had a smaller desire-to-eat/-drink those snacks than both SLs and IUs (p < .05 for all paired comparisons except for the comparison about the liking score for all snacks between SDs and SLs which was equal to .057). No effect of phenotype on reported habitual use of the snack foods and beverages constituting the food taste test was found (p > .05 for all one-way ANOVAs).

6.3.2 Effects of exposure to a high-sugar diet on aspects of the dietary intervention

Repeated measures ANOVA on liking, sweetness intensity, and desire-to-eat/-drink scores for the breakfast meal showed no effect of time (all ps > .05). Examining each breakfast item separately (Figure 6.2), porridge which, on Day 1, was the rated as the sweetest of the breakfast items (porridge vs. orange juice: t(61) = 4.369, p < .001; porridge vs. cereal bars: t(61) = 2.543, p = .014), was considered as less sweet overtime (F(1.680,102.452) = 7.342, p = .002, ηp^2 = .107). Additionally, we observed a borderline increase in liking for the orange juice overtime (F(2,122) = 2.679, p = .073, ηp^2 = .042), which was coupled with an equivocal effect of time on desire-to-drink scores (F(2,122) = 4.946, p = .030, ηp^2 = .075). On Day 1, the orange juice tended to be the least liked breakfast item (orange juice vs. porridge: t(61) = -1.869, p = .066 ; orange juice vs. cereal bars: t(61) = -1.932, p = .058), whereas it was also rated as less sweet than the porridge (t(61) = -4.369, p < .001). All other effects of time failed to reach significance.

Regarding changes in anthropometrics between the two lab visits, there was no significant effect of condition on either body weight (F(1,90) = 2.213, p = .140, ηp^2 = .024) or BMI (F(1,90) = 2.491, p = .118, ηp^2 = .027) from the between-subjects analysis. Within-subjects comparisons per condition revealed a significant increase in body weight among participants in the exposure condition by 292 ± 110 g (F(1,61) = 6.943, p = .011, ηp^2 =

.102); body weight remain unaffected among those who were not exposed to the high-sugar diet ($F(1,30) = .002$, $p = .969$, $\eta p^2 < .001$).
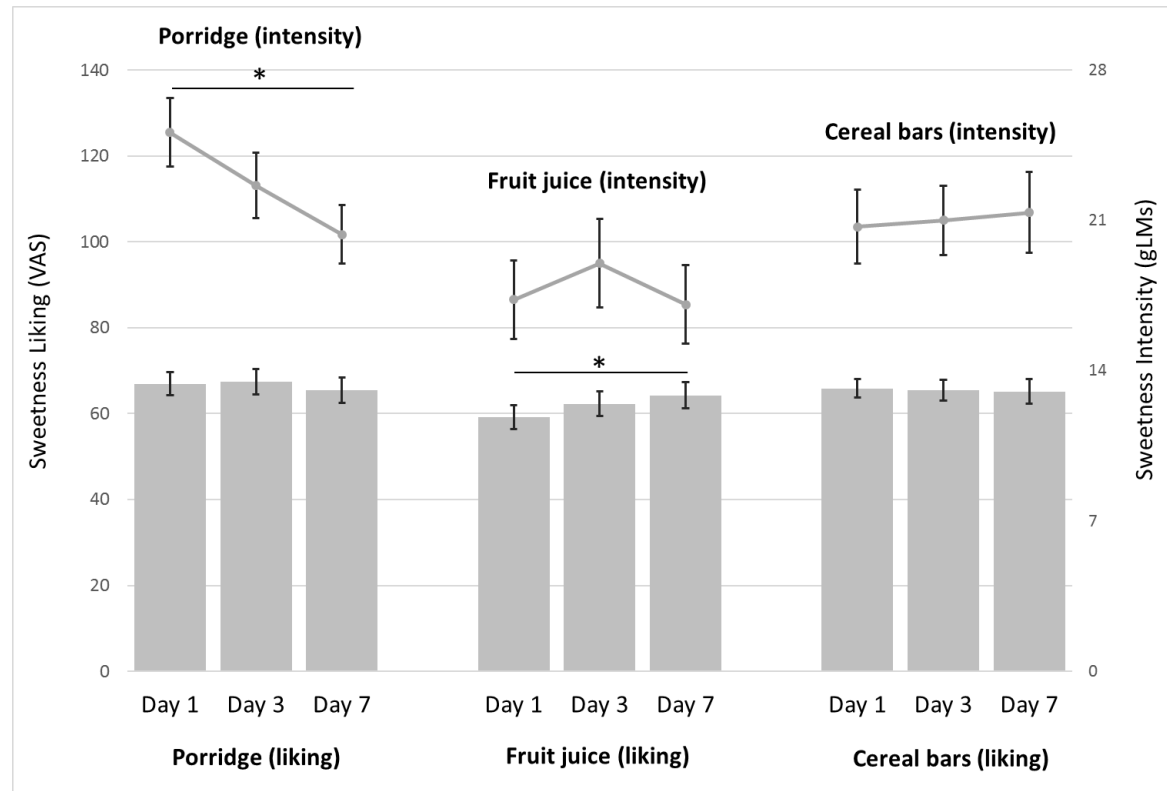
Fig. 6.2 Sweetness liking and intensity scores for the breakfast items served in the lab on Days 1, 3, and 7 of the dietary intervention. Error bars show standard error.

Asterisk (*) indicates significant overtime change in the associated ratings.

6.3.3 Effect of exposure to a high-sugar diet on liking for sweetness

A main effect of condition on post-exposure sweetness liking controlling for pre-exposure liking scores was observed ($F(1,90) = 4.047$, $p = .047$, $\eta p^2 = .043$). Liking for sweetness was significantly decreased for participants who were exposed to the high-sugar diet (t0: $M = 53.9$; $SEM = 3.7$; t1: $M = 48.6$; $SEM = 3.7$; $t(61) = -3.089$, $p = .003$) but did not differ per visit among those in the control group (t0: $M = 51.3$; $SEM = 5.1$; t1: $M = 51.6$; $SEM = 4.6$; $t(30) = .153$, $p = .879$). We found neither a main ($F(2,86) = 1.614$, $p = .205$, $\eta p^2 = .036$) nor an interaction effect of phenotype with condition ($F(2,86) = .712$, $p = .494$, $\eta p^2 = .016$) on post-exposure sweetness liking controlling for pre-exposure

relevant scores (Figure 6.3). Results from the second taste test showed that two participants (6.4%) in the control group versus eleven participants (17.7%) in the exposure condition experienced a change in liking for sweetness that qualified them for classification into a different sweet-liking phenotype than their baseline phenotype; 2 x 2 (change in phenotype x condition) cross-tabulation was not significant ($\chi^2(1) = 2.191$, $p = .139$).

Condition did not affect post-exposure intensity scores for sweetness accounting for pre-exposure relevant values ($F(1,90) = .143$, $p = .706$, $\eta p^2 = .002$). Overall, the 1 M sucrose solution was rated as less sweet during the second lab visit (t1), but the overtime decline reached significance only in participants who were exposed to the high-sugar diet ($F(1,61) = 5.326$, $p = .024$, $\eta p^2 = .080$).
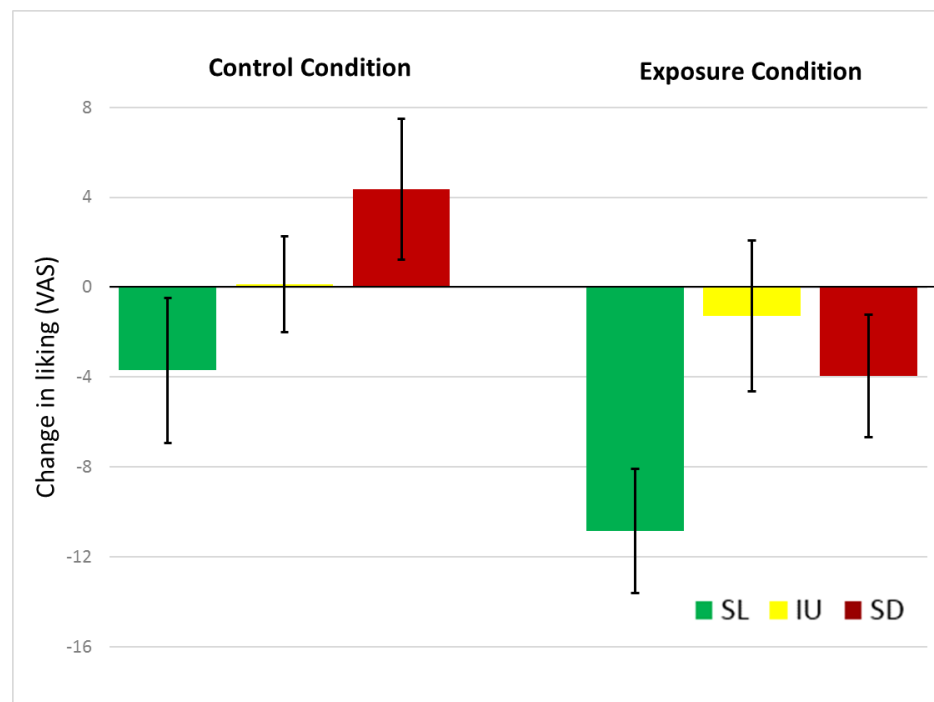
Fig. 6.3 Mean (± SEM) change in liking of the 1 M sucrose solution after the 8-day intervention per condition per phenotype.

6.3.4 Effect of exposure to a high-sugar diet on liking for and desire-to-eat snack foods and beverages

If considering all snack foods and beverages together (Table 6.5), there was no main effect of condition on post-exposure average liking after adjusting for relevant pre-exposure values ($F(1,89) = .453$, $p = .503$, $\eta p^2 = .005$), nor was there for the post-exposure average desire-to-eat scores ($F(1,89) = .021$, $p = .886$, $\eta p^2 < .001$). Within-subjects repeated measures ANOVA per condition, revealed a significant change (decline) in average liking scores in the control group ($F(1,30) = 4.388$, $p = .045$, $\eta p^2 = .128$) but not for participants in the exposure condition ($F(1,60) = 1.340$, $p = .252$, $\eta p^2 = .022$).

Exploratory analysis also revealed that post-exposure liking for sweet-tasting snacks providing energy exclusively from sugars (Table 6.5), i.e. the sweetened lemonade with 2% lemon juice and the regular sweets (sweetened lemonade with 16% lemon juice and fizzy sweets were not considered due to their possible sour after taste) tended to differ by condition after correcting for relevant pre-exposure values ($F(1,89) = 3.267$, $p = .074$, $\eta p^2 = .035$). Specifically, participants who were exposed to the high-sugar diet experienced no overtime decline in their liking for the sweetened lemonade with 2% lemon juice and regular sweets ($F(1,60) = .001$, $p = .892$, $\eta p^2 < .001$) as participants in the control group did ($F(1,30) = 7.715$, $p = .009$, $\eta p^2 = .205$).

The two-way ANCOVA for an interaction effect of sweet-liking phenotype with condition on post-exposure average liking for all snack foods and beverages after correcting for relevant pre-exposure liking scores was statistically significant ($F(2,85) = 5.962$, $p = .004$, $\eta p^2 = .123$). No such effect was evident for the average desire-to-eat scores ($F(2,85) = 1.125$, $p = .004$, $\eta p^2 = .122$). As shown in Figure 6.5, the interaction effect on liking was primarily due to the differences in responses by participants classified into the SD phenotype ($F(1,29) = 4.121$, $p = .052$, $\eta p^2 = .124$).

Table 6.5 Food taste test's liking and desire-to-eat ratings by condition and phenotype

	Snack foods and beverages (all)				Snack foods and beverages (sweet/sugar only)			
	t0 (pre)		t1 (post)		t0 (pre)		t1 (post)	
	Liking	Desire	Liking	Desire	Liking	Desire	Liking	Desire
				Mean (SEM)				
Control Group								
All	68.9	56.7	65.9	52.7	65.5	43.1	58.0	35.8
	(2.1)	(2.5)	(2.0)*	(2.6)*	(3.1)	(3.8)	(3.2)*	(4.1)*
SL	68.7	58.2	70.4	56.7	64.0	42.5	63.1	38.8
	(3.6)	(2.7)	(2.8)	(2.8)	(6.9)	(8.2)	(5.5)	(7.4)
IU	71.7	61.8	68.2	58.1	70.0	46.5	61.4	38.0
	(3.2)	(4.2)	(3.4)*	(3.1)	(2.8)	(5.9)	(3.4)*†	(5.2)
SD	66.0	49.5	58.7	42.8	62.0	40.1	49.4	30.5
	(4.1)	(5.3)	(3.0)†	(5.8)	(6.2)	(6.2)	(7.1)	(8.8)
Exposure Condition								
All	64.9	51.2	64.0	49.4	56.2	34.3	56.4	33.2
	(1.5)	(2.0)	(1.4)	(1.7)	(2.8)	(3.4)	(2.9)	(3.4)
SL	67.0	55.1	64.2	50.8	61.2	43.1	59.7	34.5
	(2.4)	(3.2)	(2.3)†	(2.9)*	(4.6)	(6.4)	(4.7)	(5.8)*
IU	68.2	55.1	66.8	55.4	57.8	32.2	59.5	37.5
	(2.2)	(2.9)	(1.9)	(2.4)	(4.0)	(4.5)	(4.3)	(5.9)
SD	59.9	43.8	61.2	42.4	49.9	27.5	50.1	27.9
	(3.0)	(3.8)	(2.9)	(3.1)	(5.6)	(5.9)	(5.8)	(6.1)

The asterisk (*) indicates a significant within-subject effect ($p < .05$ for repeated measures ANOVAs) on liking or desire-to-eat within each row. The dagger (†) denotes a significant difference in liking or desire-to-eat between conditions for the total sample and within each phenotype ($p < .05$ for one-way ANCOVAs).
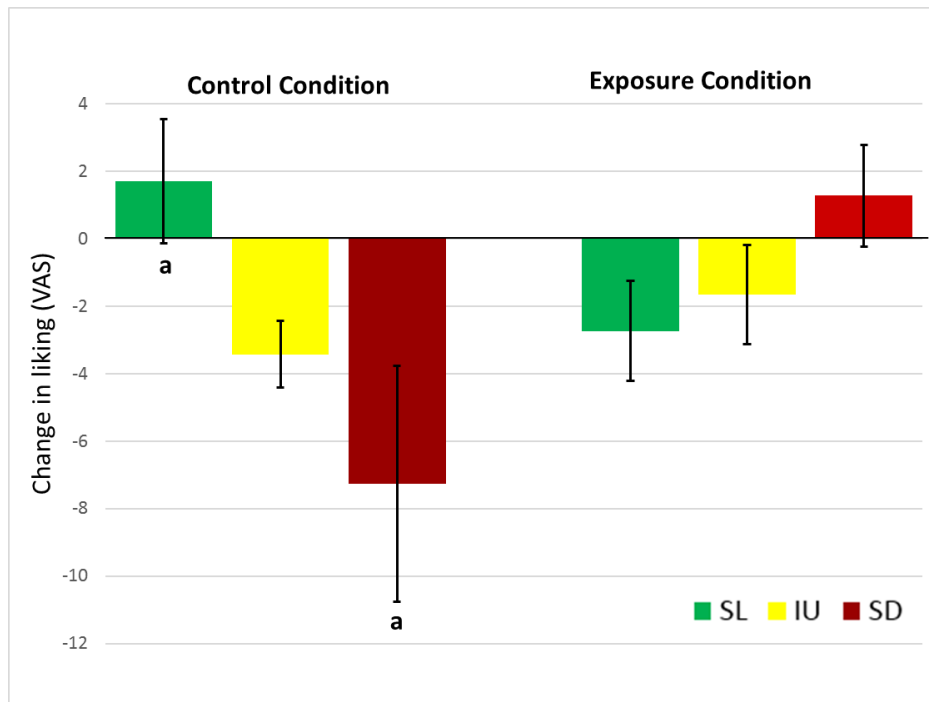
Fig. 6.4 Mean (± SEM) change in liking of the snack foods and beverages after the 8-day intervention per condition per phenotype. Change in liking was calculated by subtracting average liking scores for all snack foods and beverages at baseline (pre-exposure) from relevant average liking scores at the end of the intervention (post-exposure). Bars with same lowercase letter, i.e., alpha, are statistically significantly different from each other (comparisons per condition).

6.4 Discussion

Findings from the present study suggested that liking for sweetness and highly palatable snacks of various taste qualities can be influenced by repeated (8-day) exposure to a diet which provides at least double the recommended amount of energy from sugars in the UK (SACN, 2015), i.e. at least 10% of estimated energy requirements as sugars. However, the direction of these effects was anything but straightforward: type and/or taste quality of the stimulus and individual variation in liking for sweetness were associated with different outcomes.

First, while sweet-liking measured through simple taste solutions (1 M sucrose) was found to be a stable trait, i.e. control group's pattern of hedonic response to sweetness remained relatively unaffected between the different lab visits, exposure to the high-sugar diet was followed by a decline in liking for sweetness without alterations in perceived intensity. There were also no phenotypic differences in the susceptibility to

the effects of the exposure to the high-sugar diet on generalised sweet liking. Therefore, the observed reduced liking for sweetness due to repeated exposure to sugars from the diet is likely to be robust. It is also in line with the general principles of sensory specific satiety (Rolls et al., 1981) which, in the present context, could be interpreted as that repeated exposure to a specific taste drives perceived pleasantness from similar tastants downwards. Such stimulus satiation for rating of liking following repeated exposure to the same stimulus has been reported elsewhere, too (Hetherington et al., 2000, 2002).

Given that perceived sweetness is known to predict sugar content (Cox et al., 2018; Teo et al., 2018; van Langeveld et al., 2017), it was expected that participants repeatedly exposed to a diet high in sugars would, accordingly, like sweet-tasting stimuli less overtime. Contrary to this assumption and the observed decline in liking for generalised sweetness mentioned above, we failed to observe the same pattern of change in liking for the breakfast items repeatedly consumed by participants in the exposure condition. One explanation might be that the duration of our exposure protocol and/or the achieved level of exposure to sugars were inadequate for equivocal changes in liking for food stimuli associated with more complex sensory processing to emerge. However, in a study where young healthy adults consumed SSBs daily for 21 days, no difference between pre- and post-exposure liking scores for the exposure beverage was reported (Burger, 2017). Alternatively, it could have been that, unlike the effects on pleasantness derived from exposure to high-fat/high-sugar products such as exposure to chocolate in Hetherington et al. (2002) and Tey et al. (2012), when sugars prevail (e.g., in our exposure protocol utilising low-fat/high-sugar products), the well-evidenced potent self-reinforcing effects of sweetness (Berridge et al., 2010; Sclafani, 2018) may override those of sensory fatigue. Liem & De Graaf (2004) and Burger (2017), who used a fixed amount of sweetened fruit juice as the means to increase exposure to sugars, i.e., a product containing sugars exclusively, also failed to show a hedonic devaluation of the exposure product. To note, in the present trial, participants in the exposure condition experienced a significant overtime decline in perceived sweetness intensity for the breakfast porridge. Although, the role of dietary manipulation in real life sugar intake was not assessed, when sweetness intensity responses are low, it has

been argued that there may be a compensatory increase in sugar and/or energy intake to achieve the desired level of sensory stimulation (Wittekind et al., 2018).

Providing some support in favour of 'sugar addiction', we also found that, as opposed to participants in the control group who, during the second food taste test, rated the highly palatable snacks as less pleasant, there was no significant difference, i.e., no decrease, between the relevant pre- and post-exposure liking scores for those exposed to the high-sugar diet. Preliminary evidence suggested that these effects on ratings for liking were specifically relevant to the sweet-tasting snacks providing energy exclusively from sugars. When the individual differences in liking for sweetness were taken into account, a significant effect of the exposure to a high-sugar diet on liking for snack foods and beverages independently of their taste quality and macronutrient composition was revealed. Although alterations in the relevant ratings for desire-to-eat/-drink for did not reach significance, our findings highlight a potency of exposure to high-sugar diets to manipulate liking for, and potentially intake of foods and beverages of dissimilar tastes which acquire intrinsic characteristics that promote palatability beyond sweetness. In other words, a potential increasing dependence on overstimulation of the reward circuits resulted from an exposure to high-sugar diets (Wiss et al., 2018) may lead to a generalised enhanced pleasure seeking related to food choice and intake. This is an important observation, as it has been proposed that exposure to high-sugar and/or highly sweet diets could adversely affect diet quality provided that induced enhanced preference or appetite for sweetness encourages overall consumption of foods and beverages that are intrinsically nutrient poor (Wittekind et al., 2018).

A possible interpretation of the above finding is that exposure to sugars might have somewhat offset the observed drop in pleasantness for the highly palatable snacks among participants in the control group when these products were reassessed for liking. Tey and colleagues have also reported attenuated sensory specific satiety scores after a 12-week exposure to chocolate (Tey et al., 2012). Accordingly, it may be hypothesised that, if exposure to sugars had sustained for longer, such addictive-like effects on liking for highly palatable foods and beverages may have become more potent and ultimately resulted in increased liking even independent of the sweet-liking phenotype. In support to this assumption, the prominent concept of hedonic hunger described as motivation

to consume palatable foods beyond homeostatic needs could be considered (Lowe & Butryn, 2007). Given our evidence of some effects of exposure to the high-sugar diet on liking for highly palatable snack foods and beverages without regards to their taste quality or macronutrient composition, this chain of thinking cannot be disregarded. Building up on the same idea, in a fully controlled dietary intervention where participants were exposed to a predominantly sweet tasting diet high in sugars for a single period of 24 hours, ratings for liking and desire-to-eat of foods high in sugars were lower relative to those of salty snacks; authors concluded that effects were through sensory specific satiety (Griffioen-Roose et al., 2012). Whether effects of sensory specific satiety may dominate after acute exposure to a stimulus, but that effect is modulated after longer exposure periods has to be researched further. On the other hand, given that the sweet-liking phenotype-dependent effect of condition on responses to the food taste test was mainly due to the difference in liking ratings between SDs in the control group and SDs in the intervention group (Figure 6.4), a counterargument may arise: a significantly longer exposure to the high-sugar diet would, indeed, be required for the subgroup of participants with the lowest baseline liking and desire-to-eat ratings for the various Westernised foods and beverages to experience the effects of sensory specific satiety and to ultimately express a decreased liking for these highly palatable snacks. If so, a non-significant effect of exposure to a high-sugar diet or even a reverse effect (i.e., exposure decreases liking) could be hypothesised. Questioning that hypothesis, the current dataset considered, the aforementioned difference in liking between SDs in the control group and SDs in the intervention group resulted from a significant drop in liking at post- versus pre-exposure in SDs in the control group, whilst a merely subtle rise in liking in SDs exposed to the high-sugar diet was observed.

Based on the evidence from the present trial, monitoring change in liking for simple taste stimuli to study the dietary consequences of exposure to sugars might not be indicative of subsequent alterations in food preferences, and in turn food choice and intake. However, identifying one's sweet-liking phenotype proved important in elucidating individual differences in the susceptibility to the effects of sugar overconsumption. Specifically, SDs were affected the most by the exposure to the diet high in sugars showing a post-exposure rise in liking for snack foods and beverages

typical of a Westernised diet, even though the sweet-liking phenotype classification remained essentially unaffected: at post exposure only 1 of 21 SDs exposed to the high sugar diet was reclassified as non-SD (IU). A true effect of the exposure to sugars on dependence on reward seeking is suggested over a restoration of former liking for sweet tasting foods which, due to learning, had evolved into liking for less sweet gustatory stimuli. In similar lines, in a study where habitual SSB consumers were advised to substitute SSBs with either water or beverages with non-nutritive sweeteners in an attempt to reduce dietary exposure to sugars, SDs faced fewer difficulties with discontinuing caloric beverages relative to SLs that is SDs appeared to respond faster to manipulations of the food environment (Turner-McGrievy et al., 2016). Considering the contemporary view about the robust and rather unconditional relationship between disliking and non-use/non-intake (Hayes, 2020), our observation that exposure to high-sugar diets primarily affect individuals who innately dislike sweetness and, hence, follow diets low in sugars, may have serious implications in their subsequent ingestive behaviour; shifts toward highly palatable options and deterioration of their overall dietary quality may occur.

A final consideration that also constitutes a limitation of the current study is the lack of monitoring of participants' dietary intake prior to, during, and after the dietary manipulation with implications for both the interpretation and applicability of our findings. For example, it cannot be concluded whether the observed phenotypic-specific shift in liking for highly palatable foods and beverages following the exposure to a high-sugar diet translates to increased consumption. Nonetheless, despite being unable to statistically confirm that baseline dietary and/or sugar intake did not differ by study group (i.e., between exposure condition and control group) as we did with other baseline characteristics (Table 6.4), participants were randomly assigned to the two conditions, whereas they were also of a relatively narrow age range (18-34 years old) and similar socioeconomic background (predominately university students) that is eating habits are likely to resemble. On the other hand, instructing participants to maintain a similar diet throughout the 8-day exposure as a means to overcome the above limitation was incompatible with the study's objectives. For the control group, as discussed in detail in 6.2.2, accounting for special influences of the external environment on habitual dietary

intake was deemed critical. Likewise, in the light of the 2019 Public Health England report on the progress of the multifaceted sugar reduction programme demonstrating a significant decrease in consumption of the taxed sweetened beverages but an overall small increase in sugar sold from foods found to mostly contribute to the population's sugars intake (Public Health England, 2019), a downward compensation for the additional sugar supply from the high-sugar breakfast and snacks in participants in the exposure condition cannot be disregarded. Conversely, in accordance to our hypothesis, i.e., the possible effect of exposure to a diet relatively high in sugars on liking for highly palatable snack foods which in turn may increase their consumption, limiting participants' change in voluntarily dietary intake would be equally problematic.

6.5 Conclusion

In this randomised controlled trial, we provided convergent data for a role of repeated exposure to a high-sugar in altering liking for generalised sweetness with the pattern of effect following the principles of sensory specific satiety. Repeated exposure to a diet that approximates the average sugar intake in adults in the UK (i.e., 10% of energy intake from sugars: NDNS, 2018) may also influence liking for highly palatable snack foods and beverages which are typical of a Westernised diet. However, this effect appears to be of a dissimilar direction relative to the effect observed for generalised sweetness and also largely dependent on one's sweet-liking phenotype. Considering that results on desire-to-eat failed to follow the patterns observed for liking and that literature in the link between sweet-liking and overconsumption of sugars has also been inconclusive (Tan & Tucker, 2019), further research to elucidate potential alterations in real life intake of sugars and/or snacks of low nutritional value following a repeated exposure to a high-sugar diet is needed.

Authors' contribution

VI conceptualized this study, developed study's protocol, collected and analysed the data, interpreted the results, and drafted the manuscript. JEH and MRY contributed to development of study's protocol, while MRY also critically reviewed the manuscript.

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