Unconscious manipulation of human diet-related behaviors by the internal and external environment

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List of Abbreviations

AA	Amino acid
aal	Automatic anatomic labeling
ACC	Anterior cingulate cortex
AQ	Autism spectrum quotient
BA	Brodman area
BMI	Body mass index
BOLD	Blood-oxygen-level-dependent
dlPFC	Dorsolateral prefrontal cortex
DNA	Deoxyribonucleic acid
CI	Confidence interval
CSF	Cerebrospinal fluid
DTI	Diffusion tensor imaging
EPI	Echoplanar imaging/images
FD	Framewise displacement
FFQ	Food frequency questionnaire
fMRI	Functional magnetic resonance imaging
FEW	Family-wise error
GLM	General linear model
GM	Gray matter
GPCR	G-protein-coupled receptor
IBS	Irritable bowel syndrome
IFG	Inferior frontal gyrus
IQR	Interquartile range
MNI	Montreal Neurological Institute
MPE	Marketing placebo effect
NAcc	Nucleus accumbens
NHST	Null-hypothesis significance testing
OFC	Orbitofrontal cortex

PANAS	Positive and negative affect schedule
PET	Positron emission tomography
PLC	Placebo
POMS	Profile of mood stages
PPI	Psychophysiological interaction
ROI	Region of interest
rRNA	Ribosomal ribonucleic acid
rs-fMRI	Resting-state fMRI
SCFA	Short-chain fatty acids
SD	Standard deviation
SE	Standard error of the estimate
SPM	Statistical parametric mapping
SV	Subjective value
T1w	T1-weighted
TFEQ	Three-factor eating questionnaire
VER	Verum
vmPFC	Ventromedial prefrontal cortex
vStr	Ventral striatum
wfu	Wake Forest University
WM	White matter
WTP	Willingness to pay

Statement about projects included in this thesis

This thesis contains two separate projects and based on these projects, a review and a working paper have been published/prepared:

Review:
Plassmann H, Schelski DS, Simon M, Koban L. How we decide what to eat: Toward an interdisciplinary model of gut–brain interactions. WIREs Cogn Sci 2021; 13:1–22; https://doi.org/10.1002/wcs.1562

Working paper:
Schelski DS, Scheele D, Schmidt L, Hurlemann R, Weber B, Plassman H. Does trust play a role for placebo effects of marketing actions? An oxytocin administration study in men.

The first project of this thesis, "Study I: Manipulated by Marketing and Hormones? The relevance of Oxytocin for Marketing Placebo Effects on Food Product Perception", I already started during my Master studies. Thus, parts of the data were already included in my Master's thesis. During my PhD, I extended the data collection and analyses of this project and further revised and improved the parts of the analysis that I already conducted during my Master's. In the following, I will describe in detail in which aspects the parts included in the dissertation exceed what I did for my Master's thesis:

The project consists of two parts with the first part investigating Marketing Placebo Effects (MPEs) on taste pleasantness and the second part investigating MPEs on cognitive performance. During my Master's thesis, I collected data for both parts but only analyzed and described the taste pleasantness part. Thus, all theoretical background, results, figures, and discussion of the cognitive performance part (chapters 2.2.7, 2.2.10, 2.4, parts of chapters 2.5.1, 2.5.4, Fig. 8, Tab. 3, Tab. A 9 to Tab. A 13) are new and only included in this dissertation.

For my Master's thesis, I recruited and tested 289 participants, from which I could include 202 datasets for my analyses of the taste pleasantness part. During my PhD, I collected data from 54 additional participants to also have sufficient datasets for the cognitive performance task based on our pre-registered sample size. Thus, all analyses of the taste part have been repeated for this dissertation with a larger sample size than for the Master's thesis. In addition to the increased sample size, I updated and optimized all statistical analyses models (i.e. using non-robust models instead of robust models, including manipulation type as moderator instead of having a random intercept for manipulation type, including covariates). Thus, none of the analyses from the Master's thesis is included in exactly the same way in this dissertation and all results and tables in this dissertation are new (chapters 2.2.8, 2.2.9, 2.3.1 to 2.3.4, Tab. 2, Tab. A 1 to Tab. A 8). I further added a Bayesian analysis in this dissertation (chapter 2.3.4), which was not included in the Master's thesis. Moreover, I also prepared new figures to include the additional data and for optimizing the way of data visualization (Fig. 5 - Fig. 7). The figures in the methods section (Fig. 3 and Fig. 4) were specifically created for this dissertation and the working paper, but were not included in the same way in the Master's thesis. Only Tab. 1, presenting the consumables of the tasting task, was adapted from the Master's thesis.

All texts from introduction, methods, results, and the discussion are unique for this dissertation and were not used in the same way in the Master's thesis before. Content wise, this dissertation exceeds the Master's thesis because it discusses newly published studies that only became available during my PhD. Moreover, in this dissertation, I specifically discuss the contrasting results of the taste part and the cognitive performance part, which was not done in the Master's thesis, which only included the taste part.

Conclusively, the project presented in this dissertation exceeds the work done during my Master's in many ways and thus represents an independent scientific achievement.

1. General Introduction

1.1 How much control do we have over our dietary decisions?

Based on the title of this thesis, suggesting that human dietary decision-making is unconsciously manipulated, many questions might come to mind. Probably the most burning and provoking ones being:
"*How much control do I have over my dietary decisions?*" and "*Is it really my fault if I cannot withstand a tasty looking and heavenly smelling pizza while being on a diet*?".
More and more research acknowledge that a multitude of unconscious factors affect the way we perceive and consume food. Product labels and the description of food products can change how tasty we expect and experience a product to be (Maimaran and Fishbach, 2014; Plassmann et al., 2008; Raghunathan et al., 2006; Schmidt et al., 2017b). For example, expensive products are reported to taste better than identical products with a cheaper price tag (Plassmann et al., 2008; Schmidt et al., 2017b). Labels that put the focus on the health benefits of the food lead to lower taste expectations and lower experienced taste pleasantness (Maimaran and Fishbach, 2014; Raghunathan et al., 2006).
Mindsets and beliefs about food products purely induced by product information and context do not only affect expectations and taste perception but even physiological responses to food, perceived satiety, appetite, and even the amount of food intake (Brown et al., 2020; Crum et al., 2011; Finkelstein and Fishbach, 2010; Ogden et al., 2018; Park et al., 2020; Potthoff et al., 2019). Ghrelin, for example, is a gastrointestinal hormone that signals hunger and motivates us to eat. The consumption of calories induces the peripheral levels of the ghrelin to fall (Zigman and Elmquist, 2003). However, not only the consumed calories but also the belief about the food's calorie content can modulate ghrelin levels. When provided with a high-calorie information the same drink led to a stronger decline in ghrelin levels than when provided with a low-calorie information (Crum et al., 2011).

Eating pasta labelled as “snack” and served in a container while standing rather than labelled as “meal” and served on a plate at a table made participant eat more unhealthy snack foods afterwards (Ogden et al., 2018).

In addition to these cognitive factors, also peripheral homeostatic and metabolic signals can affect the perception of tastiness and can reinforce the desire to eat a certain food via neural mechanisms in the brain (De Araujo et al., 2020; 2013; Thanarajah et al., 2019). Repeated consumption of flavors paired with carbohydrate-derived calories led to increased liking of the flavors as compared to the same non-caloric flavors (De Araujo et al., 2013). Thus, the nutritional value of foods as sensed by the glucose metabolism can modulate preferences. However, not only our own metabolism but also the metabolism of our gut microbial community interacts with our eating behavior (Alcock et al., 2014; Gupta et al., 2020; Plassmann et al., 2021).

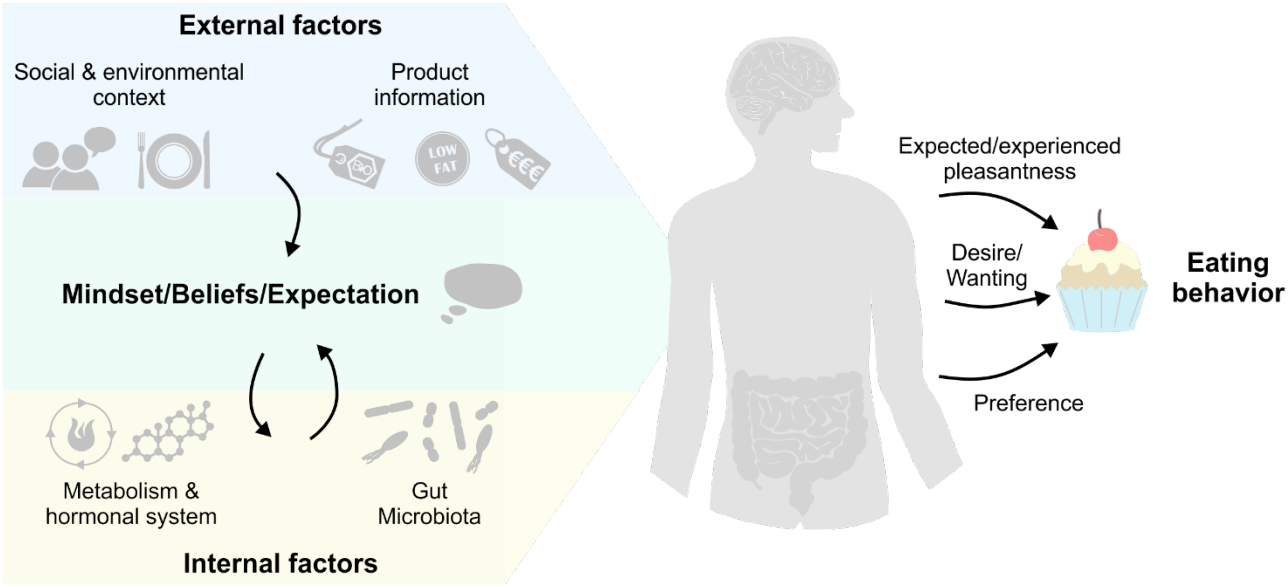

Fig. 1: Unconscious external and internal factors that interactively affect human eating behavior. External factors, including social and environmental context of food consumption and product information, shape beliefs and expectations about food products. Metabolism, hormonal system, and gut microbiota constitute internal factors that influence appetitive mindsets and are themselves sensitive to beliefs about the consumed food. External and internal factors can affect eating behavior by modulating experienced pleasure derived from eating, by changing the desire to eat, or by changing preferences and choice processes.

Conclusively, there are many external and internal factors that are not fully accessible to our awareness and our control but that affect our eating behavior (Fig. 1). The view that unhealthy eating habits and an unhealthy body weight are purely caused by a lack of willpower for a healthy diet and sufficient exercise is clearly outdated (Grannell et al. 2021). The growing knowledge about these unconscious determinants of eating behavior enables to develop better interventions to nudge healthier eating behavior (e.g. Turnwald et al., 2019).

1.2 Consequences of unhealthy eating

Obesity rates worldwide are rising with more than 13 % of the population being obese and more than a third of the population being overweight and thus at risk of developing obesity (World Health Organization, 2022). The World Obesity Federation even declared obesity as a chronic relapsing progressive disease that affects all ages, including pre-born babies, children, adolescents, adults and elderly (Bray et al., 2017).

The consequences of obesity are enormous and range from physical to psychological and economic effects (Chu et al., 2018; 2019). Obesity-associated physical health consequences include cardiovascular diseases, high blood pressure, type II diabetes, cancer, reproductive problems, and arthritis (Chu et al., 2018). Psychological consequences comprise depression, emotional and behavioral disorders, low self-esteem, and motivational problems that all lead to low quality of life (Chu et al., 2019). Social stigmatization inflicts further psychological harm on those affected (Rubino et al., 2020). Overall, obesity is associated with decreased life expectancy of affected individuals (Abdelaal et al., 2017). Additionally, the economic burden of obesity was estimated with US $ 2.0 trillion in 2014, which includes health care costs for treating obesity and its comorbidities but also indirect costs due to reduced productivity at work (Chu et al., 2018; Tremmel et al., 2017).

Thus, the maintenance of a healthy body weight is essential for the survival and well-being of the individual and the population and is achieved via the regulation of energy expenditure and energy intake in form of food (Prentice and Jebb, 2004). On this basis, the WHO recommendations for the prevention and reduction of overweight and obesity are not surprising: limited energy intake from total fats and sugars, increased consumption of fruits,

vegetables, whole grains, and nuts, as well as regular physical activity (World Health Organization, 2022). Surely, a healthy eating behavior is key for maintaining a healthy body weight, but actually eating healthy is not trivial in light of the above outlined unconscious external and internal influencing factors (Fig. 1).

In light of the described rising prevalence of overweight with all its consequences, the relevance of better understanding the unconscious drivers of unhealthy eating behavior become more important than ever.

1.3 Studying eating behavior

When studying the underlying mechanisms of eating behavior, one relevant distinction to make is between the experienced pleasantness (liking) of a food, wanting of food, and the preference for or choice of a food (Berridge and Robinson, 2016). Experienced pleasantness is the pleasure derived from orosensory stimulation during food consumption. Food wanting is the desire to eat a certain food and food preference describes the favoring of one food over the other(s) (Mela, 2006). All three are strong, separate drivers of eating behavior. In the laboratory setting, food wanting is usually measured indirectly via the effort individuals are willing to expend to get a food or their reaction times when approaching food (Finlayson and Dalton, 2012). Experienced pleasantness of food is commonly measured via self-reports after tasting, while preferences and choices are studied via forced food choice tasks (De Araujo et al., 2020). Experienced pleasantness of food products partially, but not completely, explains food choices with discrepancies probably arising from unconscious metabolic signals (De Araujo et al., 2020). In general, all three, experienced pleasantness, food wanting, and food preferences, are vulnerable to unconscious manipulations.

As outlined and illustrated above (Fig. 1), external and internal factors that can affect liking, wanting, and preference are of very diverse nature. Thus, it is not surprising that several different disciplines study eating behavior and its influencing factors from different perspectives. Among these disciplines are psychology, neuroscience, neuroeconomics, nutrition science, marketing, and microbiology. However, until today, these disciplines mostly remained separate (Berthoud, 2011; Plassmann et al., 2021; Rangel, 2013).

Neuroeconomics, for example, study the cognitive and neural processes of decision-making (Fehr and Rangel, 2011). Nutrition research specializes on physiological factors and the homeostatic control of eating behavior while microbiology specifically looks at the interaction of gut-microbiota and host metabolism (Boscaini et al., 2021; Koliaki et al., 2020). Marketing research investigates how consumer's experiences and choices are affected by different marketing means (Enax and Weber, 2015). However, all these factors do not act in isolation. To better understand unconscious drivers of eating behavior, different areas of research need to be brought together for a more comprehensive perspective.

Therefore, we used a multidisciplinary approach to study unconscious influences on eating behavior in two distinct projects:

In study I, we investigate subjective, and objective (taste) experiences derived from food consumption and the interactive impact of external and internal factors on these experiences. More specifically, we focus on the influence of the hormone oxytocin (OXT) on consumer's reaction to product information and social and environmental context during consumption.

This way, we combine research about marketing effects on food perception with the neuroscience of the OXT system.

In study II, we investigate the impact of a synbiotic intervention, which modulates the gut microbial composition, on behavioral and neural correlates of food preference. This way, we bring together neuroeconomic methods of studying dietary decision-making with nutrition research and microbiology.

2. Study I: Manipulated by Marketing and Hormones? The relevance of Oxytocin for Marketing Placebo Effects on Food Product Perception.

2.1 Introduction

2.1.1 Food choices in the framework of value-based decision-making

Human eating behavior is composed of more than 200 food-related decisions every day and most of these decisions and especially their underlying processes happen completely unconsciously (Wansink and Sobal, 2007). To better understand how and when during decision-making unconscious drivers can attack, we first need to take a closer look at the decision-making process itself.

Imagine being at a street food festival and being confronted with an overwhelming variety of different foods to choose from - ranging from Mexican burritos, vegan hotdogs, falafel sandwiches, to traditional German soup. Of course, at such a food-focused event, your choice of dinner will not remain unnoticed to you. However, the cognitive computations that ultimately lead to your choice of the potato soup mostly happened unconsciously. How did you come up with your decision for the soup?

Dietary decisions are value-based decisions, they depend on the decision maker's valuation of the individual choice options and the comparison of their values (Rangel, 2013; Rangel et al., 2008; Rangel and Clithero, 2014). The value of food options reflects their importance for the decision maker and how rewarding the decision maker expects the choice options to be (Brosch and Sander, 2013; Rangel and Clithero, 2014). In other words, the value that is put on choice options represents subjective preferences. At the street food festival, you preferred potato soup over the other food options because you expected the soup to be most rewarding and thus satisfying for you.

Under optimal conditions, a decision maker would always maximize the value of every choice and thus always decide for the best option. However choice processes cannot always perform optimally (Fehr and Rangel, 2011). First, we might miss or neglect some food attributes that are relevant for properly valuing the choice options (Fehr and Rangel, 2011).

For example, you might not have noticed that the potato soup is served with parsley, which you find disgusting. Second, even when having and considering all relevant information for valuation, the calculation of values in the brain is noisy. The brain is not perfect in computing and comparing two very similar food values and it might happen that we decide for the slightly worse option (Kable and Glimcher, 2009; Rangel and Clithero, 2014). Third, on top of these inherent inaccuracies of value computation and comparison, external and internal factors unconsciously can manipulate the value-based decision-making process at various steps (Fig. 1, Fehr and Rangel, 2011; Plassmann et al., 2021; 2012).

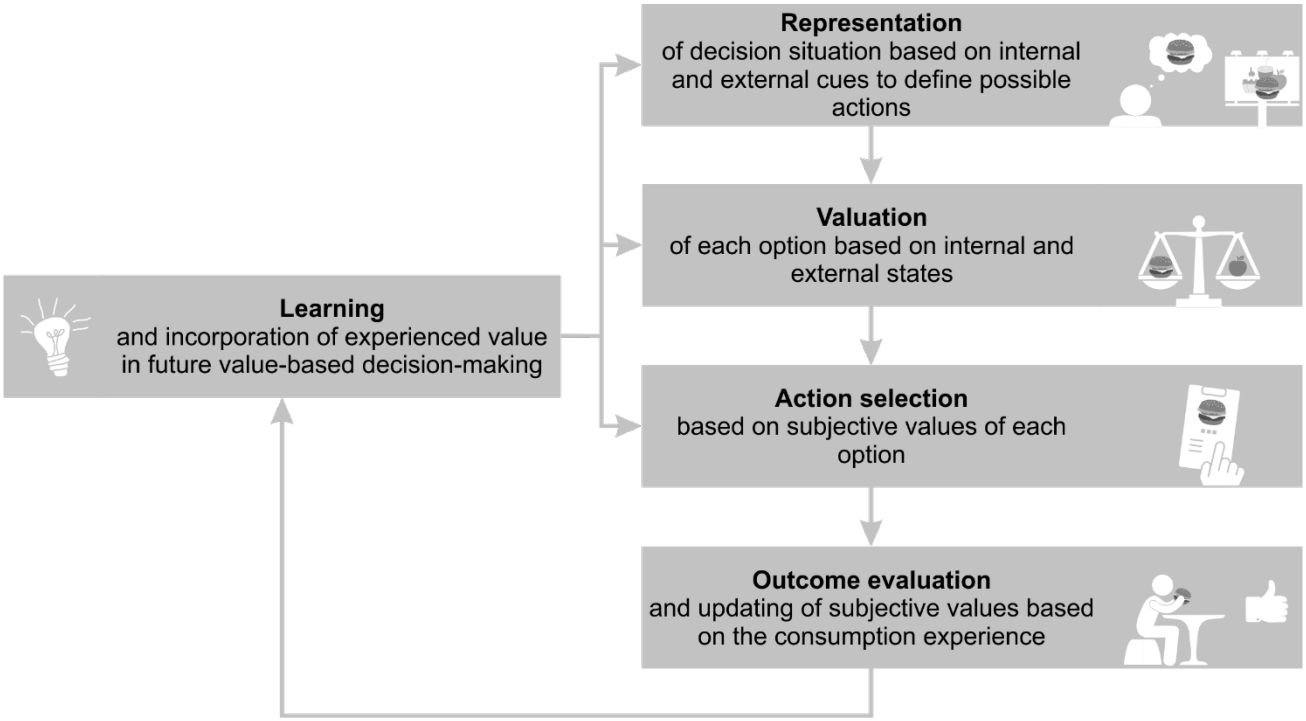

Fig. 2: Framework of value-based decision-making for food choices. The computations during dietary decision making can be divided into five distinct steps. The food choice process starts with the formation of a representation of internal needs and external options. Feasible options are subjectively valued and compared to then be able to select the optimal option. The value of the chosen option gets updated during and after consumption with the actual experienced value. This outcome evaluation allows to inform and improve future decision-making processes via learning. Adapted by permission from: Springer Nature, Nature Reviews Neuroscience, A framework for studying the neurobiology of value-based decision making, Rangel, Camerer, Montague, Copyright (2008).

The value-based decision-making process involves five computational steps (see Fig. 2, based on Rangel, 2013 and Rangel et al., 2008):

In the first step, the decision maker assesses internal (e.g. hunger level) and external (e.g. availability and appearance of food options) cues to form a representation of the decision situation and to define possible actions. You might for example be attracted to the street food festival by the smell of the fried food (external cue) and while approaching the festival you realize that you start getting hungry (internal cue) and should look for some food. With the first sight of the different food trucks, you directly exclude the falafel sandwich because of your chickpea allergy (internal cue) and the vegan hotdogs because their price exceeds your amount of cash (external cue). With this you have defined your set of feasible options from which to choose from.

In the second step, the subjective value of each option is determined under consideration of the external and internal situation. Your remaining options at the food festival encompass the Mexican burrito and the potato soup. The fact that the burrito looks more satiating increases the value of the burrito because you are very hungry (internal state). On the other hand, the queue for the burrito is much longer (external state), which dampens its subjective value again. This valuation process is highly complex and subjective because people differ in which aspects they consider for choice and how strongly they weight these aspects. Subjective valuation with its neural mechanisms and potential unconscious modulations will be discussed in detail for study II in chapter 3.1.

In the third step, the previously determined individual values of the choice options are compared to each other and the best action with the maximum predicted value is selected. In this action selection process, you came to the conclusion that you value the warm and comfy soup with shorter waiting time more than the more satiating but cold burrito with longer waiting time.

The fourth step occurs during and after food consumption. The value of the chosen food gets updated based on the actual consumption experience. This way an experienced value is formed. The potato soup was less good than you expected, which can have different reasons. It could be due to some herbs that you did not like or because it was served in a cheap looking plastic bowl. Previous research demonstrated that experienced values are not purely based

on the actual food and its ingredients but are sensitive to modulations by cognitive processes (Plassmann et al., 2012; Rangel et al., 2008). Modulation of subjective experiences are the topic of the next chapter.

Nevertheless, the experienced value is essential to update the previously predicted value and to improve future decision-making processes via learning. Learning happens in the fifths and last step in value-based decision-making. Next time you are at the street food festival, you will probably decide for the burrito.

The five steps in the framework of value-based decision-making do not only apply to complex choice situations like the street food festival with many choice options and external and internal cues to consider but to every decision. Even seemingly simple decisions when standing in front of your food basket at home and deciding whether you should eat the apple or the banana (Rangel and Clithero 2014).

2.1.2 Expectations modulate outcome evaluation (Marketing Placebo Effects)

During food consumption, a decision maker experiences a food product with all senses and evaluates how rewarding the outcome of the choice is. This so-called hedonic reward processing is essential to improve future decisions and to avoid dangerous foods (Rangel, 2013). Hedonic processing of reward involves three psychological components (Berridge and Kringelbach, 2008; Berridge and Robinson, 2003): Liking is the actual pleasure that is consciously and unconsciously derived from the sensory consumption experience. Wanting is the motivational aspect of reward and reflects the desire for the rewarding food. Past research revealed that liking and wanting to have separable neural mechanisms in the brain. Liking relies on the opioid circuitry while the motivational wanting is caused by dopamine signaling (Berridge and Robinson, 2003). Learning as the third component of hedonic reward processing ultimately links initial reward expectation, action, and actual outcome. Learning allows to update initial reward expectations and to inform future decisions about the current consumption experience.

The hedonic reward processing of the consumption outcome, and especially the wanting component, strongly influences future food intake (de Araujo et al., 2020; Berridge and

Robinson, 2003). However, hedonic reward does not simply guide eating behavior to the most rewarding, pleasant, and safe food but it leads to eating for pleasure and beyond physiological needs (Lowe and Butryn, 2007). Wanting itself arises from internal states (e.g. hunger), external cues (e.g. social situation, food availability), and the subjective liking of the approachable food (Mela, 2006; 2001b; 2001a). Thus, subjective consumption experiences are key for future dietary decisions and eating behavior. But what determines our subjective experiences during food consumption?

Basic economic theories presume that subjective consumption experiences arise from intrinsic product properties (e.g. ingredients, texture) and the internal state of the consumer (i.e. hunger) (Kahneman et al., 1997). Indeed, research demonstrated that food ingredients and satiation interactively affect food liking (as well as wanting) (Finlayson et al., 2007; Havermans et al., 2009; O'Doherty et al., 2000). On the neural level, past research found that the pleasure derived from the sensory perception during food consumption and its dependency from satiation is reflected in the orbitofrontal cortex (OFC) of the brain (for reviews see Kringelbach, 2005; Small et al., 2007).

However, product composition and physiological state are not the only determinants of the subjective consumption experience. Cognitive processes, like expectations, are strong and often unconscious modulators of subjective and even objective consumption experiences (Rangel et al., 2008; Rangel and Clithero, 2014). Via the unconscious modulation of experiences, expectations can bias outcome evaluation and thus learning and future value-based decisions in the context of eating behavior (Mela, 2001a).

Expectations are beliefs about product induced experiences that are formed before the product is consumed. Such expectations can arise from past experiences of the product, current perception and knowledge of the product, or knowledge about related products (Piqueras-Fiszman and Spence, 2015).

In the scope of this project, we focus on expectations driven by product information and product appearance, which are extrinsic sources of expectations that are not physically or chemically related to the product itself (Piqueras-Fiszman and Spence, 2015).

Many studies nicely demonstrated that the verbal description of taste or ingredients of (unknown) food products affect consumer's reported experience of and preference for the

products (Grabenhorst et al., 2008; Lee et al., 2006; Litt and Shiv, 2012; Shankar et al., 2009; Yeomans et al., 2008). In their behavioral experiment, Lee et al. offered participants two different beers. A conventional beer and a beer, which was announced as special brew. The special brew contained a few drops of balsamic vinegar. Participants either learned about the vinegar before the tasting, after the tasting but before they stated their preference, or never. When tasting the beer without knowing about the vinegar, irrespective of staying blinded or learning about it afterwards, 59 % and 52 % of the participants preferred the special brew, respectively. Only when learning about the vinegar before the tasting, significantly less participants preferred the special brew (30 %) (Lee et al., 2006). These behavioral results point at the fact that product information change how people perceive the product's taste and not their attitude and reporting about the product at the decisional level. Further evidence for the specific modulation of perception comes from neuroscientific studies (de Araujo et al., 2005; Grabenhorst et al., 2008; Litt and Shiv, 2012; Nitschke et al., 2006). Grabenhorst and colleagues, for example, found that the neural representation of experienced pleasantness in the OFC depends on the verbal description of the food product (Grabenhorst et al., 2008). They used a water solution and added umami taste (monosodium glutamate) and vegetable odor. Receiving this stimulus labelled as "rich and delicious flavor" as compared to "boiled vegetable water" led to higher blood-oxygen-level-dependent (BOLD) signal in the OFC. Moreover, the BOLD signal in the OFC correlated with subjective pleasantness ratings (Grabenhorst et al., 2008). This neuroscientific research demonstrates that descriptive labels of food products affect the subjective perception of pleasantness via higher-cognitive processes. Descriptive labels like "rich delicious flavor" or "contains vinegar" guide consumer's attention towards this specific attribute. Being made aware of an attribute, be it positive like a delicious flavor or negative like vinegar in a beer, increases its salience and chances to be recognized and perceived as such (Piqueras-Fiszman and Spence, 2015; Stevenson, 2012).

Apart from descriptive information, consumers encounter many more marketing labels and visual cues of food products. Most of these marketing labels and cues do not directly guide attention to ingredients or taste attributes, like in the examples above. Nevertheless, these marketing cues are still able to change product perception and product preferences. For

example, pictorial cues (e.g. colors or pictures on the package), modulate expectations, perceived pleasantness, and effort exerted to get a product. This probably also works by enhancing salience of the product in general and by inducing expectations of a higher intrinsic value (Enax et al., 2015b; Mizutani et al., 2010; Underwood et al., 2016).

Marketing labels that induce expectations include price tags, organic or fairtrade logos, and brand names (Allison and Uhl, 1964; Enax et al., 2015a; Enax and Weber, 2015; Linder et al., 2010; McClure et al., 2004; Motoki and Suzuki, 2020; Plassmann et al., 2008; Schmidt et al., 2017b). In a seminal study, Allison and Uhl, nicely demonstrated the impact that brand labels have on taste pleasantness and preference. In a blind tasting, regular beer drinkers did not report any experienced taste-difference between their favorite beer and another beer. However, in a later session, when tasting the same two beers openly with knowledge about the brands, they perceived a difference and rated the taste of their favorite brand significantly better (Allison and Uhl, 1964). Adding to this, McClure and colleagues demonstrated a similar effect for soft drink brands (Coca-Cola and Pepsi) and started to shed light on the neural mechanisms behind these branding effects. In a blind tasting of both drinks, reported preferences correlated with neural responses in the ventromedial prefrontal cortex (vmPFC), which reflects experienced value (Bartra et al., 2013). However, when tasting both drinks with brand labels, participants preferred the taste of their favorite brand and their reported preference correlated with activity in hippocampus and dorsolateral prefrontal cortex (dlPFC) (McClure et al., 2004). These findings suggest that brand labels bias perceived taste preferences by inducing cognitive control mechanisms and a recall of affective information about the brands (McClure et al., 2004).

Similar effects of labels on perceived taste pleasantness have been observed for price labels. Wines with expensive labels receive higher ratings of experienced pleasantness than the same wines with a cheaper label. These price label effects on experienced pleasantness do not result from changes in basic neural processing of sensation but are rather mediated by activity in the brain's valuation system (i.e. vmPFC and ventral striatum, vStr) (Plassmann et al., 2008; Schmidt et al., 2017b).

Organic and fairtrade labels inform consumers about cultivation and trading procedures. Like brand names and price labels, organic and fairtrade labels induce product beliefs and

expectations. Based on these expectations, organic and fairtrade labels led to an increase in experienced taste pleasantness and a higher valuation of the products in form of willingness to pay more for them (Enax et al., 2015a; Fernqvist and Ekelund, 2014; Linder et al., 2010). On the neural level, being presented with such labels increased activity in brain regions known for reward-processing (vStr) and valuation (dlPFC) (Enax et al., 2015a; Linder et al., 2010).

So far, we only reported expectation induced effects on subjectively reported taste experiences and preferences. But marketing effects go far beyond subjective taste experience and can even affect objective behavioral outcomes, like cognitive performance (Fitzsimons et al., 2008; Garvey et al., 2016; Park and John, 2014; 2010; Schmidt et al., 2017a; Shiv et al., 2005a; Winkler and Hermann, 2019). A soda without any active ingredients but labelled and announced as energy drink from a famous brand led to the same strong increase in cognitive performance as the actual energy drink with the same label and announcement (Schmidt et al., 2017a).

In order to better understand why such marketing labels are able to induce powerful expectations that shape behavior and experiences, we need to take a closer look at the consumer-marketer relationship. An important prerequisite for powerful expectations is trust in the marketers and their products (Fournier, 1998; Morgan and Hunt, 1994). In the context of the consumer-marketer relationship, trust can be defined as the ability of the customer to safely rely on the best interests of the marketers and the quality of their products (Yague-Guillen et al., 2003). Studies showed that trust in marketers and their products leads to satisfaction with the product as well as attitudinal and purchase loyalty, which are both further indicators of satisfaction (Ball et al., 2004; Chaudhuri and Holbrook, 2001; Porral and Levy-Mangin, 2016). Therefore, it is assumed that familiar and famous brand names, premium prices, and labels that indicate responsibility and sustainability elicit trust in the marketers and the quality of their products (Hughner et al., 2007; Kalita et al., 2004a; Rao and Monroe, 1988). Rather than guiding attention to ingredients or specific taste aspects, like descriptive labels do, marketing labels guide attention to the reliability of the marketers and the quality of their product.

Conclusively, the here presented studies emphasize that marketing actions like descriptive information, prices, packaging, and other labels unconsciously induce expectations and manipulate the subjectively and objectively experienced value of products. Based on the terminology for expectancy induced effects on perceived pain or other physiological outcomes in the medical domain, these marketing effects were called Marketing Placebo Effects (MPEs). Mechanistically, analgesic placebo effects work the same way as MPEs, and their biological mechanisms are well studied. The reduction of pain by an inert substance is a true physiological response, which biologically depends on the dopaminergic and endogenous opioid systems (Eippert et al., 2009; Scott et al., 2008; Wager et al., 2004). Analgesic placebo manipulations decrease pain processing in pain-sensitive brain areas, including insula, thalamus, and dorsal anterior cingulate cortex (ACC) during the painful stimulus. During anticipation of the pain stimulus, neural activity in the vmPFC and dlPFC correlate with subjectively reported placebo responses, suggesting an expectancy-driven top-down control of pain processing (Wager and Atlas, 2015).

In the medical domain, positive expectations about a pain treatment are initiated for example due to trust in the physicians and their social cues, verbal suggestion of drug efficiency, and drug labels (Wager, 2005; Wager and Atlas, 2015). These commonalities between MPEs and analgesic placebo effects strongly highlight the relevance of social context, trust, and beliefs for the formation of placebo effects across domains.

2.1.3 The neuropeptide oxytocin

In the last years, the neuropeptide OXT became famous for its diverse functions in social behavior and social cognition. Not only in the public but also in the scientific literature has oxytocin received nicknames like "trust hormone", "morale molecule", and "love hormone" (Graustella and MacLeod, 2012; Quintana and Guastella, 2020). From an evolutionary perspective, OXT is an ancient hormone and has a pivotal role in reproduction and survival across species (Feldman et al., 2016).

OXT is a peptide composed of nine amino acids arranged in a cyclic structure and is produced by neurons in the paraventricular and supraoptic nuclei of the hypothalamus. OXT can be

released centrally within the brain as well as into the periphery. Thus, oxytocin has a dual function: it acts as a neurotransmitter in the central nervous system (CNS) and as a hormone in the peripheral organ system (Gimpl and Fahrenholz, 2001; Jurek and Neumann, 2018; MacDonald and MacDonald, 2010). For the peripheral release, oxytocin producing neurons project to the pituitary gland, where oxytocin is stored in vesicles until its release into the blood (Baribeau and Anagnostou, 2015; Ludwig and Leng, 2006). Dendrites and axons that project from the hypothalamus to other brain regions release oxytocin in the central nervous system, e.g. prefrontal cortex, midbrain, hippocampus, amygdala, and striatum (Gimpl and Fahrenholz, 2001; Knobloch and Grinevich, 2014; MacDonald and MacDonald, 2010). This dual mode of action explains the various observed physiological as well as behavioral effects of oxytocin that we will review below.

OXT exerts its effect by binding to a sole receptor that is expressed in both, CNS and periphery (Carson et al., 2013; Jurek and Neumann, 2018). The oxytocin receptor belongs to the G-protein-coupled receptor family (GPCR). GPCRs are membrane-spanning receptors that, upon binding of ligand on the extracellular side, activate a signaling cascade inside the cell that leads to the cellular response (Gimpl and Fahrenholz, 2001; Rosenbaum et al., 2009). Peripheral oxytocin receptors are expressed in various tissues, including uterus, testes, mammary gland, ovary, kidney, heart, and bone. In the CNS, oxytocin receptor distribution differs largely between species, but receptors were found in brain areas including hippocampus, substantia nigra, amygdala, nucleus accumbens (NAcc), and hypothalamus (Gimpl and Fahrenholz, 2001; Jurek and Neumann, 2018). Expression patterns of the oxytocin receptor can change rapidly to enable adjustment to environmental changes, e.g. a higher requirement for oxytocin receptors during parturition to induce labor (Gimpl and Fahrenholz, 2001). Moreover, oxytocin can bind back on oxytocin-producing neurons in the hypothalamus, which leads to a feed-forward loop that is essential to maintain uterine contraction during parturition and allows efficient milk let-down (Armstrong and Hatton, 2006; Carson et al., 2013; Landgraf and Neumann, 2004).

OXT levels fluctuate naturally and can be measured peripherally in blood plasma, urine, and saliva, or centrally in cerebrospinal fluid (CSF) (de Jong et al., 2015; MacLean et al., 2019). To study the causal effects of oxytocin more specifically, researchers administer exogenous

oxytocin via nasal spray. Intranasally administered oxytocin reaches the CNS, probably via direct transport along the olfactory and trigeminal nerve fibers rather than the blood-brain-barrier and increases oxytocin levels in the CSF (Quintana et al., 2020; 2016; 2015; Striepens et al., 2013).

Higher endogenous levels of oxytocin in plasma have for example been associated with greater partner support in romantic relationships and frequent close contact between partners (Grewen et al., 2005; Light et al., 2005). Thus, apart from being important for delivery and lactation, oxytocin has a unique role in romantic and maternal bonding (Galbally et al., 2011; Insel and Young, 2001; Kendrick, 2000). High endogenous oxytocin and low cortisol predicted the quality of maternal bonding behaviors, like gaze, touch, and vocalizations, shortly after birth (Feldman et al., 2007) (Feldmann et al 2007). Further, oxytocin seems to be relevant for maintaining relationships and for fidelity. For example, men perceived their female partner as more attractive and had increased activity in reward-related brain regions upon touch or visual cues from their partner when receiving exogenous oxytocin (Kreuder et al., 2017; Scheele et al., 2013).

Apart from its relevance for bonding of romantic partners and within families, a vast amount of literature has demonstrated the involvement of oxytocin in social interactions outside of relationships. A seminal study by Kosfeld and colleagues showed that exogenously administered oxytocin increased trust in others when exchanging money in an economic game (Kosfeld et al., 2005). Moreover, other reports on the diverse observations after oxytocin administration include enhanced emotional memory (Rimmele et al., 2009), empathy (Bartz et al., 2010; Hurlemann et al., 2010), social compliance and conformity (De Dreu et al., 2010; Edelson et al., 2015; Stallen et al., 2012; Xu et al., 2019), and reduced anxiety and social stress (Heinrichs et al., 2003; Kirsch et al., 2005).

However, OXT effects are not only limited to social cognition but have also been observed for non-social cognition (Eckstein et al., 2019; Fürst et al., 2015; Harari-Dahan and Bernstein, 2017). Fürst et al. found that intranasal oxytocin administration enhanced the attribution of relationship like characteristics (i.e. loyalty, intimacy, commitment, satisfaction) to brands (Fürst et al., 2015). Animal studies suggest that oxytocin is involved in the regulation of food intake and has anorexigenic effects (Sabatier et al., 2013). First studies in humans also

observed reduced calorie consumption after intranasal oxytocin administration (Burmester et al., 2019; Lawson et al., 2020; 2015; Ott et al., 2013).

In patients with psychiatric disorders like autism, depression, or schizophrenia, diminished endogenous plasma oxytocin levels have been observed (Goldman et al., 2008; Modahl et al., 1998; Scantamburlo et al., 2007). This observation together with the positive implications of oxytocin in social behaviors have made the hormone a promising treatment option for social and emotional dysregulations in autism (Guastella and Hickie, 2016), depression and anxiety (De Cagna et al., 2019), and schizophrenia (Feifel et al., 2016). However, results are inconclusive. More comprehensive replications are required to determine whether and in which context oxytocin could be used as pharmacological agent to either directly alleviate symptoms of psychiatric disorders or improve treatment outcomes by enhancing patient-physician interactions (Quintana et al., 2021).

Inconclusive results and failed replications in oxytocin research are not limited to clinical trials but are increasingly common across different research questions (Mierop et al., 2020). For example, the initial finding from Kosfeld and colleagues that intranasal oxytocin increased trust in strangers, could not be replicated in a direct replication attempt and other related studies (Declerck et al., 2020; Nave et al., 2015). Moreover, many unpublished null results and questionable, underpowered statistical results in oxytocin research prevent the formation of a clear and unifying theory about oxytocin effects (Lane et al., 2016; Mierop et al., 2020; Quintana, 2020; Walum et al., 2016). One further contributing factor to these inconsistent findings might be interindividual differences in oxytocin response and differences in environmental context between studies (Bartz et al., 2011; Declerck et al., 2020). Suggestions to increase the reliability of oxytocin research embrace open-science practices like pre-registration, open-access to datasets and analyses scripts, publication of null findings, and replications by independent labs. The use of equivalence tests or Bayesian analyses instead of commonly used frequentist statistics further enables to distinguish true null findings from null findings due to data insensitivity (Mierop et al., 2020; Quintana, 2020; 2018).

Overall, interpreting novel oxytocin findings and putting them into context in the light of these highly diverse and often non-replicable past research findings is challenging. An overarching

theory of oxytocin function in humans is missing and has just started to emerge (Quintana and Guastella, 2020). Initial theories proposed that oxytocin signaling has evolved to foster social attachment and in-group protection by enhancing the saliency of social cues (Bartz et al., 2011; Kendrick et al., 2017; Shamay-Tsoory and Abu-Akel, 2016; Striepens et al., 2011). More recently, Quintana and Guastella proposed an allostatic function of oxytocin that enables the adaptation of social and non-social behaviors to survive in an ever-changing environment (Quintana and Guastella, 2020).

2.1.4 Influence of oxytocin on placebo effects

As described in the previous chapter, oxytocin is implicated in social trust, empathy, anxiety, stress, and learning processes (Kendrick et al., 2017), which are all relevant contributors to placebo analgesia (Wager and Atlas, 2015). Therefore, it is not surprising that Kessner et al. in 2013 investigated oxytocin for its effect on placebo analgesia. Kessner and colleagues intranasally administered 40 IU of oxytocin or saline to male participants and induced expectations about a pain-relieving effect of an inert ointment via verbal suggestions. The experimenters then applied painful heat stimuli to the forearm with the applied sham ointment and to a second site with the same ointment but introduced as control without pain relieving effect. The placebo response, the difference in pain rating between the sham ointment and control ointment sites, was compared between the oxytocin and a saline group. Kessner et al. observed that participants in the oxytocin group experienced a stronger placebo response due to the verbally suggested effect of the inert ointment than the saline group. Based on this observation, the researchers proposed that oxytocin pharmacologically enhances placebo analgesia by augmenting the patient-physician relationship and the trust in the explanations of the physician. Alternatively, oxytocin may diminish treatment related stress and anxiety, which enables stronger placebo responses (Kessner et al., 2013).

In addition to its potential role for placebo analgesia, Zhao et al. in 2018 also found that oxytocin and verbal suggestion led to placebo effects on memory performance in male participants (Zhao et al., 2018). Participants either received an oxytocin or sham spray together with either no expectancy induction or with the verbal instruction that the spray

increases their performance. OXT treatment did not have a general effect on memory performance because performance of OXT and sham group did not differ, when the participants did not receive any expectancy induction. However, when receiving the information that the spray increases memory performance, the OXT group performed significantly better than the sham group (Zhao et al., 2018). Hence, it seems that OXT boosts expectancy induced placebo effects across domains, including placebo effects on subjectively reported pain and objectively measured cognitive performance.

However, the initial study on analgesic placebo effects by Kessner et al. has been challenged and their observed OXT effect is highly questionable. Several related studies could not replicate any effect of OXT on placebo analgesia.

The first failed replication study induced pain via electrical stimulation to the hand and used 24 IU of OXT in male and female participants. The alleged pain reduction took place via a pain-relieving electrode that could either be switched on or off and whose function was introduced by verbal suggestion (Colloca et al., 2016).

In a study by Skvortsova et al. in 2018, the nasal spray (OXT or sham, 24 IU) itself was introduced as pain- and itch- relieving substance via verbal suggestion to female participants (Skvortsova et al., 2018). Another study by the same researchers used a higher dose of 40 IU OXT, the same as in the original study by Kessner et al., in male participants (Skvortsova et al., 2019). Placebo analgesia and nocebo hyperalgesia of electrical stimuli coupled with different light cues was induced by verbal suggestion as well as conditioning. In the conditioning procedure, participants first experienced and learned the association of electrical stimulus intensities with the different light cues. In the testing phase, participants then received identical electrical stimuli but coupled to the previously learned light cues (Skvortsova et al., 2019).

Although all three studies could successfully induce placebo responses via verbal suggestion or conditioning, exogenous OXT did not boost these placebo responses in any case.

The studies mentioned so far differed in many aspects from each other, including OXT dose, participant's gender, pain and placebo induction methods, and measured outcome. In regard to the highly context- and personality dependent effects of OXT, these differences might

explain the conflicting results compared with the initial study by Kessner et al. (Bartz et al., 2011; Borland et al., 2019; Kessner et al., 2013).

Therefore, a recent study by Liu et al. systematically tested male and female participants with different OXT doses (24 IU and 40 IU), different paradigms (verbal suggestion and conditioning), and assessed placebo as well as nocebo outcomes. Pain induction took place via electrical stimuli and placebo/nocebo responses were elicited by ointments, similar as in the original study (Kessner et al., 2013). Still, they could not observe any effect of OXT on placebo/nocebo responses, leading to the assumption that OXT is not involved in placebo analgesia (Becker et al., 2020; Liu et al., 2020). In this context, the observed positive effect of OXT on placebo responses in the cognitive domain (Zhao et al., 2018) is puzzling. It might be that OXT does not per se increase trust in the physician but acts via a different mechanism that is specifically efficient for cognitive placebo effects but not analgesic placebo effects (Becker et al., 2020).

To elaborate on this idea, it would be interesting to test the effect of OXT on other domains of placebo responses, for example MPEs.

2.1.5 Aim of this project

In this project, we extend past research on the relevance of OXT for placebo responses and investigate the role of OXT for MPEs. In our pre-registered, between-group and double-blind study, we intranasally administered either sham or OXT (24 IU) in male participants and test for the effect of OXT on MPEs.

We specifically focus on MPEs of food products that are caused by product appearance and product labels. We distinguish between MPEs of food products on experienced taste pleasantness and on cognitive performance. First, we use chocolate truffles and applesauce with superior packaging and expensive and organic labels, respectively. We record subjectively reported taste pleasantness of these products and compare the results to ratings of identical products with inferior packaging and non-organic/cheaper labels. Second, we use a soft drink and present it as an energy drink of a famous brand, advertised for its effects on cognitive performance. We measure objective performance in a numerical stroop task once

after consumption of the advertised energy drink and once after consumption of the open soft drink. To unveil potential mechanisms of OXT induced effects on marketing placebo responses, we assessed trust in marketers of the offered products and expectations about the products.

With this, we aim to elucidate whether and how OXT can affect placebo responses in the marketing domain and by this alter how consumers perceive food products. The perception of food products is highly relevant for the choice of food and a healthy eating behavior but also affects overall satisfaction and well-being.

Moreover, this research allows to expand the knowledge about neurobiological foundations of expectation driven effects on perception and behavior.

2.2 Materials and Methods

2.2.1 Ethical considerations and open science statement

The ethics committee of the Medical Faculty of the University of Bonn approved the study (Lfd. Nr. 133/17). The study was conducted in accordance with the latest revision of the Declaration of Helsinki and all participants gave written informed consent. Participants received a monetary compensation for their participation, which consisted of 30 € baseline expense allowance plus up to 13 € based on their performance. On average participants received 38.18 €.

We pre-registered the study design, power analyses, and analysis plan at the Open Science Framework (OSF) (https://osf.io/v3b2u, date of pre-registration: March 07, 2018) prior to any data creation. A detailed description of any deviations from the pre-registration and the reasons for the deviations can be found in chapter 2.2.11. Any exploratory analyses that we did not pre-register in advance are labelled as such in the statistical analysis part of the methods section. Data was collected without intermittent data analysis. All data, analyses scripts, and study material will be made available via OSF once the project is published.

2.2.2 Participants

We recruited participants via internet, social media channels, participant pool mailing lists, word of mouth, and flyers and online advertisements at the University and University clinic of Bonn. Recruitment took place between March 2018 and February 2019.

After signalizing their interest in the study, participants filled in an online screening via Qualtrics (Qualtrics, Provo, Utah, USA) to check for exclusion criteria. We applied the following exclusion criteria: Female gender, age below 18 or above 60 years, kidney insufficiency, cardiovascular diseases, excessive smoking (more than five cigarettes per day), excessive energy drink consumption (more than once per week), knowledge of the German language below native level (due to the extensive verbal and written instructions), regular intake of any (psychiatric) medication apart from antiallergenic agents), and food allergies to any of the sample products. We further excluded participants with an educational background in psychology or previous participation in a marketing placebo study to reduce the chances that participants recognize the manipulation and purpose of our study.

We only included male participants for two reasons: First, our study was inspired by the finding from Kessner et al. on OXT effects on analgesic placebo responses, which was found in males. (Kessner et al., 2013). Second, we wanted to reduce noise in the data due to previously observed gender-related interindividual differences in OXT response and endogenous OXT levels (MacDonald, 2013; Salonia et al., 2005).

We determined the required sample size with G*Power (Faul et al., 2007) based on two previous datasets. For the taste task, we had pilot data with an effect size of Cohen's *d* = 0.18 for the difference in MPE between OXT group and sham group. For the cognitive performance task, we had data from a previous study with an effect size of Cohen's *d* = 0.48 for the label effect, irrespective of OXT treatment (Schmidt et al., 2017a). We used these respective effects sizes to calculate the needed sample size for between-group comparisons with a standard error probability of α = 0.05 and a power of 1- ß = 0.9. This way, we yielded a minimum sample size of 91 participants per group for the taste task and 92 participants for the cognitive performance task. We increased this sample size 100 datasets per group after

exclusions due to the manipulation check, to be on the safe side considering that our study design differed from the studies that provided the effect sizes.

We invited 344 participants to the lab in the Life&Brain research institute at the University clinic in Bonn. Participants received the information that the study would test how OXT affects taste perception, cognitive performance, and how it interacts with the stimulants caffeine and taurine. We left participants unaware about our marketing focus. We instructed participants to maintain their regular bed and waking times, abstain from caffeine and larger meals 2 hours and energy drinks 24 hours prior to the study. Adherence to these rules was confirmed verbally upon arrival at the lab. Participants further confirmed that they did not take any medication since the online screening and currently do not suffer from any nasal congestion that interferes with nasal spray administration. Before the start of the experiment, participants underwent an additional screening procedure. In this screening we checked for current physical diseases via a questionnaire and current or past psychological disorders. An experimenter assessed current or past psychological disorders via the Mini-International Neuropsychiatric Interview (MINI) (Lecrubier et al., 1997). Based on the MINI, we could not enroll nine of the invited participants in our study (due to indications of depression, generalized anxiety disorder, drug abuse, manic episodes, or antisocial personality disorder). One further invited participant could not be enrolled due to insufficient understanding of the German instructions.

Thus, we tested in total 334 participants. Based on the manipulation check and our pre-registered data exclusion criteria, we had to exclude several datasets from the analyses of the two tasks.

For the taste task, 109 datasets were excluded from the analysis due to the following pre-registered reasons: i) 97 participants recognized that they received identical chocolate truffles and/or applesauce; ii) 16 participants realized that we tested marketing effects. Note that four participants were excluded because both exclusion criteria applied to them. We further excluded two datasets due to reasons that we did not foresee and pre-register, but that were essential for ensuring data integrity: i) one participant received a wrong dosage of nasal spray; ii) one participant mixed up products and labels. Thus, we excluded in total 111 datasets and our analyses for the taste task are based on a total n = 223 (mean age: 26.70

years, *SD*: 7.94 years, n_{sham} = 111, n_{OXT} = 112). This sample size exceeds our pre-registered limit of 100 participants per group and resulted from the higher data exclusion rate for the cognitive performance task. We needed to test more participants for the cognitive performance task than for the taste task because more participants failed the manipulation check of the cognitive performance task. For consistency and comparability reasons, all participants conducted the full study with taste and cognitive performance tasks in the same order. Therefore, we ended up with more datasets for the taste task. We report the results for *n* = 223 but verified that the results of the pre-registered main hypotheses do not differ significantly for *n* = 200.

For the cognitive performance task, 129 datasets were excluded from the analysis due to the following pre-registered reasons: i) 16 participants recognized that the drinks were identical; ii) 113 participants reported to not have felt any effect of the energy drink; iii) 17 participants realized that we tested marketing effects. Note that 17 participants were excluded because several exclusion criteria applied to them. We further excluded three datasets due to reasons that we did not foresee and pre-register, but that were essential for ensuring data integrity: i) one participant received a wrong dosage of nasal spray; ii) two participants did not understand the cognitive performance task. In total, we excluded 132 datasets and based our analyses for the cognitive performance task on a total *n* = 202 (mean age: 26.5 years, SD: 7.4 years, n_{sham} = 99; n_{OXT} = 103). We did not exactly achieve the 100 participants per group due to logistic reasons.

2.2.3 Pre-testing and choice of food stimuli

We conducted several pre-tests for finding the optimal food stimuli and marketing manipulations for the tasting and the cognitive performance tasks.

For the taste task, we tested different food stimuli, labels, and packaging in one online pre-test and two lab-based pre-tests. First, in the online pre-test, we used pictures of chocolate bars, chocolate truffles, chips, and apple juice as food stimuli. Labels encompassed information about price, country of origin, and manufacturing. Each food stimulus was

presented three times with all three label information. However, one type of information (either price or manufacturing) changed across the three food repetitions. The other information served as distractors. For chocolate bars, chocolate truffles, and chips we manipulated the price information and provided identical food images with a high, medium, and low price. For apple juice we manipulated the manufacturing information and provided identical juice images with organic, traditional, or natural claims. These label manipulations aimed at inducing expectations about the taste of the products. We recruited 142 male participants (mean age: 27.2 years, *SD*: 5.2 years, 1.50 € expense allowance) via Clickworker. Participants rated their expected taste pleasantness of the presented products with their labels on a 9-point Likert scale. We randomized the order of the product categories and the three stimuli within each category. We then calculated the MPE as the difference in expected taste between the expensive/organic and cheap/natural products. We found that for all three products the expensive labels successfully induced MPEs with the strongest effect for the chocolate truffles. For the apple juice, the organic label did not enhance the expected taste pleasantness compared to the natural product. Therefore, we decided to continue with chocolate truffles and their respective price labels and updated the labels for the apple juice (organic, traditional, and naturally cloudy instead of natural). We used these updated stimuli in our lab-based pre-test with ten male participants (male, mean age: 25.1 years, *SD*: 5.7 years, same procedure, and same payment as for main study). Participants saw the product labels (but not the actual product itself) announced on a screen and received the announced product together with the label from the experimenter, one after the other. Before tasting each product, participants rinsed their mouth with water. Participants rated their experienced taste pleasantness on a 9-point Likert scale. In contrast to the expected taste pleasantness in the online pre-test, the experienced taste pleasantness was on average not higher for the expensive chocolate truffles compared to the cheap ones. Moreover, also the organic apple juice was on average not rated better than the naturally cloudy apple juice. Therefore, we decided to not only manipulate the label information but also the product appearance. We further wanted to test whether applesauce samples are better suited than apple juice to elicit organic MPEs.

We conducted a second lab-based pre-test with 25 male and female volunteers (no data about age, no payment). In this pre-test, we used chocolate bars and chocolate truffles with price label manipulation and different packaging that fitted the respective prices. We further used applesauce and apple juice with organic label manipulation and different packaging. Participants saw the labels and pictures of the products with their packaging on a rating sheet and received the products from the experimenter. Taste pleasantness ratings revealed that only the labelling and packaging of the chocolate truffles and of the applesauce could elicit significant MPEs.
Therefore, based on all pre-tests, we achieved the most efficient MPEs with chocolate truffles and applesauce when combining marketing labels with different packaging. The exact final labels and packaging is depicted in Fig. 3B.

For the cognitive performance task, we decided for the soft drink based on an onsite pre-test with 17 male and female student volunteers (no information about age, no payment). We aimed to find a soft drink that tasted most similar to energy drinks. Thereby, we would reduce the chances that our study participants recognize that they received two times the same soft drink although once labeled as energy drink. We conducted a blind tasting in two parts to determine which of four soft drinks (Schweppes Lemon®, Sprite®, Campari Group LemonSoda®, San Pellegrino Limonata®) would most likely be accepted as energy drink.
In the first part, participants sampled all four drinks and reported their liking of the taste, how refreshing and how energizing they were, and how familiar the drinks seemed to them. In the second part, participants received the same four drinks again but this time we announced that one of them would be the Red Bull Silver Edition® and participants should guess which. Overall, Schweppes Lemon® appeared as the most suited drink, which was least familiar and had the highest resemblance with an energy drink.

2.2.4 General experimental procedure

Participants arrived at the lab between 8:30 am and 5:15 pm. We only invited one participant per session to avoid any distraction and prevent any communication that could have

compromised our manipulation. The experiment was conducted by female experimenters only and an overview of the whole experimental procedure is shown in Fig. 3A. After picking up participants at the meeting point, the experimenter verbally confirmed adherence to inclusion criteria, as mentioned above. First, participants read and signed the participant information and informed consent. Next, the experimenter conducted the MINI and participants who passed the interview filled in questionnaire block 1 with state and trait scales. Questionnaire block 1 contained the Autism Spectrum Quotient (Baron-Cohen et al., 2001) to test autistic-like personality traits, a questionnaire on current health, well-being, hunger, recent sports activity, sleep during last night, time since waking up, a general trust questionnaire (translated version from the IPIP by Goldberg, 1999 and Goldberg et al., 2006, representation of the revised NEO Personality Inventory from Costa and McCrae, 1992), and the positive and negative affect scale (PANAS, Watson et al., 1988).

We recorded autistic-like personality traits to ensure that the two treatment groups did not differ in regard to these traits as they might affect social and non-social behaviors (Bianco et al., 2020; Frith, 2001; Watson et al., 2015). Moreover, autistic-like traits are promising moderators of OXT effects (Bartz et al., 2010; Fürst et al., 2015) on behaviors. Such an analysis is however outside of the scope of this thesis.

The questionnaire on current health and well-being was collected to rule out any medical or psychological state that could bias OXT effects or behavior. We asked participants about any intensive physical activity on the study day because previous research showed that endogenous OXT levels increase after intensive physical exercise (de Jong et al., 2015). No participant reported any medical condition or sports activity shortly before the study that required exclusion from data analysis. Information on hunger, sleep, and general trust served as control variables to ensure that the two treatment groups did not differ and to rule out any covariation with our dependent variables. With the PANAS we aimed to control for any differences in mood at before the start of the study and any potential effects of OXT thereon.

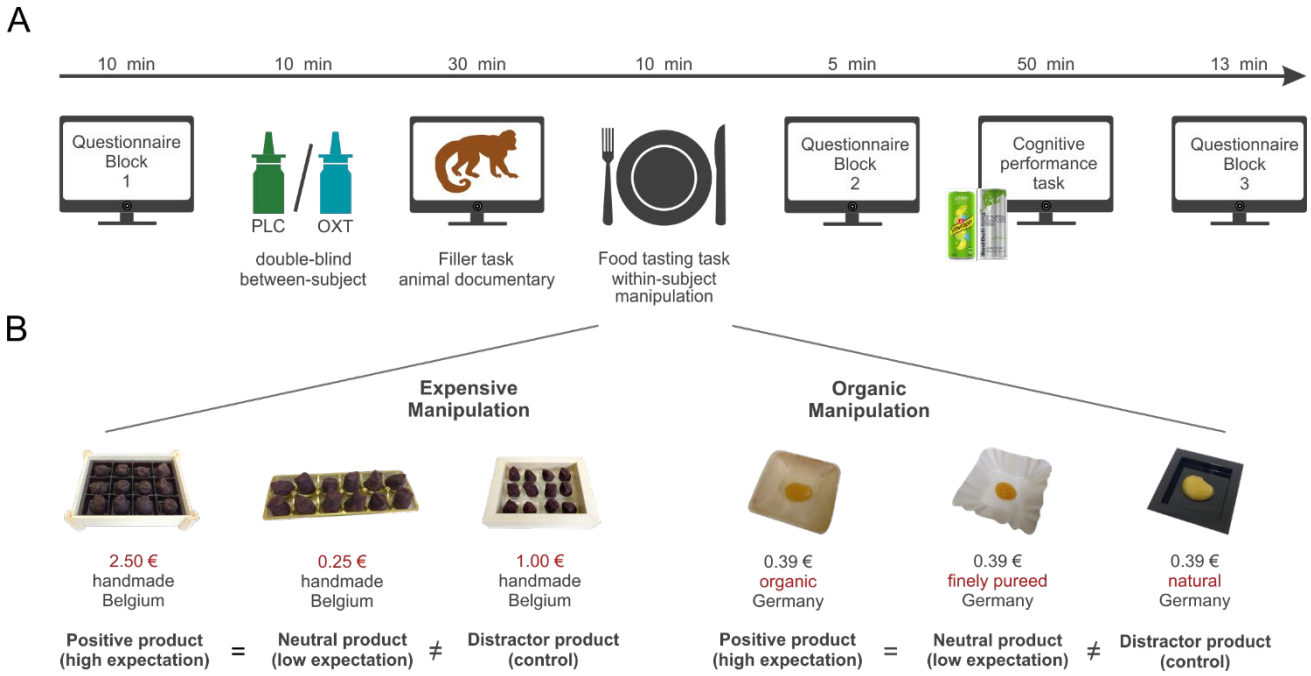

Fig. 3: Experimental procedure (A) and stimuli of food tasting task (B). (A): The timeline on the top depicts the duration of the individual tasks and questionnaire blocks (in min). The second row shows the experimental procedure with all questionnaires and tasks. Questionnaire blocks were filled in at the computer via Qualtrics and the exact questionnaires of each block are described in the text. Participants self-administered sham or OXT nasal spray under supervision from the experimenter. For the food tasting, participants received the food products in their respective packaging on their table in front of the computer. Product information appeared on the computer screen together with the respective picture of the food and its packaging. After sampling a product, participants rated the experienced taste pleasantness of the respective product on the computer. The cognitive performance task was performed on the computer twice, once after consumption of a soft drink and once after the consumption of the same soft drink but labelled and advertised as energy drink. (B): In the tasting task, participants received two product types with their respective manipulations: chocolate truffles with an expensive manipulation and applesauce with an organic manipulation. Products were served to the participants exactly the way they are depicted on the pictures. Red writing highlights the manipulated label of interest (note that the information was not highlighted for the participants). The other information served as distraction and was identical for all three products within each product type.

After questionnaire block 1, participants self-administered the sham or OXT nasal spray (for details see chapter 2.2.5) and waited for 30 min for the OXT to be acting (Quintana et al., 2020; Spengler et al., 2017). Next, participants conducted the tasting task (details in chapter 2.2.6) in a self-paced way in the presence of an experimenter. Afterwards, questionnaire

block 2 and cognitive performance task followed in an intermixed way. Participants filled in questionnaire block 2 during a waiting time of the cognitive performance part. For details on the cognitive performance part see chapter 2.2.7.

Questionnaire block 2 contained a modified and translated version of the brand trust scale (Delgado-Ballester, 2003) to sample participant's trust in the marketers of organic and expensive products. We replaced the placeholder "brand [X]" with "expensive products" and "organic products" to reflect our marketing manipulations of the taste task. Moreover, we used a 7-point Likert scale instead of a 5-point Likert scale. Lastly, we omitted one intentionality item ("I could rely on [X] brand to solve the problem.") and added one item to the reliability category ("With the purchase of brand [X], I get what I expect from a product."). These changes were made for a more nuanced rating and to better capture trust in marketers of certain product labels and claims. It should be noted that our brand trust questionnaire did not ask about a specific marketer or marketers of specific product types (e.g. food products in general or chocolate truffles) but about all marketers of expensive/organic products.

To further evaluate whether MPEs in our taste task rely on quality and taste expectations, we added the following two statements and asked for participant's level of agreement: "In general I believe that more expensive/organic products have a higher quality than cheaper/non-organic products" and "In general I believe that more expensive/organic products taste better than cheaper/non-organic products". This last question differed from the rest of the brand trust questionnaire as it specifically asked for edible products. The questions about expectations were intermixed with the brand trust questions. All questions appeared in a randomized order.

After the cognitive performance task, participants filled in questionnaire block 3, which contained a brand trust questionnaire for marketers of brand products and control questions. The questionnaire for trust in marketers of brand products was structured in the same way as the brand trust questionnaire for marketers of organic/expensive products. We replaced the placeholder "brand [X]" with "brand products" to reflect our marketing manipulation of the cognitive performance task. We did not ask about trust in Red Bull or energy drink marketers but about all brand products in general.

The control questions comprised the manipulation check, sociodemographic questions, food consumption questions, and PANAS. In the manipulation check, we asked about obscurities or remarks about the tasks, the potential aim of the study, treatment guess, the experienced effects of the ostensible energy drink, and characteristics of the two drinks (taste, citrus flavor, thirst-quenching, energizing). Moreover, we asked whether participants noticed that some of the products (foods or drinks) were identical. As pre-registered, we excluded datasets from the analysis when participants reported that they did not feel any effect of the energy drink, recognized that they received identical products, or recognized that the aim of our study was related to marketing.

In the sociodemographic questions we asked about age, years of education, income, current job. Furthermore, we sampled the liking of our offered products (chocolate truffles, applesauce, energy drink) and usual consumption habits. With these questions we wanted to rule out that the two groups differed in their attitude towards these products. PANAS was sampled for a second time after the experiment to check for any changes in mood due to OXT treatment.

All participants conducted the tasks and questionnaires in the same order. In total, the whole study lasted around 120 to 130 min. At the end, the experimenter retrieved the result of the cognitive performance task and calculated the respective bonus to pay the participants. Participants received a debriefing about the true aim of our study via email after we finished data collection. We did not debrief participants directly after participation to avoid spoiling of our cover story by communication between past and future participants.

2.2.5 Oxytocin administration

We used a randomized, double-blind, sham-controlled, between-participant design. Participants either self-administered OXT (24 IU, Syntocinon® spray, Novartis, Basel, Switzerland) or sham (same ingredients except the neuropeptide). Nasal spray administration took place in a different room to avoid that the air in the testing room gets enriched with OXT. During self-administration participants were instructed and supervised by the experimenter. Participants administered 6 puffs per nostril, each with 2 IU, which in total roughly equals

600 mg spray. The experimenter took the time to ensure an inter-puff interval of 45 seconds to allow proper absorption of the spray into the nasal epithelium. Moreover, the experimenter weighted the spray bottle and participants administered additional puffs if the administered volume fell below 600 mg. We decided to use 24 IU of OXT because this dosage was identified as most effective in triggering brain responses and behavioral change in a previous dose dependency study (Spengler et al., 2017). Moreover, previous research studying OXT effects on placebo responses used the same dosage (Colloca et al., 2016; Liu et al., 2020; Skvortsova et al., 2018; Zhao et al., 2018).

In the 30 min waiting time after the nasal spray administration, participants watched an animal documentary to avoid boredom and to keep their activity and emotions during this time as comparable as possible. We ensured that participants of the OXT and sham were not influenced differently in their mood by this documentary by two control questions. We asked about participant's happiness during the movie and the emotionality of the movie and did not find any differences in these measures (see Tab. 2 and Tab. 3).

2.2.6 Tasting task

With the tasting task, we aimed at manipulating participant's expectations about food products by means of marketing labels and product packaging. We then wanted to test whether these marketing cues lead to better subjectively reported taste pleasantness and whether these marketing effects are boosted by OXT. Therefore, we used two product types, chocolate truffles and applesauce, and combined them with an expensive and an organic manipulation, respectively. Expensive and organic marketing labels have previously been shown to manipulate experienced taste pleasantness (Linder et al., 2010; Plassmann et al., 2008; Schmidt et al., 2017b)

For each product type with its respective manipulation, we had three products that were labelled and packaged differently. The different products with their labels and packaging are displayed in Fig. 3B. All three products of both product types contained information about price, country of origin, and the way of manufacturing. For the chocolate truffles with the expensive manipulation only the price information varied across the three products.

Accordingly, for the applesauce with the organic manipulation only the information about the way of manufacturing varied across the three products. The other product information, which remained constant across all three products served as distraction and made the product label more realistic. Although labelled and packaged differently, two of the three products of each product type were the exact same kind of chocolate truffle/applesauce (see Fig. 3B). One of these two identical products contained a high price/organic label and had a superior packaging. The other product had a cheaper/non-organic label and an inferior packaging. Differences in taste pleasantness ratings of these two products can solely arise from the marketing cues as, unbeknownst to the participants, the actual ingredients and taste were identical. We classify these products as positive products (associated with high expectations due to the promising marketing cues) and neutral product (associated with lower expectations due to less promising labels and appearance). The third product was a different kind than the other two products but still visually hardly distinguishable. This third product served as distractor and control product. For reproducibility reasons, the exact food products and packaging materials are listed in Tab. 1.

At the start of the task, the experimenter placed a cup of water and all six products in random arrangement (but sorted according to the product type) on the table in front of the participant. Participants read the instructions at the computer and could conduct the tasting at their own pace with the experimenter being present in the same room. Importantly, the experimenter could not see how the participants rated the products to avoid any demand effects. Participants received the instruction to rinse their mouth with water before tasting each product. The order of the product types and the three products within each product type was randomized.

The product that should be sampled next was announced to the participants on the computer screen via photographs. Participants saw a photograph of the product with its experimental packaging. The packaging on the photograph was identical to the packaging of the taste stimuli on the table and enabled participants to identify the next sample. Additionally, participants saw the product labels on the screen below the photographs and were instructed to read them carefully. Moreover, participants received the instruction to only eat one of the chocolate truffles provided in the package and to eat the whole 5 g of applesauce.

Tab. 1: Consumables of tasting task.

Product	Type	Company
Chocolate truffles (positive and neutral)	"Truffes fantaisie natural"	La Praline Gothenburg
Chocolate truffles (control)	"Fine French Cocao Truffles"	Chocolate Mathez
Applesauce (positive and neutral)	"Apfelmus aus ausgesuchten Äpfeln"	Gut&Günstig
Applesauce (control)	"Apfelmus, extra Qualität"	HAK
Water	Naturelle soda	Volvic
Paper cups for water	Organic cardboard, white, 300 ml	Kaufdichgrün
Small spoons	Coffee spoon, 11.5 cm, plastic	Papstar
Packaging chocolate truffles (positive)	Wood, for 3 x 4 chocolates	Hussel Confiserie
Packaging chocolate truffles (neutral)	Plastic, for 2 x 6 chocolates, brown/golden	Hussel Confiserie
Packaging chocolate truffles (control)	Cardboard, for 3 x 4 chocolates, creme-white, (Item number: 0530)	Wohlers Versandhandel
Packaging applesauce (positive)	Palm leave, small bowl, 80 ml, 8 x 8 cm, quadratic	Kaufdichgrün
Packaging applesauce (neutral)	Cardboard bowl, 9 x 9 x 3 cm, angular	Papstar
Packaging applesauce (control)	Fingerfood-plates, PS, 7 x 7 cm, black	Papstar

After each sample, participants rated their experienced taste pleasantness on a 9-point Likert scale with the anchors “not good at all” (1) and “exceptionally good” (9). The rating difference between the positive and the neutral product reflects the MPE value and served as our dependent variable.

2.2.7 Cognitive performance task

With the cognitive performance task, we aimed at manipulating participant’s expectations about the effects of a drink on cognitive performance via a brand name and advertisement. We then wanted to test whether these marketing cues lead to better objectively measured

cognitive performance and whether this marketing effect is boosted by OXT. Therefore, we provided a soft drink (Schweppes Lemon®) in an energy drink can (Red Bull Silver Edition®) together with extensive verbal and written advertisement for the effects of the energy drink. A previous study showed that enhancement of cognitive performance is not purely based on drink ingredients but is instead strongly influenced by expectations about the drink (Schmidt et al., 2017a).

We used a two (treatment: OXT or sham, between-participant) by two (label: energy drink or soft-drink, within-participant) design. Participants performed a cognitive performance task twice (i.e. two runs), once after consuming the soft drink and once after consuming the same soft drink but labelled and advertised as energy drink (see Fig. 4A). The order of the two labels was randomized and counterbalanced across treatment groups. To measure cognitive performance, we use a numerical stroop task. This stroop task was used before to measure cognitive performance and incentive motivation in dependence from drink ingredients and drink labels (Schmidt et al., 2017a).

Numerical stroop task

The numerical stroop task consisted of 48 trials and was programmed in the in-house software ScenarioDesigner. For a detailed overview of the task see Fig. 4B. In the effort phase, participants could earn points by identifying the numerically greater number in number pairs that differed in numerical and physical size. In each trial, participants saw a vertical ladder with ten of these number pairs arranged from bottom to top. Numbers ranged from 0 to 9 and the numerical difference between the two numbers in a pair varied from 1 to 5, with each difference occurring twice in each trial. Exact numbers changed with every new trial. The difference in physical size of the numbers (i.e. font size) was identical for all number pairs.

We used an equal mixture of 50 % easy trials and 50 % difficult trials in random order. In easy trials, the numerically greater number was also always the physically greater number. Thus, physical and numerical size were congruent. In difficult trials, the numerically greater number was only in 50 % of the number pairs also physically greater. In the other 50 % of the number pairs, numerically greater numbers were physically smaller. This incongruency

leads to a cognitive conflict and requires mental effort to ignore the incongruent but irrelevant information (i.e. physical size).

Starting at the bottom of the ladder, participants selected the numerically greater number by pressing the left or right arrow key and this way indicating the location of the numerically greater number. After each successful decision, a blue arrow pointing at the current number pair moved up one step to the next number pair. In case of an error, participants had to repeat the current number pair but were locked for 1 s. Only after this 1 s, a correct decision led them to the next number pair. Participants had 3.5 s in each trial to solve as many number pairs as possible. Each correctly solved number pair and thus each step on the ladder yielded one-tenth of the maximum points at stakes in each trial. Before each trial, participants received an information about the maximum number of points that they could earn in the next trial, when solving all ten number pairs and reaching the top of the ladder. The maximum number of points of the next trial was displayed before the effort phase for 1000 ms in a yellow circle on the screen. Additionally, the same but smaller yellow circle was shown in the top left corner during the effort phase. In 50 % of the trials, participants could maximally earn one point and in the other 50 % of trials participants could maximally earn ten points. Order of the points at stake was randomized across all trials.

Conclusively, our cognitive performance task consisted of four conditions in a two (difficulty: 100 % congruent or 50 % congruent) by two (reward: one point or ten points) factorial design. We used twelve repetitions of each of the four conditions, yielding in total 48 trials per run. After each trial, participants saw for 500 ms the summed number of points that they earned across all previous trials of a run. After an intertrial interval of 500 to 1,000 ms length, the next trial started. At the end of the run, the earned number of points were converted into monetary rewards with 1 point equaling 0.025 €.

To assess anticipated performance and confidence in performance, we asked participants how many steps on the ladder they expect to climb up. Participants had 3000 ms to indicate their expected performance by moving a blue arrow with the right arrow key to the ladder step they expected to reach in the upcoming trial. We sampled these expectations before the first trial of each run and after every sixth trial. Before the first trial of each run, expectation about the own performance might depend on the expectations about the drink efficacy and serves

as measure of anticipated performance. The expectations sampled every sixth trial during the run are influenced by the actual performance in previous trials and serve as measure of confidence in performance. Note that in the second run anticipated performance does less strongly depend on the expectations about the drink but instead also relies on the experiences with the task in the previous run.

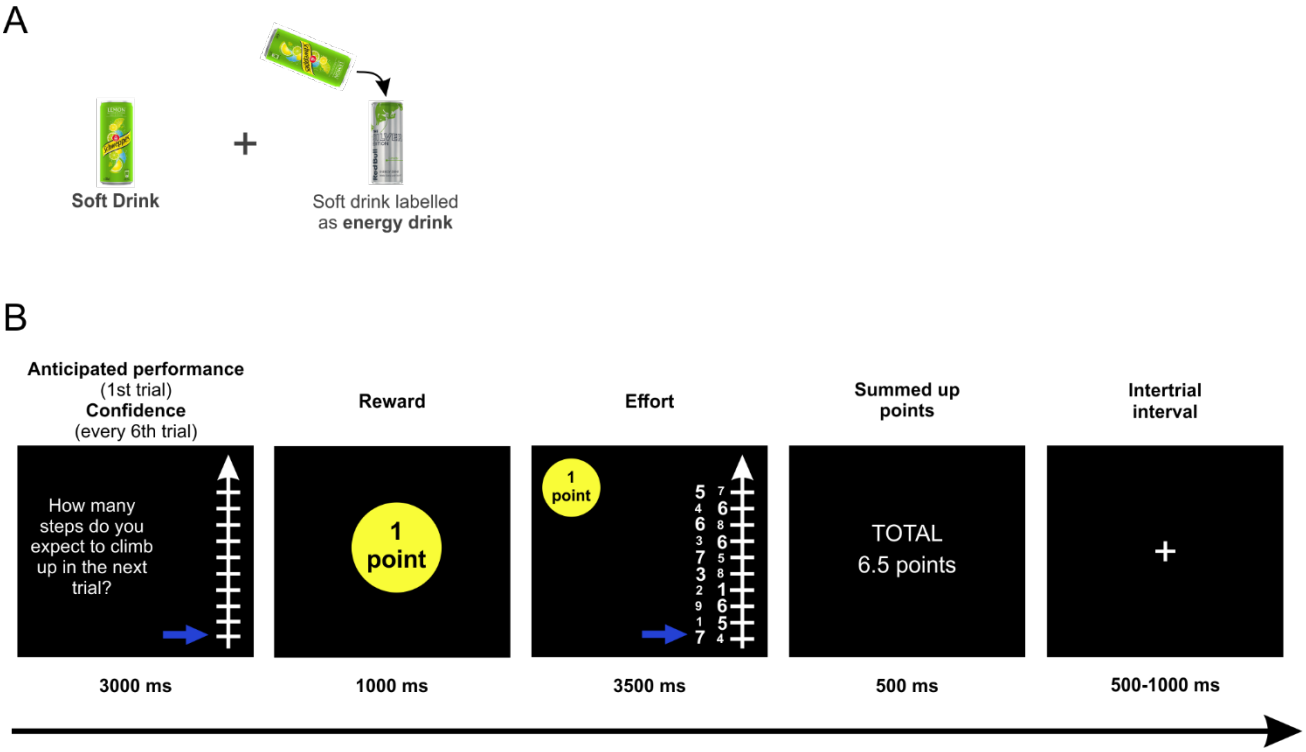

Fig. 4: Experimental design of cognitive performance task. (A): In a within-participant design, participants conducted the cognitive performance task twice: once after consuming a soft drink and once after consuming an energy drink, which was, unbeknownst to the participants, the same soft drink but presented and advertised as energy drink. (B). Trial design of the numerical stroop task for measuring anticipated performance, confidence in performance and actual performance. The task consisted of 48 trials per drink condition.

Experimental procedure of cognitive performance task

We embedded the numerical stroop task in a large cover story with extensive verbal suggestions with drink advertisement, written instructions, and a second decoy task of no interest. Overall, this whole cognitive performance part proceeded in the following way:

After the animal documentary in the remaining waiting time before the experiments started, participants received written instructions for the numerical stroop task. Moreover, participants received written and verbal information about the purpose of this cognitive performance part and the benefits of energy drinks. The experimenter told the participant that the energy drink, which he would receive, would be a new, fast and strong acting energy drink version. Introducing the energy drink as a new and differently acting energy drink version was possible because the Red Bull Silver Edition® was not available and unknown in Germany at that time. The experimenter informed the participant that official tests showed that this new energy drink version enhances cognitive performance already 5 to 10 min after drink consumption. Moreover, these tests showed that cognitive performance enhancing effects last for around 15 to 20 min before performance goes back to baseline. Participants further learned that the active ingredients of the energy drink, caffeine and taurine, are quickly taken up into the blood, reach the brain, and stimulate the central nervous system. This way, caffeine and taurine lead to the well-known energizing effects of energy drinks on physical and mental performance. An official-looking poster, which we specifically designed for the study, hung on the wall in front of the participant and further confirmed the mode of action and benefits of the Red Bull Silver Edition® (see Fig. A 1). During the verbal instructions, the experimenter mentioned the poster and hinted at it.

We had to specifically mention and emphasize these unusual but allegedly new, short timings of the energy drink effects to avoid suspicion about our study design and timing. A previous study on OXT kinetics showed that OXT effects can be expected for up to 90 min after nasal spray administration (Spengler et al., 2017). We needed to conduct all experimental parts for which we wanted to test for OXT effects (tasting task, cognitive performance task, brand trust questionnaire) safely within 90 min while also accounting for individual differences in the self-paced parts. Due to this limited amount of time, we could not introduce a longer waiting time than 5 minutes after drink consumption before assessing cognitive performance. Thus, we explained this short waiting time with the faster absorption of caffeine and taurine into the blood. Moreover, our within-participant design required that participants drank the drinks and conducted the cognitive task twice with the time constraints prohibiting a long break in between. Especially participants with the energy drink in the first run could become

suspicious about why the effect of the energy drink is not measurable anymore only 15 - 20 min later in the second run with the soft drink. To avoid this suspicion, we mentioned that the performance enhancing effects of the new Red Bull Silver Edition® were only measurable for up to 20 min in previous tests.

Concerning the purpose of our study, participants were told that our study aimed at investigating how the hormone OXT interacts with the performance enhancing effect of the new Red Bull Silver Edition®. For this we would use typical exam tasks for finance and accounting - tasks for which individuals often use energy drinks to boost their performance. One of these tasks was the above described numerical stroop task, the other task is described further below and was a memory task that only served as decoy.

After the food tasting task, we informed participants about the upcoming cognitive performance task and their individual drink order. The experimenter had already prepared the alleged energy drink in a different room while the participant watched the animal documentary. The experimenter had decanted the soft drink from its original soft drink can into the energy drink can. Thus, the energy drink can was already open. To have both drink conditions as comparable as possible and to avoid any suspicion about one drink already being open, the experimenter proceeded in the following way: Irrespective of whether the participant received the soft drink in its original can or the soft drink in the energy drink can first, the experimenter opened the original soft drink can in hearing distance but out of sight of the participant. Depending on the drink order, the experimenter then brought the open soft drink or open energy drink can to the participant. In case the participant asked why the drink was already opened, the experimenter explained that this just served as a precaution to avoid spilling the sugary drink on the testing table and computer keyboard when opening it in the testing room.

The soft drink can contained a larger volume (300 ml) than the energy drink can (250 ml). Therefore, the experimenter also brought a paper cup (same type as listed for the tasting task in Tab. 1) and instructed the participant to pour the drink into the cup. In case of the energy drink, participants poured the whole volume of the can. In case of the soft drink, participants poured the drink up to a manually prepared 250 ml mark. This way, we ensured that participants consumed the same amount of drink in both conditions.

Then participants consumed the drink while the experimenter was sitting in the same room. To keep both drink conditions comparable, participants then waited for 5 min irrespective of their actual drink. This was the time that the energy drink supposedly needed to become active. During this time, participants conducted a test run of the numerical stroop task and could ask questions in case of problems with the task. The test run differed from the experimental run because participants had 10 s instead of 3.5 s per trial to reach the top of the ladder. The points achieved in the test run did not contribute the payout. Next, participants started the actual experimental run and received a reminder that now every earned point increases their payout and that they only have 3.5 s for every trial.

Once participants finished the numerical stroop task, they conducted the decoy memory task. In this Qualtrics-based task, participants had to memorize stock market symbols from 14 different companies. Each symbol appeared on the screen together with the respective company for 3 s. In a subsequent distraction period participants had 30 s to write down as many European capitals or US states as possible. Finally, participants were presented with seven of the initially learned stock market symbols and had to fill in the corresponding companies in 1 min. Since this task only served as decoy for our cover story, this data was not analyzed. The data was only used to identify the five participants, who memorized most stock market symbols and won a 15 € Amazon vouchers.

After the memory task, the first drink condition was finished and immediately followed by the second drink condition that paralleled the first one. This time, during the 5 min waiting time participants did not perform a test run of the numerical stroop task but answered the brand trust questionnaire about marketers of organic and expensive products as related to the taste task. The numerical stroop task and the decoy memory task did not differ from the first run except of different companies and stock market symbols. In the second run, the memory task did not immediately follow the stroop task. Instead, participants first answered the brand trust questionnaire about marketers of brand products as related to the cognitive performance task. This way we wanted to ensure that the brand trust questionnaire safely fell within the 90 min for which we can expect an OXT effect.

2.2.8 Statistical analysis – General Procedure

We performed all analysis with the R language and environment (version 4.0.3, R Core Team, 2017) and R Studio (version, 1.0.143, RStudio Team, 2016). We used the following packages for data cleaning, visualization, and analyses: *arsenal*, *BayesFactor*, *coin*, *compareGroups*, *dplyr*, *ggplot2*, glmmTMB, *Hmisc*, *lme4*, *lmerTest*, *lsr*, *pacman*, *parameters*, *patchwork*, *performance*, *psych*, *reshape2*, *Rmisc*, *robustlmm*, *sjPlot*, *tidyr*.

For statistical testing, we used linear mixed-effects models with the *lmer* function from the *lmerTest* package (version 3.1.3, Kuznetsova et al., 2017). Schielzeth et al. tested the robustness of linear mixed-effects models to violations of assumptions (in particular normal distribution and equal variance of residuals). They found the impact of such violations on model estimates to be very small and linear mixed-effects models to be highly robust (Schielzeth et al., 2020). On this basis, we decided to use linear mixed-effects models for our data analysis with degrees of freedom determined via Satterthwaite's method. We report rounded degrees of freedom. All linear mixed effects models contain random intercepts for participants $\mathrm{u}_j \sim N(0, \sigma_{\mathrm{u}}^2)$ to account for repeated measures within-participants, and residuals $\varepsilon_{ij} \sim N(0,\ \sigma_{\varepsilon}^2)$:

$$DV_{ij} = \beta_0 + \beta_1 IV1_{ij} + \beta_2 IV2_{ij} + \ \ldots + \ \mathrm{u}_j + \ \varepsilon_{ij}$$

(Equation 1)

The subscripts *j* and *i* depict individual participants and individual observations per participant, respectively. *DV* and *IV* stand for the dependent variable and a flexible number of independent variables, respectively. For binary independent variables we either used dummy coding (0/1) or effect coding (-0.5/0.5) for optimal interpretation of the estimates. In case of effect coding, the estimates code the main effects and the intercept represents the average of all conditions. In case of dummy coding, the estimates code the simple effects and the intercept represents the reference condition (Schad et al., 2020). The exact dependent variables and independent variables and their coding are indicated in the description of the respective analyses and in the legend of the result tables. Continuous variables were z-scored across participants.

We visually check whether model assumptions were fulfilled via the *plot_model* function of the *sjPlot* package. In case the visual inspection hinted at a violation of model assumptions, we confirmed that our results did not differ substantially when using the robust linear mixed model *rlmer* from the *robustlmm* package (Field and Wilcox, 2017; Koller, 2016). All statistical tests were performed two-tailed with a significance threshold of $\alpha \leq 0.05$.
Data was plotted with the *ggplot2* package (version 3.3.2, Wickham, 2016). For continuous data we used boxplots and individual datapoints. For ordinal Likert-scale data we used individual data points overlayed with the mean value and error bars. We depicted paired data points from repeated measures with connecting lines between the data points.

For both study populations separately (i.e. participants of the tasting task and participants of the cognitive performance task), we first conducted control analyses to rule out differences between the treatment groups. Demographics, psychometric, and other control variables were compared between the two treatment groups via Kruskal-Wallis tests due to non-normality of most of the variables. Differences in positive and negative affect and affect changes from pre to post experiment were analyzed with two separate linear mixed-effects models. Positive/negative affect were regressed on the variables treatment (OXT = 1, sham = 0), time (post = 1, pre = 0), and their two-way interaction. Treatment guesses were analyzed with Chi-squared tests

2.2.9 Statistical analysis of taste task

Marketing effects on experienced taste pleasantness

First, we were interested whether our marketing cues (labels and packaging) successfully induced MPEs on subjectively perceived taste pleasantness across both treatment groups. Thus, we analyzed whether taste-ratings differed between positive and neutral products. We used a linear mixed-effects model and regressed taste pleasantness ratings across both manipulation types on the within-participant variables product appearance (positive = 0.5, neutral = -0.5), manipulation type (expensive = 0.5, organic = -0.5), and their two-way interaction. In post-hoc *t*-tests with Holm-correction for multiple comparisons we compared

taste pleasantness ratings of positive and neutral products separately for the expensive and organic manipulation.

Trust and expectations as potential basis of marketing effects on experienced taste pleasantness

Second, we wanted to know whether MPE are associated with trust in marketers and product expectations. We calculated a MPE value by subtracting the taste pleasantness ratings of the neutral products from the taste pleasantness ratings of the positive products. In a linear mixed-effects model, we regressed the MPE value across both manipulation types on trust in marketers of organic/expensive products, taste expectation about these products, quality expectations about these products, manipulation type (expensive = -0.5; organic = 0.5), and the two-way interactions of manipulation type with the other three variables. We ensured that no severe multicollinearity of trust and expectations confounded the model results by determining variance inflation factors (all variance inflation factors < 1.73) (Shrestha, 2020).

In two Pearson correlations with Holm correction for multiple comparisons, we tested across both manipulation types whether trust in marketers correlates with taste and quality expectations.

We did neither pre-register to analyze the relation between MPEs and product expectations, nor the correlations between trust and expectations. Thus, these analyses need to be considered as exploratory only.

The role of oxytocin for marketing effects on experienced taste pleasantness

Third, we investigated whether endogenous OXT administration affects the consumer-marketer relationship and MPEs. We used four separate linear mixed-effects models and regressed trust in marketers, taste expectations, quality expectations, and MPE values (calculated as described above) across both manipulation types on treatment (sham = 0 and OXT = 1) and manipulation (expensive = -0.5; organic = 0.5) and their two-way interaction.

To test for the robustness of the obtained OXT results, we repeated the models with covariates for demographic and psychometric control variables. For the included covariates

and results see model tables in appendix. Note that the models for taste and quality expectations were not pre-registered and are exploratory analyses.

In a further control analysis, we aimed to ensure that OXT administration does not affect taste perception irrespective of marketing means. We regressed the taste pleasantness ratings of the distinct distractor products on treatment (sham = 0 and OXT = 1), manipulation (expensive = -0.5; organic = 0.5), and their two-way interaction.

Bayesian hypothesis testing

We additionally used Bayesian hypothesis testing for our main hypothesis of OXT effects on MPE. The null-hypothesis significance testing (NHST) and its *p*-values in the frequentist approach, only allow to reveal evidence against the null hypothesis H_0 (*p*-values < 0.05). Thereby, the *p*-value represents the probability of obtaining the measured data, given that H_0 is true. However, NHST does not allow to quantify evidence for H_0. With *p*-values, we cannot know whether a null-result stems from data insensitivity and an insufficiently small sample size or from the true absence of an effect. Moreover, *p*-values do not inform about the likelihood of the alternative hypothesis (H_1) being true (Keysers et al. 2020).

Bayesian hypothesis testing is superior to NHST because it quantifies and compares evidence for both hypotheses. The Bayesian approach is based on a probabilistic framework. Bayesian statistics consider prior beliefs about the effect of interest (e.g. knowledge from prior studies), which are updated based on the collected data to form posterior beliefs. For two opposing hypotheses, H_0 and H_1, the prior belief is the ratio of the probability of one hypothesis over the probability of the other. Similarly, the posterior belief is the ratio of the probability of one hypothesis given the data compared to the other hypothesis given the data. These ratios can be described as odds. The factor that determines the degree of updating from prior to posterior odds is the Bayes factor. The Bayes factor is the ratio of the probabilities of the observed data given the two opposing hypotheses (Baig, 2020; Keysers et al., 2020; Wei et al., 2022). Together this updating can be described with Bayes rule:

$$\underbrace{\frac{p(H_0|data)}{p(H_1|data)}}_{\text{posterior odds for } H_0 \text{ vs. } H_1} = \underbrace{\frac{p(H_0)}{p(H_1)}}_{\text{prior odds for } H_0 \text{ vs. } H_1} \; x \; \underbrace{\frac{p(data|H_0)}{p(data|H_1)}}_{\text{predictive updating factor} = \textbf{Bayes Factor}} \qquad \text{(Equation 2)}$$

The Bayes factor quantifies evidence in favor of one hypothesis compared to the other and can quantify both, evidence for H_1 and evidence for H_0, depending on which hypothesis is used as nominator or denominator.

For the Bayesian analysis, we used the *lmBF* function with its default settings from the *BayesFactor* package (Morey and Rouder, 2018). We estimated Bayesian mixed-effects model that exactly paralleled our frequentist analysis with MPE value regressed on treatment, manipulation type and the two-way interactions. To obtain a Bayes factor for the OXT effect on MPE, we compared this full model with all predictors to a null model without the predictor for treatment. This way, we quantified the evidence in favor of an OXT treatment effect on MPEs (BF_{10}).

2.2.10 Statistical analysis of cognitive performance task

The role of OXT for marketing effects on cognitive performance

To test whether OXT affects the impact that drink label and advertisement have on cognitive performance, we employed a linear mixed-effects model based on the analysis from Schmidt et al. (Schmidt et al., 2017a).

We regressed cognitive performance of each trial (i.e. number of steps climbed up) on treatment (OXT = 1, sham = 0), label (energy drink = 1, soft drink = 0), trial (mean centered across runs), run (second = 0.5, first = -0.5), reward (ten points = 0.5, one point = -0.5), drink order (energy drink first = 0.5, soft drink first = -0.5), difficulty (incongruent = 0.5, congruent = -0.5), and the two-way interactions of treatment by label, treatment by reward, and treatment by difficulty.

To test for the robustness of the obtained OXT result, we repeated the model with covariates for demographic and psychometric control variables. For the included covariates and results see model tables in appendix.

We repeated this analysis with a Bayesian mixed-effects model (*lmBF*, Morey and Rouder, 2018)) and determined a Bayes factor (BF_{10}) for the interaction of treatment by label. We obtained the Bayes factor by comparing the full model (as described above for the frequentist analysis) to the reduced model without the interaction of treatment by label.

The relevance of trust, expectations, and confidence for energy drink induced marketing placebo effects on cognitive performance

Next, we analyzed the relation of trust in marketers, anticipated performance, and confidence in performance with cognitive performance and OXT administration.

First, we compared reported trust in marketers of brand products between OXT and sham group via a two-sided, unpaired *t*-test.

Second, we used two separate linear models and regressed anticipated performance and confidence in performance on treatment (OXT = 1, sham = 0), label (energy drink = 1, soft drink = 0), and their two-way interaction. In the model with confidence as dependent variable we additionally added trial (mean centered) as a fixed effect, because confidence was sampled repeatedly every sixth trial. For both models we only used the data of the first run because in the second run anticipated performance and confidence rely less on label induced expectations but are biased by experienced performance from the first run. Thus, label is a between-participant variable in this case and the model does not contain random intercepts for participants. To test for the robustness of the obtained OXT result, we repeated the model with covariates for demographic and psychometric control variables. For the included covariates and results see model tables in appendix.

Overall, these models enable us to determine whether anticipated performance and confidence in performance depend on drink label and/or OXT.

Third, in an exploratory, not pre-registered analysis, we used a linear model and regressed average performance across all trials of the first run on label (energy drink = 1, soft drink = 0), trust in marketers of brand products (z-scored), anticipated performance (z-scored), and

the two-way interactions of label by trust and label by anticipated performance. Again, we only used the data of the first run for the same reason as above. This model allows to determine whether trust in the marketer and/or expectations (i.e. anticipated performance) moderate a label effect on cognitive performance.

2.2.11 Deviations from Pre-registration

Our analyses deviated in some points from the pre-registered analysis plan. Changes and their reasons are explained in the following separately for the two tasks:

Taste task

First, our sample size exceeded the pre-registered 100 participants per treatment group. This larger sample size resulted from unequal data exclusions from the taste and the cognitive performance tasks as described in detail in chapter 2.2.2. The larger sample size did not change the results substantially.

Second, we did not conduct a mediation analysis to test whether OXT effects on subjectively experienced MPEs are mediated via enhanced trust in marketers. Since OXT did neither affect MPEs, nor trust in marketers, our hypothesized mediation pathway is impossible.

Third, we did not add a random intercept for manipulation type (expensive or organic). The effectiveness of the expensive and organic manipulations differed strongly across participants. Thus, we decided that it is important to ensure that the manipulation type does not moderate and possibly mask a potential OXT effect on MPEs. Therefore, we added manipulation type as moderator to the models. Moreover, we adjusted the variable coding for a more straightforward interpretation of model estimates. Adjusting variable coding does not affect the results.

Fourth, we decided against using robust linear mixed-effects models per se because they do not that easily allow to determine degrees of freedom and *p*-values. Based on recent simulations, linear mixed-effects models are quite robust against violations of model assumptions. Therefore, we only used robust models in case model assumptions were strongly violated and confirmed in this case that model estimates did not substantially differ between the robust and the non-robust model.

Fifth, we did not pre-register to conduct a Bayesian analysis. However, we already described above (chapter 2.2.9) the additional benefit that a Bayesian analysis provides especially for null findings. Confirming null-results with Bayesian statistics is especially relevant for the recent replication crisis in OXT research (Lane et al., 2016; Mierop et al., 2020; Quintana, 2020; Walum et al., 2016).

Sixth, we did not analyze whether marketing placebo responders show stronger OXT treatment effects. Due to our between-participant administration of either sham or OXT, we cannot make any statement about the strength of individual OXT effects.

Cognitive performance task

First, our pre-registered model specification for our main model of cognitive performance regressed on treatment and all task parameters was incorrect. We pre-registered that we would calculate the performance difference between the energy drink and the soft drink condition (i.e. a MPE on performance, similar as the MPE in the taste task). This would require calculating an average performance per run and would not allow to include fixed effects for trial, difficulty, and reward, which vary trial by trial. Instead, we decided to use cognitive performance (i.e. number of steps climbed up) of every trial as dependent variable, paralleling the analysis of Schmidt et al. (Schmidt et al., 2017a). This way, our analysis is more powerful and allows to analyze the impact of trial-level parameters. Due to this model adjustment, we further needed to include a fixed effect for label and run. Moreover, we adjusted the variable coding for a more useful interpretation of model estimates. Adjusting variable coding does not affect the results.

Second, we decided to not add a random slope for participants per level of reward because the variance of this random effect was zero. Dropping this random effect from the model did not change the results substantially.

Third, we updated our analysis of the anticipated performance and confidence in performance and only included data of the first run in the models. In the second run, previously experienced performance in the first run would bias the true effect of label on anticipation and confidence. Hence, we used a linear model rather than a linear mixed-effects model as we did not have

any repeated measures. We made the same adjustments for the analysis of the confidence in performance.

Fourth, as also mentioned for the taste task, our between-group design did not allow to analyze whether marketing placebo responders show stronger OXT effects.

Fifth, paralleling the analysis approach of the taste task, we also extended our frequentist analysis of the cognitive performance task with a Bayesian analysis.

Sixth, the model-based approach via a cost-benefit model, which we mentioned in the pre-registration, is outside of the scope of this thesis.

2.3 Results Part I: Marketing Placebo Effects on experienced taste pleasantness

2.3.1 Characteristics of study groups

We included the data of 223 male participants (n_{sham} = 111; n_{OXT} = 112) in our analysis of the taste data. The mean age of our whole study sample was 26.70 years (M_{sham} = 27.33 years, SD_{sham} = 8.50 years; M_{OXT} = 26.06 years, SD_{OXT} = 7.94 years). To make sure that the sham and the OXT group did not differ in their demographics, psychometrics, or product liking, we compared relevant variables of both groups via Kruskal-Wallis tests. We did not find any significant difference between the two groups, which verifies that we successfully randomized the two groups in our double-blind between-group design (Tab. 2).

Tab. 2: Demographic, psychometric and other control variables from the participant groups of the taste task compared via Kruskal-Wallis tests.

Variables	sham (*n* = 111)	Oxytocin (*n* = 112)	Total (*n* = 223)	*p*-value
Age [years]	27.33 (8.50)	26.06 (7.31)	26.70 (7.94)	0.314
Income [€]	665.58 (604.41)	634.01 (585.94)	649.80 (593.90)	0.247
n_{Miss}	15	16	31	
Years of education	14.00 (2.22)	14.08 (2.26)	14.04 (2.23)	0.779
AQ	14.91 (4.65)	15.52 (5.39)	15.22 (5.03)	0.504
General trust	50.66 (6.99)	49.56 (7.23)	50.11 (7.12)	0.405
Hunger[1]	3.00 (1.06)	3.09 (1.09)	3.04 (1.07)	0.525
Liking chocolate truffles[2]	4.84 (1.56)	4.96 (1.50)	4.90 (1.53)	0.631
n_{Miss}	1	0	1	
Liking applesauce[2]	5.23 (1.40)	5.21 (1.38)	5.22 (1.39)	0.946
Consumption frequency chocolate truffles[3]	2.08 (0.79)	2.14 (0.81)	2.11 (0.80)	0.537
Consumption frequency applesauce[3]	2.97 (0.78)	2.93 (0.76)	2.95 (0.77)	0.725
Movie – happiness[4]	4.59 (0.89)	4.62 (0.83)	4.61 (0.86)	0.702
Movie – emotionality[5]	3.24 (1.42)	3.19 (1.44)	3.22 (1.43)	0.779
PANAS - positive mood	30.66 (5.27)	30.59 (5.52)	30.62 (5.39)	0.950
PANAS - negative mood	11.53 (1.97)	11.99 (2.73)	11.76 (2.39)	0.190

Notes: Table depicts means and standard deviations. [1] Hunger reported on a 6-point Likert scale: 1 = not hungry at all, 6 = very hungry; [2] Liking of products reported on a 7-point Likert scale: 1 = not at all, 7 = exceptionally good; [3] Consumption frequency reported on a 8-point scale: 1 = never, 2 = < 1 x year, 3 = every few months, 4 = 1 – 3 x per month, 5 = 1 – 2 x per week, 6 = 3 – 4 x per week, 7 = 5 – 6 x per week, 8 = > 6 x per week; [4] Happiness after movie reported on a 7-point Likert scale: 1 = very unhappy, 7 = very happy; [5] Emotionality after movie reported on a 7-point Likert-scale: 1 = neutral, 7 = very emotional. PANAS scores before the administration of the intranasal OXT are reported here. Missing data points for variable income due to voluntary nature of the question; missing data points for the liking of chocolate truffles because one participant forgot to answer this question. AQ, Autism Spectrum Quotient; PANAS, positive and negative affect schedule.

To control for confounding effects of OXT on mood, we analyzed PANAS (Watson et al., 1988) results from pre- and post-experiment by means of a linear mixed-effects regression model (Tab. A 1). Neither positive affect (β = -0.068, SE = 0.798, 95 % CI [-1.63 – -1.50], $t_{(301)}$ = -0.09, p = 0.932) nor negative affect (β = 0.460, SE = 0.270, 95 % CI [-0.07 – 0.99], $t_{(383)}$ = 1.70, p = 0.090) differed between the two groups before OXT administration (simple effect of treatment before OXT administration). While the change in positive affect from pre-

to post-experiment was similar for the sham and the OXT group (interaction treatment x time: β = 0.481, *SE* = 0.641, 95 % CI [-0.77 – 1.74], $t_{(219)}$ = 0.75, p = 0.454), the change in negative affect differed significantly between sham and OXT group (interaction treatment x time: β = -0.706, *SE* = 0.307, 95 % CI [-1.31 – -0.10], $t_{(203)}$ = -2.30, p = 0.022). Negative affect scores decreased significantly stronger in the OXT group than in the sham group. Note that the assumption of equal variance and normality of model residuals was not fulfilled for the negative PANAs scores. However, repeating the linear-mixed effects model with a robust model did not substantially change the results.

To make sure that these changes in negative affect did not confound any of our following OXT analyses, we run control models with the difference in scores (post- minus pre-experiment) and other relevant demographic and psychometric data as covariates.

After the experiment, participants indicated whether they thought that they received sham or OXT treatment or whether they did not have any idea about their treatment. We used these treatment guesses to verify that participants were blind to their treatment via Chi-squared tests. The treatment guess of the OXT group was not significantly different from chance level (correct guess = 29.6 %, $\chi^2_{(2)}$ = 3.88, p = 0.144). Moreover, sham and OXT group did not significantly differ in their treatment guesses ($\chi^2_{(2)}$ = 0.05, p = 0.974). No participant reported any side effects during or after the experiment.

2.3.2 Marketing effects on experienced taste pleasantness

We aimed to elicit MPEs on subjectively reported taste pleasantness of identical food products by providing the identical products with different information and appearance. We used organic and expensive product labels and different packaging for applesauce and chocolate truffles, respectively. We expected that organic and expensive products that are nicely packaged (positive products) are experienced better compared to identical non-organic and less expensive products in a standard packaging (neutral products) (Linder et al., 2010; Plassmann et al., 2008; Schmidt et al., 2017b). To confirm that our manipulation of product appearance was successful we analyzed taste pleasantness ratings in a linear mixed-effects model. We conducted this analysis irrespective of the treatment group and included the data

from both, sham and OXT group, in the model. Results did not substantially change when only including the sham group in this analysis.

We found significantly higher taste pleasantness ratings for positive products compared to neutral products (β = 0.332, *SE* = 0.095, 95 % CI [0.15 – 0.52], $t_{(666)}$ = 3.51, $p < 0.001$) across both manipulation types. The taste pleasantness of the positive product was on average across both manipulation types 0.33 rating points and thus 5.4 % higher (neutral product: *M* = 6.17, *SD* = 0.78; positive product *M* = 6.50, *SD* = 0.78).

Across both, positive and neutral products, participants rated the taste pleasantness of the applesauce significantly worse than the taste pleasantness of the chocolate truffles (β = -1.067, *SE* = 0.095, 95 % CI [-1.25 – -0.88], $t_{(666)}$ = -11.29, $p < 0.001$). However, the effect of product appearance did not significantly differ between both manipulation types (indicated by the non-significant interaction of product appearance x manipulation: β = -0.242, *SE* = 0.189, 95 % CI [-0.61 – 0.13], $t_{(666)}$ = -1.28, p = 0.201). The results are depicted in Tab. A 2 and Fig. 5A.

In post-hoc paired t-tests with Holm-correction we found that the expensive manipulation of the chocolate truffles significantly enhanced taste pleasantness ratings of the positive product (*M* = 7.10, *SD* = 1.46) compared to the neutral product (*M* = 6.65, *SD* = 1.64; $t_{(222)}$ = 4.18, $p_{corr.} < 0.001$, see Fig. 5B). However, the organic manipulation of the applesauce showed a similar but non-significant trend of enhanced taste pleasantness ratings for the positive product (*M* = 5.91, *SD* = 1.76) compared to the neutral product (*M* = 5.70, *SD* = 1.70; $t_{(222)}$ = 1.84, $p_{corr.}$ = 0.068, see Fig. 5C).

Although the effect of the organic manipulation was smaller and not significant, it still pointed in the same direction as the expensive manipulation. Therefore, and since we were interested in MPEs and their psychobiological mechanisms more generally across different marketing means, we pooled both manipulations for all further analyses. Hence, we analyzed the two manipulations as repeated measures and included the manipulation type as moderator in all analyses.

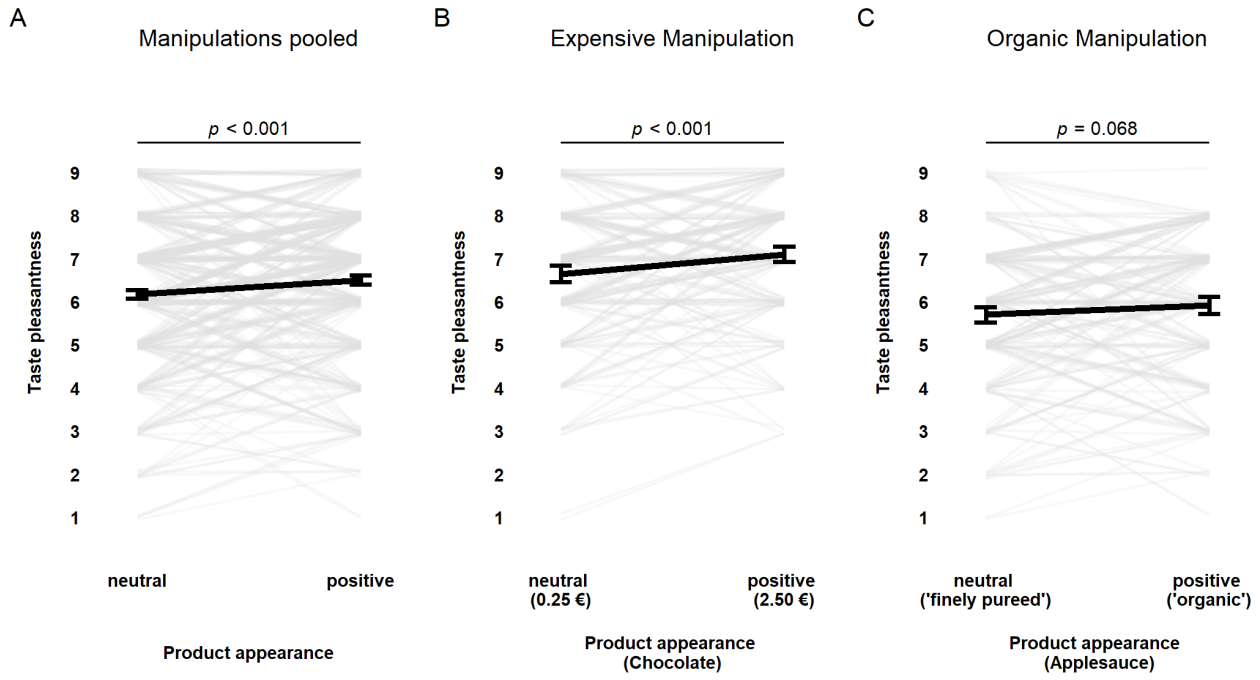

Fig. 5: Effects of product appearance, manipulated by expensive and organic labels and packaging, on experienced taste pleasantness of identical food products. Participants rated the taste pleasantness of identical but differently presented (via labels and packaging) food products on a 9-point Likert-scale. (A) Across both types of manipulations (i.e. expensive and organic) taste pleasantness was significantly higher for the product with positive appearance compared to the more neutral product. The effect of product appearance was statistically tested via linear mixed-effects model (Tab. A 2). (B) The expensive manipulation increased taste pleasantness of the positive product significantly as compared to the neutral product. (C) The organic manipulation only weakly but not significantly increased taste pleasantness of the positive product as compared to the neutral product. The effects of the individual manipulations in (B) and (C) were statistically tested in paired *t*-tests with Holm-correction for multiple comparisons. Light grey lines represent the paired ratings of each participant. The black line connects the mean values of both product appearances. Error bars denote 95 % confidence intervals of the means.

2.3.3 Trust and expectations as potential basis of marketing effects on experienced taste pleasantness

Product expectations and purchase loyalty rely on trust in the product and the marketer of the product (Chaudhuri and Holbrook, 2001; Fournier, 1998; Morgan and Hunt, 1994; Porral

and Levy-Mangin, 2016). Thus, we expected expectations and trust in the marketer to also be related to the strengths of MPEs.

In a linear mixed-effects model, we did not find any significant association of trust in marketers (β = 0.125, *SE* = 0.104, 95 % CI [-0.08 – 0.33], $t_{(438)}$ = 1.21, p = 0.226), quality expectations (β = -0.190, *SE* = 0.102, 95 % CI [-0.39 – 0.01], $t_{(438)}$ = -1.86, p = 0.063), nor taste expectations (β = 0.174, *SE* = 0.097, 95 % CI [-0.02 – 0.36], $t_{(438)}$ = 1.79, p = 0.073) with the MPEs (see Tab. A 3). These associations did also not depend on the type of marketing manipulation (all interactions with manipulation p > 0.8) and results did not substantially change when controlling for demographical and psychometric variables (Tab. A 3).

However, for both manipulations, expensive and organic, trust in marketers significantly correlated with quality as well as taste expectations (all p_{corr} < 0.001, Pearson correlation corrected for multiple comparisons via Holm-method).

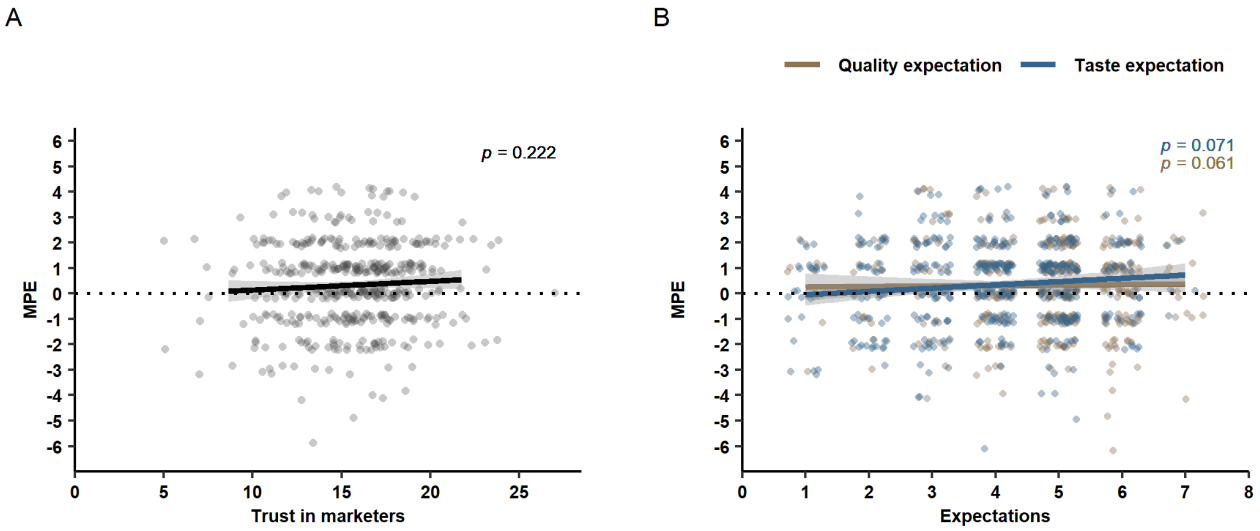

Fig. 6: MPEs were not related to trust in marketers and expectations. The MPE represents the difference in taste pleasantness rating of the positive product compared to the neutral product (across both manipulations). MPE was not associated with trust in marketers (A) and quality as well as taste expectations (B). Individual dots represent the individual data points of each participant (for both manipulation types, n = 446), the shaded grey area shows the 95 % confidence interval, and the dotted vertical line highlights an MPE of zero. MPE, marketing placebo effect.

2.3.4 The role of oxytocin for marketing effects on experienced taste pleasantness

Next, we sought to investigate the involvement of OXT in the consumer-marketer relationship and the relevance of OXT for MPEs on taste experiences.

First, we analyzed the effect of the intranasal OXT treatment on trust in the marketer, quality expectations, and taste expectations.

In linear mixed-effects models, neither trust in marketers (β = -0.140, SE = 0.342, 95 % CI [-0.81 – 0.53], $t_{(221)}$ = -0.41, p = 0.683, Tab. A 4), nor quality expectations (β = -0.132, SE = 0.143, 95 % CI [-0.41 – 0.15], $t_{(221)}$ = -0.92, p = 0.359), nor taste expectations (β = -0.183, SE = 0.143, 95 % CI [-0.46 – 0.10], $t_{(221)}$ = -1.28, p = 0.201) were significantly different between sham and OXT group (see Tab. A 4 - Tab. A 6 and Fig. 7A-C). The manipulation type did not moderate the effect of OXT on any of the three variables (all p-values > 0.46). The null-effect of OXT on all three dependent variables remained robust when controlling in for demographical and psychometric variables in model 2 (see Tab. A 4 - Tab. A 6). Note however, that we did not ask about specific products but products with such labels in general.

Second, we analyzed the effect of the intranasal OXT treatment on MPEs. To rule out that OXT affects general product valuation or taste perception independent of marketing, we analyzed the taste pleasantness ratings of the distractor products in linear mixed-effects models. Taste pleasantness ratings for the distractor product did not differ between sham and OXT group (β = 0.022, SE = 0.171, 95 % CI [-0.31 – 0.36], $t_{(221)}$ = 0.13, p = 0.897, see Tab. A 7).

After ensuring that intranasal OXT treatment did not affect taste pleasantness ratings per se, we analyzed MPE value (taste pleasantness difference: positive product minus negative product) in dependency from the treatment and manipulation type. The intranasal OXT treatment did not change MPEs as compared to the sham group (M_{sham} = 0.29, SD_{sham} = 1.13; M_{OXT} = 0.38, SD_{OXT} = 1.09; β = 0.087, SE = 0.158, 95 % CI [-0.22 – 0.40], $t_{(442)}$ = 0.55, p = 0.584, see Tab. A 8 and Fig. 7D). The manipulation type did not moderate the effect of OXT treatment on MPE (indicated by the non-significant two-way interaction treatment x manipulation: β = -0.088, SE = 0.316, 95 % CI [-0.71 – 0.53], $t_{(442)}$ = -0.28, p = 0.782).

Repeating the same model with covariates for demographic and psychometric variables did not change the non-significant result of OXT treatment (see model 2 in Tab. A 8).
This null result stands in contrast to our main hypothesis. Therefore, to confirm this result and further quantify the evidence in favor of this null result of intranasal OXT administration on MPEs, we conducted a Bayesian analysis. We obtained a Bayes factor in favor of the OXT effect on MPE (BF_{10}) of 0.018. This Bayes factor supports the null-hypothesis with very strong evidence (Wetzels and Wagenmakers, 2012) and thus confirms our frequentist result.

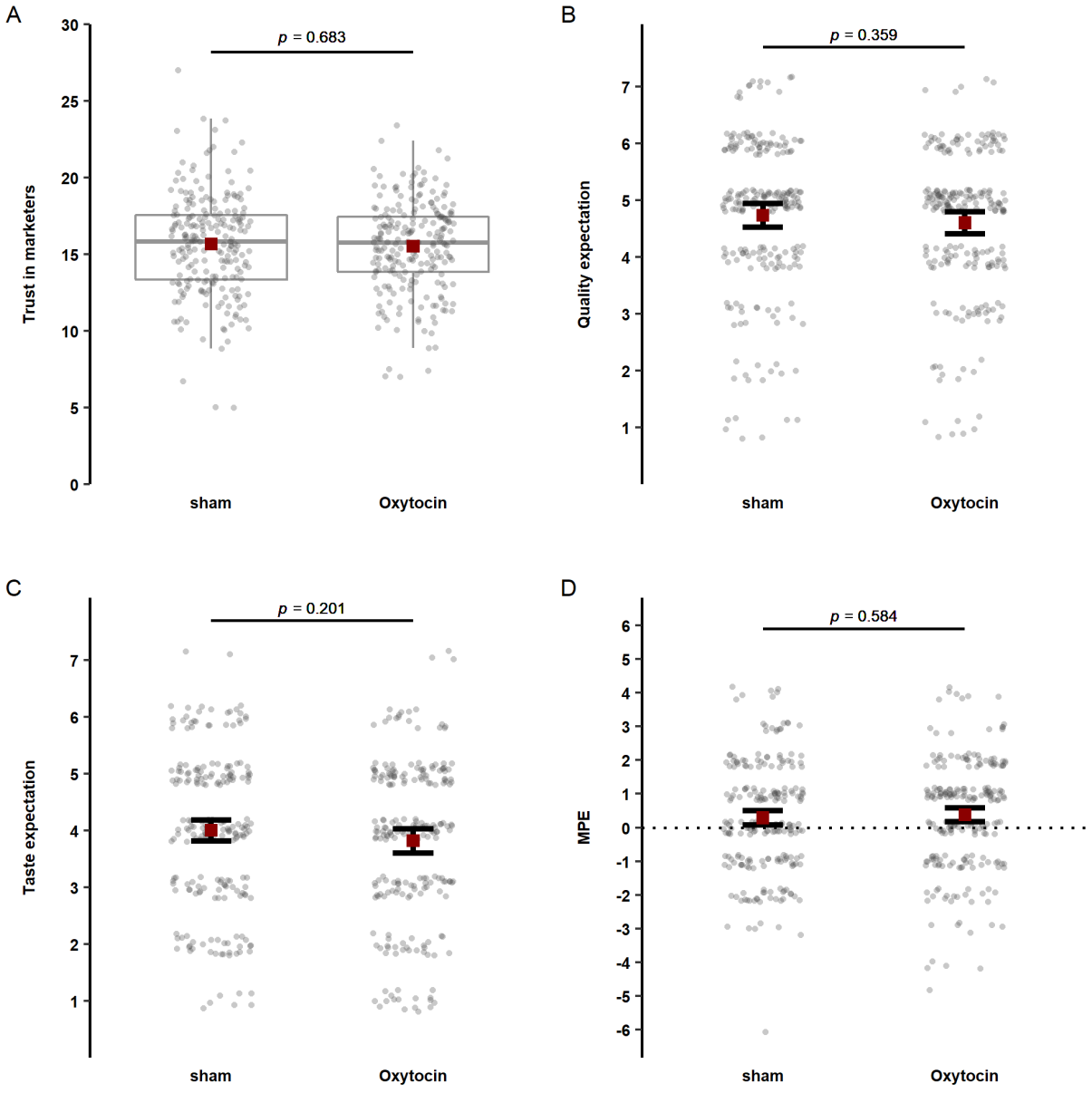

Fig. 7: Intranasal OXT treatment did not affect consumer-marketer relationship and marketing induced product perception. (A) Trust in marketers, (B) quality expectations, (C) taste expectations, and (D) MPEs of organic and expensive products remained unchanged after intranasal OXT treatment. Dots represent individual data points of participants for both manipulations pooled (n_{sham} = 222, n_{OXT} = 224). Red squares show mean values. We used a boxplot for continuous data and depicted mean values with error bars for ordinal Likert-scale data. Error bars for ordinal Likert-scale data (B, C, C) denote 95 % confidence intervals and whiskers of boxplot for discrete data (A) denotes 1.5 x interquartile range with the black line representing the median value. MPE, marketing placebo effect.

2.4 Results Part II: Marketing Placebo Effects on energy drink induced cognitive performance

2.4.1 Characteristics of study groups

For the analysis of the cognitive performance part of the study, we used the data of 202 male participants (n_{sham} = 99; n_{OXT} = 103). Participants had a mean age of 26.51 years (M_{sham} = 26.61, SD_{sham} = 7.33; M_{OXT} = 26.43, SD_{OXT} = 7.42). We compared sham and OXT group via Kruskal-Wallis tests to make sure that participants of the two groups did not differ by chance in any relevant demographic, or psychometric variable (Tab. 3).

We found a significant difference in the regular consumption frequency of energy drinks (p = 0.041). Participants in the OXT group reported to consume energy drinks on average more often than participants in the sham group. All other variables did not differ significantly between the two groups.

We further analyzed in two linear mixed-effects models whether positive and negative affect scores changed differently from pre- to post-experiment for the sham and the OXT group (Tab. A 9). With these analyses we wanted to rule out any OXT induced effects on mood. Positive affect did not change differently from pre- to post for the two groups (non-significant interaction of treatment and time: β = 0.194, SE = 0.650, 95 % CI [-1.08 – 1.47], $t_{(198)}$ = 0.30, p = 0.765). However, the change in negative affect differed significantly between sham and OXT group (interaction of treatment x time: β = -0.927, SE = 0.364, 95 % CI [-1.64 – -0.21], $t_{(189)}$ = -2.55, p = 0.012). Negative affect decreased significantly stronger in the OXT group than in the sham group, similar as we also observed it for the participants of the taste task (2.3.1). Note that the assumptions of the linear mixed-effects model about equal variance and normality of model residuals were not fulfilled for the negative PANAs scores. However, repeating the analysis with a robust linear-mixed effects model, which is less sensitive to violations of model assumptions, did not substantially change the results (Erceg-Hurn and Mirosevich, 2008; Field and Wilcox, 2017).

Tab. 3: Demographic, psychometric and other control variables from the participant groups of the cognitive performance task compared via Kruskal-Wallis tests.

Variables	sham (*n* = 99)	Oxytocin (*n* = 103)	Total (*n* = 202)	*p*-value
Age [years]	26.61 (7.33)	26.43 (7.42)	26.51 (7.36)	0.817
Income [€]	709.84 (615.37)	576.01 (519.55)	643.71 (572.30)	0.069
n_{Miss}	13	19	32	
Years of education	13.85 (2.34)	13.91 (2.20)	13.88 (2.26)	0.906
AQ	15.30 (4.42)	15.94 (5.42)	15.63 (4.95)	0.573
General trust	50.61 (7.81)	49.07 (7.58)	49.82 (7.71)	0.157
Time since waking up [h]	4.91 (2.81)	4.98 (3.00)	4.95 (2.90)	0.970
Sleep duration [h]	7.45 (1.04)	7.15 (1.05)	7.30 (1.06)	0.076
Consume frequency of energy drinks [1]	2.69 (1.10)	3.07 (1.21)	2.88 (1.17)	**0.041 ***
Belief in energy drink effects [2]	4.13 (1.13)	4.34 (1.02)	4.23 (1.08)	0.166
Movie – happiness [3]	4.75 (0.87)	4.71 (0.72)	4.73 (0.80)	0.841
Movie – emotionality [4]	3.17 (1.32)	3.33 (1.41)	3.25 (1.36)	0.337
PANAS - positive mood	30.41 (5.35)	30.73 (4.99)	30.57 (5.16)	0.562
PANAS - negative mood	11.53 (2.00)	12.40 (3.63)	11.97 (2.97)	0.096

Note: Table depicts means and standard deviations. [1] Consume frequency of energy drinks reported on 8-point Likert scale: 1 = never, 2 = < 1 x per year, 3 = every few months, 4 = 1 – 3 x per months, 5 = 1 – 2 x per week, 6 = 3 – 4 x per week, 7 = 5 – 6 x per week, 8 = > 6 x per week. [2] Belief in energy drink effects was calculated as mean of three items (enhancement of focus and attention, enhancement of cognition, enhancement of physical strengths), each reported on a 7-point Likert scale: 1 = strongly disagree, 7 = strongly agree; [3] Happiness after movie reported on a 7-point Likert scale: 1 = very unhappy, 7 = very happy; [4] Emotionality after movie reported on a 7-point Likert-scale: 1 = neutral, 7 = very emotional. PANAS scores before the administration of the intranasal OXT are reported here. Missing data points for variable income due to voluntary nature of the question. AQ, Autism Spectrum Quotient; PANAS, positive and negative affect schedule.

To make sure that unintended effects of OXT on mood do not obscure our results, we conducted control models for all analyses involving OXT. These control models included affect differences (post- minus pre-experiment) as well as other relevant demographic and psychometric variables (including frequency of energy drink consumption) as covariates.

Analysis of the treatment guess revealed that the participants of the cognitive performance task remained unaware of their treatment. Treatment guesses in the OXT group did not significantly differ from chance (correct guess = 35.0 %, $\chi^2_{(2)} = 2.58$, $p = 0.275$) and from

guesses of the sham group ($\chi^2_{(2)}$ = 1.57, p = 0.456). No participant reported any side effects during or after the experiment.

2.4.2 The role of Oxytocin for marketing effects on cognitive performance

To test for label and advertisement induced MPEs and their interaction with OXT administration on cognitive performance, we used a linear mixed effects model (see Tab. A 10 for model details and results).

First, intranasal OXT treatment did not per se increase cognitive performance in the soft drink condition across all trials, rewards, difficulties, runs, and orders (β = 0.014, SE = 0.1354, 95 % CI [-0.25 – 0.28], $t_{(19180)}$ = 0.11, p = 0.916).

Second, in the sham group we could not observe an effect of drink label across all trials, rewards, difficulties, runs, and orders (β = 0.007, SE = 0.028, 95 % CI [-0.05 – 0.06], $t_{(19180)}$ = 0.26, p = 0.795). Thus, our energy drink label and advertisement did not per se lead to a MPE on cognitive performance.

Third, trial (β = 0.005, SE = 0.0007, 95 % CI [-0.01 – 0.00], $t_{(19180)}$ = -7.02, p < 0.001), run (β = 0.928, SE = 0.040, 95 % CI [0.85 – 1.01], $t_{(19180)}$ = 23.36, p < 0.001), reward (β = 0.079, SE = 0.028, 95 % CI [0.02 – 0.14], $t_{(19180)}$ = 2.80, p = 0.005), and difficulty (β = -2.332, SE = 0.028, 95 % CI [-2.39 – -2.28], $t_{(19180)}$ = -82.23, p < 0.001) significantly affected the cognitive performance in general in the sham group for the soft drink condition, thus irrespective of any marketing and OXT treatment. The directionality of these effects was in such a way that cognitive performance decreased with increasing trial number (probably due to fatigue effects) and increasing difficulty. Cognitive performance increased from first to second run (probably due to learning effects) and with increasing reward (probably due to higher motivation).

Fourth, we found a significant interaction of treatment with label (β = 0.095, SE = 0.040, 95 % CI [0.02 – 0.17], $t_{(19180)}$ = 2.40, p = 0.016, see Fig. 8). This interaction shows that in the OXT group the effect of the drink label on cognitive performance was significantly different than in the sham group. While in the sham group, drink label did not have any effect on performance (sham: $M_{\text{soft drink}}$ = 6.06, $SD_{\text{soft drink}}$ = 1.06; $M_{\text{energy drink}}$ = 6.06, $SD_{\text{energy drink}}$ = 0.94),

cognitive performance in the OXT group was around 2 % higher for the alleged energy drink than for the soft drink (OXT: $M_{\text{soft drink}}$ = 6.06, $SD_{\text{soft drink}}$ = 1.03; $M_{\text{energy drink}}$ = 6.18, $SD_{\text{energy drink}}$ = 1.04).

None of the results substantially changed when repeating the same model with covariates for demographic and psychometric variables (see model 2 in Tab. A 10).

In addition, we conducted a Bayesian linear mixed-effects model to confirm this observed impact of OXT for MPEs on cognitive performance. The BF_{10} was 0.16 and did not support our frequentist finding but instead provides substantial evidence for the null hypothesis (Wetzels and Wagenmakers, 2012).

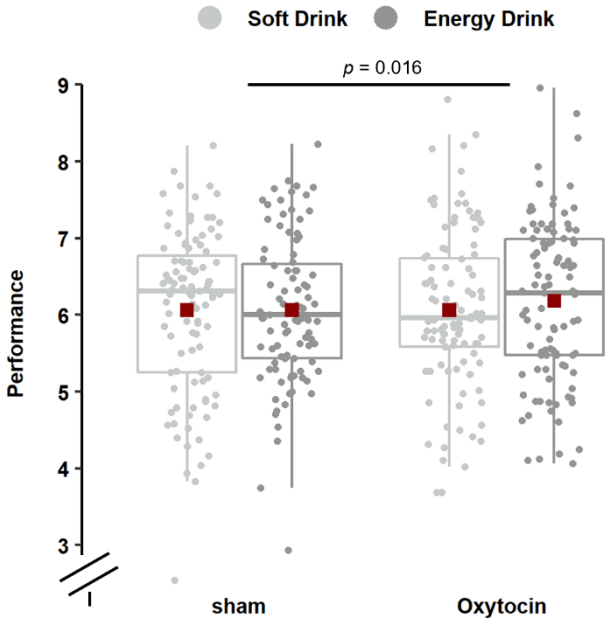

Fig. 8: Interaction of drink label and OXT treatment caused MPE on cognitive performance. Performance was measured within-participant in two runs of the numerical stroop task, one for the soft drink and one for the energy drink condition. The performance increase in the OXT group for the energy drink label compared to the soft drink label differed significantly from the equal performance across both drink labels in the sham group. data points represent mean performance of all 48 trials within each drink label condition for every participant (n_{sham} = 99; n_{OXT} = 103). Lines represent median values, squares represent mean value, and whiskers denote 1.5 * interquartile range.

2.4.3 The relevance of trust, expectations, and confidence for energy drink induced marketing placebo effects on cognitive performance

Next, we wanted to elucidate the role of trust in marketers of brand products (e.g. Red Bull), performance anticipation, and confidence in performance for MPEs on cognitive performance. Note that we did not specifically sample trust in marketers of energy drink brands, like Red Bull, but trust in marketers of any brand.

Trust in marketers of brand products did not differ between the sham and the OXT group (M_{sham} = 16.46, SD_{sham} = 2.90; M_{OXT} = 16.48, SD_{OXT} = 3.06, two-sided unpaired *t*-test: $t_{(200)}$ = 0.043, p = 0.966).

Our linear model showed that in the soft drink condition, anticipated performance did not differ between the sham and the OXT group (β = -0.419, SE = 0.433, 95 % CI [-1.27, 0.44], $t_{(198)}$ = -0.97, p = 0.335, see Tab. A 11). Anticipated performance in the sham group was not significantly different between the two drink labels (β = 0.209, SE = 0.439, 95 % CI [-0.66, 1.08], $t_{(198)}$ = 0.48, p = 0.635). OXT treatment did not have an effect on the relation of drink label and anticipated performance (β = 0.179, SE = 0.615, 95 % CI [-1.03, 1.39], $t_{(198)}$ = 0.29, p = 0.772). These results were robust when adding covariates to the model (model 2 in Tab. A 11).

Similar as for anticipated performance, also confidence in performance did not differ between sham and OXT group in the soft drink condition (β = 0.184, SE = 0.264, 95 % CI [-0.33, 0.70], $t_{(198)}$ = 0.70, p = 0.485, see Tab. A 12). Confidence in performance was unaffected by the drink label in the sham group (β = 0.301, SE = 0.268, 95 % CI [-0.22, 0.83], $t_{(198)}$ = 1.12, p = 0.263). The interaction of treatment and label was not significant (β = -0.293, SE = 0.376, 95 % CI [-1.03, 0.44], $t_{(198)}$ = -0.78, p = 0.436). Results did not substantially change when repeating the model with covariates (model 2 in Tab. A 12).

Conclusively, the drink label and advertisement did not increase participant's trust in marketers of brand products and also not their beliefs about their own performance. This relation remained unaffected by intranasal OXT administration.

Nevertheless, we further tested whether the effect of drink label depended on trust in marketers of brand products and anticipated performance. With this, we investigated

anticipated performance and trust as moderators rather than mediators of drink label effects on cognitive performance. This analysis was independent from the OXT treatment and purely focused on the cognitive mechanism of MPEs on performance. We limited this analysis to anticipated performance rather than confidence in performance as a measure of expectations. Anticipated performance is unaffected from any experiences with task difficulty and reflects product induced expectations best. In a linear regression model, we did not find a correlation between anticipated performance and average performance in the soft drink condition (β = 0.049, SE = 0.103, 95 % CI [-0.15, 0.25], $t_{(196)}$ = 0.47, p = 0636). The drink label effect on average performance did not depend on anticipated performance (interaction label x anticipated performance: β = -0.117, SE = 0.136, 95 % CI [-0.39, 0.15], $t_{(196)}$ = -0.86, p = 0.393) and trust in marketers (interaction label x trust in marketers of brand products: β = 0.075, SE = 0.137, 95 % CI [-0.20, 0.35], $t_{(196)}$ = 0.54, p = 0.588, Tab. A 13).

2.5 Discussion

Although marketing placebo is a widely known phenomenon affecting human behavior and decision-making, exact psychobiological underpinnings are still unknown. With our study, we sought to shed light on the neurobiological mechanisms of MPEs and their potential commonality with analgesic placebo effects. For our main hypothesis, we investigated the neurobiological mechanisms of MPEs on subjectively experienced taste pleasantness. In an exploratory part of the project, we focused on objectively measured placebo responses to drinks due to brand advertisement. First, this approach allows us to gain more insights into the broad impact of food marketing for consumer preferences and behavior as well as its psychological mechanisms. Second, by administering intranasal OXT, we were able to investigate whether MPEs depend on the OXT system.

2.5.1 The impact of marketing on subjective and objective placebo responses to food cues

To evoke MPEs on subjectively experienced taste pleasantness of food products, we used two different food product types, each associated with a different marketing label. We provided the exact same chocolate truffles once with an expensive price tag in a valuable wooden box and once with a cheap price in a simple plastic holder. Similarly, we provided the exact same applesauce once with an organic label in a valuable palm leave bowl and once without organic label in a simple cardboard bowl. First, we tested whether we were able to elicit MPEs and replicate previous findings with these labels (Linder et al., 2010; Plassmann et al., 2008; Schmidt et al., 2017b). We analyzed whether products with marketing labels and superior packaging had higher taste pleasantness ratings as compared to the identical products without these labels in an inferior packaging. When pooling both products and labels, we found that taste pleasantness ratings of the labelled, superior products were significantly higher than for the inferior product, confirming a successful manipulation by our marketing means. When analyzing the expensive manipulation of the chocolate truffles and the organic manipulation of the applesauce separately, we found that these two manipulations differed in their effectiveness. The expensive manipulation of the chocolate truffles showed a significant positive effect on taste pleasantness rating, but the organic manipulation of the applesauce did not. The organic manipulation did only lead to a strong but not significant increasing trend in taste pleasantness ratings. The effect of the expensive manipulation of chocolate truffles echoes previous work with differently priced wines and thus confirms a product type independent strong effect of price labels on product evaluation (Plassmann et al., 2008; Schmidt et al., 2017b). Our non-successful manipulation by the organic label of the applesauce stands in contrast to previous studies that demonstrated an increased valuation and liking of organically labelled products (Fernqvist and Ekelund, 2014; Linder et al., 2010). The inefficient manipulation by the organic label can have different reasons.

First, Linder *et al.* used willingness to pay (WTP) as measure of product valuation rather than directly assessing experienced taste pleasantness. Participants might be willing to pay more

for organic products not necessarily because they expect them to taste better but because of environmental concerns, nutritive value, and other quality features not directly reflected in taste (Shafie and Rennie, 2012; Yiridoe et al., 2005).

Second, consumers are used to organic products being more expensive than non-organic products. Thus, consumers probably not only perceive the organic label but also the price of the organic product as an indicator of high quality and good taste. In that case, the design of our product labels obliterated his usual link between organic labels and product prices. To distract participants from our manipulation, each label included information on price, manufacturing, and origin of the product. However, only the label of interest varied for the test products while the other labels were identical. Thus, the organic applesauce and the non-organic applesauce had the same price label. Consumers might perceive an organic product that is cheaper as it is expected to be in comparison to a non-organic product as less good (Rao, 2005; Simonson et al., 1994). Having more information than necessary on the label might on the one hand help to distract from our manipulation. On the other hand, more product information also increases the chances that participants only respond to the provided information that is most relevant to them and neglect all other information (Kähkönen et al., 1997). As most of our participants were students, the price label might have been of higher relevance for them then the organic label.

Third, according to Gneezy *et al.* taste pleasantness ratings of a food product do not solely reflect the experienced taste pleasantness but also a taste-prediction-error (Gneezy et al., 2014). That is the difference between the expected and the perceived taste of the product. A product falls short on its expectations if it raises high expectations due to marketing labels but is of low quality. Consumers will rate the taste of such a marketed product of low quality more negatively than the taste of another product of the same low quality that did not raise high expectations by marketing labels (Gneezy et al., 2014). We saw in our rating data that participants rated the taste of the control applesauce, which was a different kind of applesauce than we used for the organic and non-organic product, significantly better than both the organic and non-organic ones. This might indicate that the type of applesauce, which we used as organic and non-organic product, was of noticeable lower quality than the control applesauce. Hence, the taste experience of the organically labelled applesauce might have

fallen short of the expectations that were raised by the label, thus minimizing a possible MPE by the organic label. This negative effect might have been even stronger in participants, who randomly sampled the high-quality control applesauce before the organic applesauce of lower quality, as they could directly compare both tastes.

Fourth, expectation and valuation of organic products strongly depend on the type of food (Fillion and Arazi, 2002; Lee et al., 2013). Previous studies either used several different types of food in a repeated trial design (Linder et al., 2010) or a different food product like tomatoes (Fernqvist and Ekelund, 2014), which hence renders a direct comparison difficult. Consumers might have less strong quality or taste expectations for canned applesauce than for other fresh products.

Lastly, previous research suggests that expectancy induced effects of organic labels on taste perception strongly depend on consumer's beliefs, e.g. beliefs about sustainability and healthiness (Piqueras-Fiszman and Spence, 2015). Hence, organic MPEs might be less strong due to a higher inter-individual variability. Moreover, Linder et al. found that ventral striatum activity in response to organic labels correlated with the usual buying frequency of organic food. Participants, who frequently buy and consume organic foods, seem to find organic labels more rewarding and might be more easily manipulated in their experienced taste pleasantness. Conclusively, the strengths of organic MPEs might strongly rely on the tested population. Our study population mostly consisted of students with a very low income (see Tab. 2). Therefore, it is likely that our population had a low buying frequency of organic products and thus responded less to the organic label.

Overall, our results confirm previous research by showing that product labels together with product appearance bias experienced taste pleasantness. Still, the strength of this bias seems to strongly depend on label content, product type, and inter-individual differences in responsiveness to marketing. Although it seems likely the observed bias in reported taste pleasantness also translates into biased food choices and consumption behavior (Cohen and Babey, 2012; Mueller and Szolnoki, 2010), we cannot make any conclusion about choice behavior as this was not tested in our experimental design.

We decided to pool both manipulations for the further analysis of the OXT treatment effect as we were not interested in individual labels but an overall effect of OXT on MPEs across

different products and labels. To make sure that a potential OXT effect does not depend on the type of manipulation (expensive or organic) we analyzed the manipulation type as a moderator in all analyses. The type of manipulation did not moderate the OXT effect for any of our dependent variables.

In an exploratory part of our study, we further studied MPEs on cognitive performance. As compared to placebo effects on reported pain or taste, cognitive performance is an objectively measured rather than consciously and subjectively perceived placebo outcome. We employed a numerical stroop task to test participant's performance. In a within-participant design, participants conducted the task twice, once after drinking a soft drink and once after drinking the same soft drink but labelled and advertised as an energy drink for increasing cognitive performance.

We did not find any simple effect of drink label and advertisement on performance specifically in the sham group. Meaning that in both, the soft drink and the energy drink condition, the performance of the sham group was identical. Our study could thus not confirm the MPE of energy drink label on cognitive performance that was reported previously in a very similar experimental design (Schmidt et al., 2017a). However, the previous study did not employ a within-participant design, which might have impeded the cognitive placebo effect due to the repeated and immediately consecutive task conductance. In addition, literature on objectively measured placebo effects is mixed and conflicting about whether and for which aspects of cognition such placebo effects occur robustly (Schmidt et al., 2017a; Schwarz and Büchel, 2015; Turi et al., 2018; Walach et al., 2002; Winkler and Hermann, 2019). Together, this suggests that subjectively reported (marketing) placebo effects are more consistent than objectively measured ones. Still, the neurobiological mechanisms of MPEs on subjective and objective outcomes might be similar.

2.5.2 Effect of Oxytocin on marketing induced placebo responses

We focused on the neuropeptide OXT as potential neurobiological driver of MPEs because a seminal study by Kessner *et al.* found an increased analgesic placebo response after OXT treatment (Kessner et al., 2013).

First, according to our main hypothesis we predicted that intranasally administered OXT increases subjectively experienced placebo responses. Against our main hypothesis, we did not find evidence that OXT administration led to stronger MPEs of food product labels and appearance on subjectively experienced taste pleasantness. We complemented our frequentist analysis with a Bayesian analysis, which also yielded very strong evidence in favor of the null hypothesis. Especially regarding recent skepticism about the robustness and replicability of OXT findings, a Bayesian analysis is essential to allow more solid inferences from null results (Lane et al., 2016; Quintana, 2020; 2018; Walum et al., 2016).

Several studies suggested that OXT decreases (sweet) food and calorie intake and specifically dampens reward-driven food intake in humans and animals (Burmester et al., 2019; Kerem et al., 2020; Lawson, 2017; Lawson et al., 2020; 2015; Ott et al., 2013; Skinner et al., 2019). To rule out that such effects of OXT interfere with taste pleasantness ratings and might bias any effects specific to marketing cues, we confirmed that taste pleasantness ratings of control products did not significantly differ between OXT and sham group.

The absent evidence of an OXT effect on MPEs for experienced taste pleasantness is in line with recent research, which could not replicate the initially observed positive effect of OXT on analgesic placebo responses (Colloca et al., 2016; Kessner et al., 2013; Liu et al., 2020; Skvortsova et al., 2019; 2018). Most importantly, Liu et al. systematically tested male and female participants with different OXT doses (24 IU and 40 IU), paradigms (conditioning and verbal suggestion), responses (placebo and nocebo) and could not confirm any effect of OXT on analgesic placebo/nocebo responses (Liu et al., 2020). Thus, our study adds to this highly compelling lack of evidence for OXT effects on subjectively perceived placebo responses and extends this finding to MPEs on experienced taste pleasantness.

Second, in our exploratory analysis we investigated whether OXT treatment led to a brand label and advertisement effect on cognitive performance after consuming an alleged energy drink. Interestingly, we observed a significant interaction of treatment and drink label in our frequentist analysis, revealing that the label increased performance by 2 % in the OXT group (as compared to 0 % in the sham group). This increase in performance remained however unconscious to the participants as their reported anticipated performance and confidence in performance was unchanged. Note that this exploratory finding needs to be interpreted and discussed with caution because our Bayesian analysis did not confirm the frequentist analysis but instead yielded moderate evidence against a relevant interaction of OXT treatment and drink label. Future studies are clearly required to replicate or reject this finding before drawing any strong conclusions. Nevertheless, an enhancing effect of OXT on cognitive placebo responses is conceivable as recent research showed such an effect for working memory performance (Zhao et al., 2018). Becker *et al.* proposed already possible explanations of why OXT might affect cognitive rather than subjective placebo effects that can greatly be transferred to our observations (Becker et al., 2020). First, OXT might be more efficient in enhancing placebo responses that are mild or even absent without OXT treatment as they are less prone for ceiling effects. This idea clearly pertains to our MPEs on subjectively perceived taste pleasantness that were already strong without OXT treatment while the MPE on objective performance was absent without OXT treatment. Second, OXT might affect placebo responses due to a trustworthy interaction with and social conformity to expert opinion. In our tasting task, participants did not interact with the experimenter and did not receive any verbal advertisement for the products. Instead, we raised expectations only via product labels and product appearance. In the cognitive part, participants received extensive verbal instructions from the experimenter about the benefits of the energy drink for performance in the task and its mechanism of action. Thus, the cognitive part involved considerable social interaction and the experimenter provided an expert opinion. Participants could conform to this opinion by believing in the advertised effect and by being highly motivated or putting more effort in their performance (Schmidt et al., 2017a). Effects of OXT treatment strongly rely on social cues and previous research demonstrated that OXT treatment increases conformity to expert opinion (De Dreu and Kret, 2016; Edelson et al.,

2015; Luo et al., 2017; Stallen et al., 2012; Xu et al., 2019). Therefore, it is conceivable that OXT requires social interactions and some opinion to conform to for causing or boosting placebo responses via dopaminergic and opioidergic reward pathways (Itskovich et al., 2022). Just labels or experimenters, who treat but also cause physical pain, might not be trustworthy and efficient enough for OXT induced conformity. Previously reported effects of intranasally administered OXT were highly context dependent (Bartz et al., 2011). Moreover, a recent pre-print did not find any evidence that OXT administration increases bonding with the physician (Jongerius et al., 2021). Thus, OXT probably does not simply facilitate stronger placebo responses due to an improved patient-physician or consumer-marketer relationship. Instead, it is likely that OXT effects on placebo responses strongly depend on the exact social context and conformity to the instructor/experimenter (Itskovich et al., 2022). To confirm this idea, it would be interesting for future studies on OXT and placebo responses to assess trust in the experimenter or the perception of the experimenter as an expert.

2.5.3 Effect of Oxytocin on trust in marketers and product expectations

Instead of measuring trust in the experimenter, we rather focused on the consumer-marketer relationship. We asked about trust in marketers of expensive and organic products (related to the tasting task), and trust in marketers of brand products (related to the cognitive performance task). Previous research demonstrated that OXT boosted trust in social interactions (Baumgartner et al., 2008; Kosfeld et al., 2005). However, these OXT effects on social trust did not replicate in more recent studies and are thus highly debatable and potentially sensitive to the exact setting and to inter-individual differences in personality traits (Declerck et al., 2020; Nave et al., 2015). Interestingly though, endogenous OXT levels positively correlated with reported relationship-like qualities (i.e., trust, satisfaction, intimacy, self-connection) of brands (Fürst et al., 2015). Moreover, OXT administration increased brand attachment via enhanced perception of brand competences (Barraza et al., 2021). These findings suggest a role of OXT not only in social interactions but also in consumer-marketer relations, even irrespective of whether these relations lead to MPEs.

On this basis, we hypothesized that OXT also strengthens the relationship to marketers that specifically employ premium prices, organic labels, or brand advertisement to signal product quality (Kalita et al., 2004b; Rao and Monroe, 1988).

We did not find any significant effect of OXT treatment on the consumer-marketer relationship in form of consumer's trust in and expectations (quality and taste) of marketers. Our results agree with the null-finings of OXT effects on social trust but contradict the above-mentioned previous studies on brand-relationships. Deviations from these previous studies might be explained by experimental differences. Previous studies asked about a concrete set of brands while we asked more generically about all marketers of expensive, organic, or brand products. The vague mass of all marketers of these products might be too distant and unspecific and thus less sensitive to OXT induced enhancement of trust and attachment. Additionally, generically asking about marketers of expensive, organic, or brand products might cause a lot of inter-individual variability as every participant might think of different products (e.g. food, clothing, cars) and their respective marketers. Different marketers can be perceived differently and have individual levels of trustworthiness (Schivinski and Dabrowski, 2014).

2.5.4 Trust and Expectations as psychological foundations of marketing induced placebo effects

The generic retrieval of trust in marketers might also explain why we did not find any relation between trust in marketers of organic, expensive, or brand products and the MPEs measured in our tasks. Further, there was no link between expectations and the measured MPEs. In other words, participants with higher trust in marketers or higher expectations did not necessarily also show higher MPEs on experienced taste pleasantness and cognitive performance. This is surprising in the light of previous literature. There is ample data hinting at the idea that higher trust in brands leads to more satisfaction with the product and that expectations shape actual sensory experiences (Bloemer and Kasper, 1995; Piqueras-Fiszman and Spence, 2015; Plassmann et al., 2012; Porral and Levy-Mangin, 2016; Shiv et al., 2005b).

Still trust in marketers of certain types of products might be less relevant for MPEs than trust in a specific product. Moreover, marketers are a quite distant and unknown group of people and consumers might be less aware of them during actual consumption. Especially when presented with food products of certain appearance and with labels informing about price, origin, and manufacturing, the marketers behind these products might be subordinate. In such a situation, participants might rely more on previous experiences, knowledge, and own conclusions due to product appearance and label (Kytö et al., 2019).

At this point, we cannot clearly determine whether there is indeed no correlation between trust in marketers or expectations with experimentally elicited MPEs or whether this link was obscured because we did not ask about trust in and expectations of our specific food products.

2.5.5 Limitations

Our study has several limitations. One needs to be cautious when generalizing our findings to the population. Our study only included male participants to not obscure the results by inter-individual differences, which is common practice in OXT research (Declerck et al., 2020). Only testing male participants provides the advantage of excluding an additional source of noise due to potential gender-related differences of OXT effects on behavior or hormonal fluctuations during menstrual cycle in women (Gao et al., 2016; Lieberz et al., 2019; MacDonald, 2013). On the other hand, only focusing on male participants prevents us from making any reliable conclusion about our effects in females. Especially when interpreting placebo effects, one needs to keep in mind that the responsiveness to such effects can depend on gender (Enck and Klosterhalfen, 2019). As previous studies on the impact of OXT for analgesic placebo effects did not find any differences between males and females (Liu et al., 2020; Skvortsova et al., 2019; 2018), we would assume that this is also true for MPEs. Still, this study should be replicated in women to confirm this assumption. Moreover, we used a convenience sample composed primarily of students. Students often have a price-conscious lifestyle and thus might have a different mindset and susceptibility for price and organic cues than the average population.

Further, the transfer of our findings to daily life is also only possible to a limited extend. Tasting and performance task took place in an artificial experimental setting with a very restricted set of products and a much stronger emphasis on labels, advertisement, and product evaluation than it is usually the case when consuming food during daily routine. Since we used deception in our task, we can also not be sure whether participants unconsciously (or without actively reporting it in the manipulation check) were sensitive to our potential manipulation and our focus on marketing cues. Although we took precautions by excluding participants who reported their awareness in the manipulation check, we cannot rule out that vague and unreported suspicions compromised our results (Wager et al., 2004).

Additionally, the choice of our food products might have been suboptimal. The expensive chocolate truffles elicited a strong MPE, but many ratings clustered at the upper end of the Likert scale. Thus, the potential for the administered OXT to increase this MPE was limited due to a ceiling effect. On the other hand, the organic applesauce was not able to cause a significant MPE irrespective of OXT treatment, likely due to the reasons already discussed above. Although, there would have been potential for the OXT treatment to cause an organic MPE, the above discussed issues of the applesauce and organic manipulation might have prevented this.

Another limitation of our study is that we did not confirm whether our OXT administration was successful by determining peripheral OXT levels and that we cannot relate our findings to endogenous OXT levels and their natural fluctuations. However, the usefulness and comparability of measured OXT levels in saliva or blood and their correlation with central OXT levels is debated (MacLean et al., 2019). This is a common limitation of OXT research, which usually relies on previously published data about effective doses, increased endogenous levels and central availability after intranasally administered OXT (Lieberz et al., 2019; Spengler et al., 2017; Striepens et al., 2013).

Lastly, we used the same order of our two tasks, tasting first followed by the cognitive performance part, for every participant. Therefore, we cannot exclude any carry over-effects or a fatigue or motivation derived bias in our results.

2.5.6 Conclusion

In conclusion, our study demonstrated the impact that marketing labels and food product appearance have on the subjectively perceived taste pleasantness. Considering that previous research demonstrated that the choice of food can largely be explained by subjective taste-ratings, this clearly emphasizes the power that marketing has for dietary choices and health (Mela, 2006; 2001a; 2001b).

We were the first to investigate the role of the hormone OXT for these marketing induced placebo effects across domains. This work provides further evidence that OXT is not involved in subjectively perceived placebo effects. We extend previous literature from placebo effects in the medical domain to marketing induced placebo effects in the appetitive domain. Interestingly, exploratory results suggest a potential positive impact of OXT on marketing induced placebo effects on cognitive performance and seems to concur with previous findings on working memory performance (Becker et al., 2020; Zhao et al., 2018). A clear strength of our study is the large sample size and the pre-registration of our analyses (Leng and Ludwig, 2016; Walum et al., 2016). Nevertheless, having in mind that our task on cognitive performance was only an exploratory part of our study, a replication of this finding is clearly necessary. Overall, our findings help disentangling the various behavioral and psychological impacts of OXT on marketing induced food preferences. These impacts of OXT need to be considered in the therapeutical application of OXT for psychiatric disorders or as potential innovative interventions for cognitive deficits (Grinevich and Neumann, 2021; Zhao et al., 2018).

3. Study II: Manipulated by Gut Bacteria? The Impact of a Synbiotic Intervention on Food Choice Behavior and its Neural Correlates.

3.1 Introduction – Dietary preferences and dietary decision-making

3.1.1 Subjective valuation of food options

Remember the street food festival situation from chapter 2.1.1 and your choice between the Mexican burrito and the potato soup. How exactly did you decide that the potato soup is your preferred choice?

Choosing between food options is a value-based decision-making process, as illustrated in chapter 2.1.1 (see Fig. 2). The second step during this process is key to be able to prefer one option over the other. In this second step, the decision maker assigns values to each choice option, which allows to compare options (Rangel et al., 2008; Rangel and Clithero, 2014). Previous research proposed that for dietary decisions, as well as all other decisions, three types of valuation-systems exist and jointly control our decisions by assigning values to possible choices/behaviors (Rangel, 2013; Rangel et al., 2008):

First, the Pavlovian system relies on stimulus-outcome associations and comprises a fixed set of automatic, innate or learned, reactions in response to stimuli for achieving the expected outcome. Upon the presence of the stimulus, the Pavlovian system initiates physiological responses or behaviors. The Pavlovian system mainly controls approach and avoidance behaviors rather than the choice of one option over the other (Daw and O'Doherty, 2013; Rangel et al., 2008). In the vicinity of the street food festival, the strong smell of the fried food automatically activates your salivation (Legoff and Spigelman, 1987). You are probably more likely to approach food with a strong appetizing smell or attractive visual appearance rather than food without smell or visual cues.

Second, the habit system relies on stimulus-response associations. In comparison to the Pavlovian system, the habit system is not restricted to a fixed set of stimuli and responses. The habit system expands and updates its set of responses and their values via trial-and-error based on previous experienced outcomes (Daw and O'Doherty, 2013). Thus, although

flexible regarding possible actions, the habit system lacks the ability to consider eventual and previously unexperienced future effects of the action and is slow in learning (Rangel, 2013; Rangel et al., 2008). If you previously only experienced eating soup indoors and seated at a table, your habit system might associate the relaxed outdoor atmosphere at the food festival rather with the burrito than the soup. However, your habit system is unable to consider the so far unexperienced merits of having a hot soup on a cold day outdoors.

Lastly, the goal-directed system uses response-outcome-reward associations to determine the value of the responses based on the possible outcomes and how rewarding the outcomes will be. Importantly, the reward of the outcome is context- and situation-dependent and differs depending on e.g. satiety level, weather, social situation (Rangel, 2013; Rangel et al., 2008). Any type of tasty food is a less rewarding and thus a less preferred outcome when satiated as compared to when hungry (Rangel, 2013). While the habit system relies on the average reward determined from previous outcomes, the goal-directed system instead determines the rewarding nature of the outcome separately for every decision and context (Rangel and Hare, 2010). Your goal-directed system would consider that it is a cold day and that choosing a hot soup would lead to a warm and pleasant feeling, which is a valuable outcome.

Due to its high flexibility, goal-directed valuation is involved in all dietary decisions (what, where, when, how much to eat) and highly relevant for regulating eating behavior to maintain a healthy body weight (Rangel, 2013).

Goal-directed valuation requires knowledge about the response options, the expected outcomes with their likelihood, and the reward of the outcomes to estimate the value of each possible response (Rangel and Hare, 2010). At the food festival, you need to know that the Burrito is served cold, while the soup is hot and that the hot soup will keep you warm. You also need to know about the ingredients to determine whether you will like the taste or whether it contains allergens whose consumption will affect your future health.

Still, with sufficient knowledge, decisions based on goal-directed valuation outperform decisions that are solely based on previous experiences and learned values (Daw et al., 2005; Rangel and Hare, 2010).

Now, how exactly does the goal-directed system determine the value of a possible response?

The determination of a response or action value requires the separate computation of the stimulus value and the action cost. The stimulus value represents the value or benefit of the outcome while the action cost represents the effort to achieve the outcome. The integration of both forms the value of the action (Rangel and Clithero, 2014; Rangel and Hare, 2010):

$$\boldsymbol{Action\ value = Stimulus\ value - Action\ costs}$$

(Equation 3)

Action values are computed and compared between choice options by constantly accumulating evidence for every choice option until a decision boundary is reached for one of the options (Basten et al., 2010; Hare et al., 2011b; Krajbich et al., 2010a).

In complex decision problems, like in the food festival example, the stimulus or choice option value is based on all expected rewarding outcomes of a food option, like taste pleasantness, healthiness, or warmth of the food. Action costs reflect the effort of the action or choice. For the food festival, action costs could for example encompass the price of the food products and the waiting time due to queueing. In frequently occurring and simpler two-choice decisions, like choosing between an apple and a banana in your fruit basket, action costs are mostly negligible either because the costs are insignificant or very comparable between options. Thus, the stimulus value is assumed to be the main driver of most (dietary) decisions and is most extensively studied (Rangel and Clithero, 2014). For these simpler two-choice decisions, the process of information accumulation and comparison is well reflected by drift-diffusion models (Ratcliff et al., 2016; Ratcliff and McKoon, 2008).

In the laboratory setting, researchers can determine the subjective stimulus values that participants assign to food items in different ways. They either ask participants about their liking of the food items (Maier et al., 2015), assess the amount of money that participants are willing to pay for the items (Plassmann et al., 2007), or record the choice strengths during food choices (Hare et al., 2009). Dietary decisions are multi-attribute choices as they require the consideration and evaluation of several features of the choice options (Rangel et al., 2008). These features comprise the amount of calories (Tang et al., 2014), nutritive content

(Suzuki et al., 2017), aesthetic appeal (van der Laan et al., 2012), and of course the expected or previously experienced taste (Small et al., 2003).

Tang et al. observed for example that implicit knowledge about calory content of food items correlated with the subjective value in form of WTP for the food items (Tang et al., 2014). More specifically, fat, carbohydrate, protein, and vitamin content predicted WTP in a later study (Suzuki et al., 2017).

Most studies that specifically investigate the ability to make healthy dietary decisions distinguish between health and taste attributes and focus their integration into the stimulus value and their relevance for the choice (Hare et al., 2009; Maier et al., 2020; 2015; Sullivan et al., 2015; Sullivan and Huettel, 2021).

Neuroeconomic theory states that the value of the individual choice options results from the integration of information about the separate attributes (i.e. health and taste for dietary decisions) (Fehr and Rangel, 2011; O'Doherty et al., 2021; Rangel and Clithero, 2014):

$$\boldsymbol{SV(X) = \sum w_i * a_i(X)}$$

(Equation 4)

The subjective value of option *X*, *SV(X)*, is the weighted sum of item attributes (i.e. taste and health) with w_i denoting the weight assigned to each attribute (a_i) of option *X*.

The subjective valuation process is highly individual for each decision maker, as it depends on how strongly someone weights taste and health attributes. The stronger the weight on health is compared to taste the more likely it is that an individual makes a healthy choice (Hare et al., 2011a; Pearce et al., 2020). A physiological and psychological factor that affects the weight of or responsiveness to taste attributes is perceived stress. Stressed individuals weight the taste of food items stronger and are more likely to choose a tasty rather than a healthy food (Maier et al., 2015).

For having an impact on food choices, food attributes need to be considered and weighted sufficiently strong, which requires that they are accessible for the valuation process early enough (Fehr and Rangel, 2011). A choice option that is more present to the brain is more likely to be weighted more heavily and considered for the decision. How much a choice option

is visually attended can determine how present it is for the decision process. Thus, theories claim that attention can amplify value (Armel et al., 2008; Krajbich, 2019; Krajbich et al., 2010b; Smith and Krajbich, 2019, but also see Mormann and Russo, 2021 for a critical view). Not only attention towards choice options but also attention towards individual attributes of choice options determines valuation and choice (Yang and Krajbich, 2022). Bringing certain attributes, like healthiness of food items, stronger to attention increases the likelihood of these attributes to be considered, which leads to healthier choices (Enax et al., 2016; Hare et al., 2011a; Rramani et al., 2020b).

The taste of a food choice option is a basic and immediately rewarding attribute. Health instead is more abstract, and its reward is not experienced immediately during consumption but at a distant and unpredictable future time when physically benefitting from a healthy diet. This perceived difference in the distance to the reward is assumed to be the reason why people generally weight the taste of a food option stronger than its health and struggle with maintaining a healthy diet (Liberman and Trope, 2008). More specifically, health attributes were shown to enter the decision process later than taste attributes, which gives them a temporal disadvantage and makes it less likely that the healthier item is preferred over the tastier item (Maier et al., 2020; Sullivan et al., 2015; Sullivan and Huettel, 2021). A study by Lim et al. showed that overweight individuals put a smaller weight on health attributes in their decision process. Moreover, in overweight individuals, health attributes contributed to the decision process significantly later than in normal weight individuals. This difference between overweight and normal weight individuals vanished when labels informed about the calorie content during choice and thus drew attention to the health aspects (Lim et al., 2018).

Rising obesity rates and the fact than many people struggle with making healthy dietary choices clearly indicate the relevance of better understanding factors that affect the weighing of taste and health attributes and their integration into choices.

3.1.2 Brain systems of subjective valuation

Now we know, how subjective valuation of food choice options theoretically works but what do we know about the exact neural computations of subjective values in the brain?

Many human studies used functional magnetic resonance imaging (fMRI) to investigate neural activity in form of the BOLD signal during subjective valuation processes in (dietary) decisions (for the theoretical background on fMRI methodology see chapter 3.2.9). These studies allow to find associations between self-reported value and the level of brain activity in different brain regions. A variety of such studies, with stimuli including food, monetary, or emotional rewards, found that BOLD activity in the vmPFC and medial OFC consistently correlates with behavioral measures of stimulus values (Bartra et al., 2013; Plassmann et al., 2007; Rushworth et al., 2011; Tom et al., 2007; Valentin et al., 2007). BOLD signal in the medial OFC for example reflected the WTP for snack food items (Plassmann et al., 2007) and OFC signal decreased when the subjective value diminished after being fed to satiety with the respective stimulus (Valentin et al., 2007). Apart from vmPFC/OFC also dlPFC, although less consistently, was found to reflect the subjective value of choice options (Hutcherson et al., 2012; Plassmann et al., 2010; 2007). The duration of the BOLD signal in these regions scaled with the available decision time, indicating that longer decision times enable longer value computation and comparison (Sokol-Hessner et al., 2012). In addition to liked, appetitive stimuli, also disliked, aversive stimuli are associated with activity in these brain regions as the BOLD signal negatively correlated with the aversive value (Plassmann et al., 2010). Further causal evidence for the requirement of the vmPFC for the computation of subjective value comes from lesion studies (Bechara et al., 2000; Fellows, 2006). Thus, the OFC encodes a general value signal irrespective of stimulus type and valence to facilitate decisions within and between different rewards (Bartra et al., 2013; Kable and Glimcher, 2009; Levy and Glimcher, 2012).

Studies showed that the brain considers specific nutritional attributes of food options for the computation of the subjective value (Suzuki et al., 2017; Tang et al., 2014). Subjective beliefs about nutritive content did not only predict behaviorally assessed subjective value in form of WTP but were also associated with the BOLD signal in the lateral OFC (Suzuki et al., 2017). Similarly, calorie density of food items correlated with WTP and the neural response in the vmPFC during bidding (Tang et al., 2014).

Thus, not only the overall subjective value of a food item but also its distinct attributes (i.e. taste and health) are reflected in the frontal cortex (Hare et al., 2011a; 2009). The processing

of a food's health in the vmPFC is related to the ability to choose healthier but less tasty food items. Only in participants who were able to frequently decide for healthier but less tasty items in binary choices, not only subjectively reported taste but also health of the choice options correlated with BOLD signal in the vmPFC (Hare et al., 2009). Moreover, successfully choosing the healthier but less tasty item was also associated with activity in the dlPFC and its functional connection with the vmPFC. Therefore, it can be assumed that the dlPFC modulates the integration of health in the overall value formation in the vmPFC (Hare et al., 2009). Christensen et al. observed that dlPFC activity during food choice negatively correlated with body mass index (BMI). In other words, in individuals with higher BMI the dlPFC is less active during food choice, suggesting that an integration of health attributes into choice is less likely (Christensen et al., 2021). On top of that, OFC/vmPFC activity showed an inverse relationship with BMI during healthy food choices, suggesting that healthy choices are valued less with higher BMI (Petit et al., 2016). These and other studies (Berridge et al., 2010; Brooks et al., 2013; Pursey et al., 2014) indicate that the neural circuits for subjective valuation of food differ in obesity, which could be the cause, consequence, or a byproduct of overeating.

Another study found that under acute stress, taste of food was weighted stronger, which resulted in a higher likelihood of unhealthy choices (Maier et al., 2015). These behavioral changes were reflected in an increased correlation between taste value and activity in amygdala and vStr, areas of the limbic system that are relevant for motivational processes (Bartra et al., 2013; Maier et al., 2015). Moreover, perceived stress decreased the negative coupling between vmPFC and dlPFC when choosing healthier over tastier food. This result suggests that stress diminishes the ability of the dlPFC to downregulate the impact of taste attributes and thus leads to a stronger weighing of taste and less healthy choices (Hare et al., 2009; Maier et al., 2015).

As described in the previous chapter, deliberately guiding attention to health aspects of foods, leads to a stronger weighing of health attributes, which makes it more likely to be able to choose healthy (Enax et al., 2016; Hare et al., 2011a; Rramani et al., 2020b). This behavioral observation is also reflected in the neuronal processes of value computation. Salient nutrition information, like traffic light labels, compared to labels of the guideline daily amount without

coloring led to an increased BOLD signal in the dlPFC and a stronger coupling of the dlPFC with the vmPFC (Enax et al., 2016). Focusing attention on health cues caused a stronger representation of healthiness in the vmPFC during choice and a stronger connectivity of vmPFC and dlPFC (Hare et al., 2011a).

The expected subjective value during decision making strongly relies on previous experiences and learning processes that motivate us to approach a reward in goal-directed behavior (see Fig. 2, Rangel et al., 2008). The neurotransmitter dopamine has a key role in these motivational and reinforcement processes not only for drug rewards but also for food rewards. Dopaminergic neurons are located in the ventral tegmental area and substantia nigra and project to the vStr and dorsal striatum, respectively (Volkow et al., 2017). Experiencing a rewarding outcome, especially when better than expected, leads to dopamine signaling, which increases the likelihood of repeatedly choosing this outcome (Rangel, 2013; Schultz, 2013; Small et al., 2003).

The dopaminergic system does not act in isolation but is sensitive to inputs from the homeostatic system and metabolic factors that regulate energy balance (Berthoud, 2011). The impact of the homeostatic system on subjective valuation and food choice will be reviewed in the next chapter.

3.1.3 Homeostatic regulation of subjective valuation

Regardless of whether we choose between primary rewards (e.g. food) or secondary rewards (e.g. money, social benefits), the process of subjectively valuing choice options as described above works in the same way (Bartra et al., 2013; Hare et al., 2010; Levy and Glimcher, 2012). However, dietary decisions differ from other decisions because they should primarily be driven by nutritive needs and therefore rely on the homeostatic system (Rangel, 2013).

Most basically, the homeostatic system aims at balancing calory intake and calory expenditure to maintain a healthy body weight. Therefore, the homeostatic system promotes eating when nutrient-deprived and discourages eating when satiated. This regulation of eating relies on a diverse set of metabolic signals, including gastrointestinal peptide hormones that mainly act on the hypothalamus but also neurotransmitters and

neuromodulators (Plassmann et al., 2021; Plata-Salamán, 1991). During its regulation of eating behavior, the homeostatic system strongly interacts with the value-based system (Berthoud, 2011; Plassmann et al., 2021; Rangel, 2013). As briefly mentioned above, a high-calorie food is more rewarding when hungry than when satiated and thus choosing high-calorie food is valued stronger in the hungry state, which is also reflected in stronger vmPFC / OFC activity (Goldstone et al., 2009; Harding et al., 2018; Rangel, 2013). This effect of the metabolic state on food valuation can arise from the interaction of gastrointestinal hormones with the dopaminergic system in the ventral tegmental area. Dopaminergic neurons express receptors for various gastrointestinal hormones among them also ghrelin and leptin (Figlewicz et al., 2003; Skibicka et al., 2011). Ghrelin and leptin are known as orexigenic/hunger and anorexigenic/satiety hormones, respectively. After a meal, when satiated, leptin levels rise and ghrelin levels fall (Klok et al., 2007). Ghrelin has a stimulating effect on dopaminergic neurons while leptin inhibits them. Therefore, lower ghrelin leads to less stimulation and higher leptin levels to stronger inhibition of dopaminergic neurons after eating. In consequence, dopaminergic neurons are less active and the reinforcing value of food is smaller when satiated (Narayanan et al., 2010; Palmiter, 2007).

A recent study in humans combined fMRI with positron emission tomography (PET) to reveal whether gut-derived signals indeed lead to changes in the dopaminergic system (Thanarajah et al., 2019). Thanarajah et al. observed an immediate dopamine release during consumption that positively correlated with self-reported wanting of the food item and was induced by the perceived taste pleasantness. In addition, delayed dopamine release 15 - 20 min after food consumption in distinct brain regions probably reflected gut-derived signals that modulated the dopaminergic reward system (Thanarajah et al., 2019). The exact mechanism of how and which metabolic signals affect neural reward processing seems to be complex and is not yet fully understood. It seems that overall caloric load, individual macronutrients (e.g. fat and carbohydrates) and their metabolism contribute to the rewarding properties of food products. Interactively with the taste response, the metabolic response constitutes a strong reinforcer that drives food choices (de Araujo et al., 2013; 2008; DiFeliceantonio et al., 2018; Veldhuizen et al., 2017; for reviews see: de Araujo et al., 2020; Hanssen et al., 2022). Although metabolic signals are powerful drivers of future food choices, these gut-derived

reward signals remain unconscious and uncontrollable to our cognitive system. This unconscious impact is hypothesized to favor overeating despite the best intention to lose weight (de Araujo et al., 2020).

3.1.4 Microbiota-Gut-Brain axis & dietary decision making

When talking about gut-derived signals an important and not to be neglected factor is the gut microbiota - the entirety of bacteria and other microorganisms (e.g. viruses and fungi) in the gut. Up to 10^{14} bacteria colonize the human gut and their genome and metabolism have been well characterized with modern sequencing methods (Gill et al., 2006; Thursby and Juge, 2017). The exact composition of the gut microbiota changes during life and depends on many factors, including genetics, gender, age, stress, general health, environment, and most importantly diet (David et al., 2014; Rodríguez et al., 2015). In general, dietary fiber and macronutrient content jointly modulate the gut microbial composition (Ezra-Nevo et al., 2020). However, the exact effect of a type of diet on the gut microbiota is highly personalized. In other words, the same type of diet has a different impact on different people and probably depends on the baseline microbial composition (Johnson et al., 2019). In addition to the diet itself, also dietary supplements (i.e. probiotics, prebiotics, or synbiotics) or antibiotics change the bacterial pattern (Preidis and Versalovic, 2009).

Causal interactions between host physiology and gut microbiota have mainly been studied in animals in very controlled settings by means of germ-free models, bacterial eradication via antibiotics, or fecal transplants. In humans, dietary interventions with probiotics (live bacteria), prebiotics (non-digestible fiber) or a mixture of both (synbiotics) are a great tool to alter gut microbial composition and study its effects on various physiological and behavioral outcomes (Cryan et al., 2019). Such studies revealed a tremendous impact of gut bacterial community on human health by affecting the immune system and conditions like cardiovascular diseases, diabetes, and irritable bowel disease (Shreiner et al., 2015). Differences in gut microbial composition, particularly microbial richness, have also been linked to overweight and metabolic markers of overweight. More specifically, individuals with a lower gut microbial richness have a higher risk for obesity (Le Chatelier et al., 2013; Fan and Pedersen, 2021;

Turnbaugh et al., 2009; 2006). Several meta-analyses showed that pre-, pro-, or synbiotic interventions can improve metabolic markers and body weight in human populations. Their effectiveness, however, varies strongly and might depend on the duration of the intervention, the administered strains, and interindividual differences (Brahe et al., 2016; John et al., 2018; Koutnikova et al., 2019). In addition to its relevance for physiological and metabolic conditions, gut microbial patterns are also related to psychiatric conditions and behavior (Cryan et al., 2019; Dinan and Cryan, 2017). This extensive bi-directional communication between the gut, including the microbiota, and the brain been termed Microbiota-Gut-Brain axis (Rhee et al., 2009).

Gut dysbiosis, an imbalance of the gut microbiota, has been observed in autism spectrum disorder (Fattorusso et al., 2019), depression and anxiety (Simpson et al., 2021). Apart from psychological disorders, several recent studies with humans and animals also investigated the relevance of the gut microbiota for behavior in general. These studies found that the gut microbial composition affects social behavior (Archie and Tung, 2015; Sherwin et al., 2019), emotion processing (Bagga et al., 2019), and stress responses (Wu et al., 2021) and their neural correlates. More specifically, participants, who consumed a probiotic compared to a placebo, showed reduced BOLD signal in brain regions related to emotion processing while watching emotional stimuli (Tillisch et al., 2013). Moreover, Bagga et al. observed improvement in emotional attention and emotional memory that was accompanied by changes in fMRI measures after a probiotic treatment in healthy volunteers (Bagga et al., 2019). Additionally, the gut microbiota is able to interfere with the dopaminergic system and different reward-related behaviors (García-Cabrerizo et al., 2021; González-Arancibia et al., 2019). On this basis, many researchers suggest that the Microbiota-Gut-Brain axis is also involved in food reward processing and the behavioral drivers of obesity (Alcock et al., 2014; Gupta et al., 2020; Novelle, 2021; Plassmann et al., 2021).

A study in *Drosophila melanogaster* showed that when the fruit flies were fed with a diet lacking essential amino acids, they had an increased preference for amino acid rich food. This specific amino acid appetite was however prevented with a microbiota transplant (Leitão-Gonçalves et al., 2017). Similarly, a recent study in mice showed that a hypofunction of the food reward system in obese animals, manifested in altered eating preferences, could be

transferred via gut microbial transplantation to lean mice (de Wouters d'Oplinter et al., 2021). Both studies, in *Drosophila* and mice, nicely demonstrate that the gut microbial composition determines food preferences.

The interaction of the gut bacteria with the host's behavior, including eating behavior, happens via a wide range of mechanisms along the Gut-Brain axis (Cryan and Dinan, 2012; García-Cabrerizo et al., 2021). These mechanisms include the modulation of the immune system (Fung, 2020), synthesis of neurotransmitters (dopamine, serotonin, norepinephrine) or their precursors (phenylalanine, tryptophane, tyrosine) (Strandwitz, 2018), microbial metabolites like short-chain fatty acids (SCFA) (Dalile et al., 2019), and signaling along the vagus nerve (Fülling et al., 2019).

In the context of reward-related behaviors and specifically eating behavior, these mechanisms have been investigated in several animal and human studies:

The vagus nerve is a cranial nerve that connects the brain with the intestinal system and informs the brain about the state of inner organs (Breit et al., 2018). In mice, optical activation of the vagus nerve resulted in dopamine release in the brain and reward related behaviors like conditioned flavor preferences (Han et al., 2018b). In humans, vagus nerve stimulation changed the desire to work for food rewards (Neuser et al., 2020). Thus, it is conceivable that gut microbial signaling via the vagus nerve can also affect food reward processing and thereby eating behavior. A correlational study in humans found an association of the microbial metabolite indole (enzymatically derived from the amino acid tryptophan) with functional and anatomical connectivity in the extended reward network (Osadchiy et al., 2018). More specifically, the higher the fecal indole concentration the stronger the connectivity between the NAcc, a key region of the reward system, and the amygdala and anterior insula (Osadchiy et al., 2018). SCFA are a major product of bacterial fermentation of nondigestible fibers that can exert a wide range of effects on host metabolism (Den Besten et al., 2013). Increasing the level of colonic propionate, one of several different SCFA, led to decreased appeal ratings of high energy food items. Longer rating times further indicated decreased wanting of high energy food. These behavioral observations were accompanied by decreased BOLD signal in the NAcc and caudate (Byrne et al., 2016).

Taken together, few studies point at a potential highly intertwined influence of the gut microbiota on human eating behavior and the development of obesity. Still, direct evidence in humans so far mainly comes from a few correlational studies or studies of individual metabolites. For a more holistic view, future studies should experimentally manipulate gut microbial composition and study its effects on various facets of dietary decision making and its neural correlates.

3.1.5 Aim of this project

In this project, we study the relevance of the gut microbial composition for a healthy eating behavior. Therefore, we aim at experimentally changing the gut microbial composition in healthy male participants by a dietary intervention in form of a synbiotic supplement. We then measure the impact of this intervention on anthropometrics, self-reported eating behavior and dietary decision making. We use a well-established fMRI food choice task (Maier et al., 2015) to study behavioral and neuronal processes during dietary decision making. This task enables to evaluate the overall ability to make healthy choices, the valuation of food options, the relevance of individual taste and health attributes, and their underlying neuronal processes.

This approach allows to gain novel insights into the importance of the gut microbial composition for different aspects of dietary decision making that are all involved in unhealthy eating. These insights will be an important cornerstone for better understanding the complex drivers of obesity and for developing more targeted weight-loss interventions.

3.2 Materials and Methods

3.2.1 Ethical considerations and open science statement

The study was conducted in accordance with the latest revision of the Declaration of Helsinki and approved by the ethics committee of the Medical Faculty of the University of Bonn (Lfd. Nr. 347/18). All participants received at least 215 € for their participation plus an additional

monetary, food, or souvenir bonus. The exact bonus depended on the randomly selected incentivized task and trial, and the participant's decision in this trial.

We pre-registered the study design and analysis plan at OSF (https://osf.io/utsn4, date of pre-registration: November 17, 2019) after we started data collection but before we conducted any pre-registered analyses. Data was only analyzed once the pre-registered sample size was reached. Any deviations from the pre-registered analyses and exploratory analyses that we did not pre-register are indicated as such in the methods section.

Once the project is published, we will make data, analyses scripts, and study material available on OSF.

3.2.2 Participants

We determined our sample size with an a priori power analysis based on the effect size in a previous study, which investigated the impact of a stress intervention on food choices (Maier et al., 2015). Due to the innovativeness of our project, there were no effect sizes available that were more closely related to our dietary intervention. Therefore, we based our power analysis on the study by Maier et al, which found that stress impacted the relevance of taste attributes for food choice with an effect size of Cohen's d = 0.6. Based on this moderate effect size we calculated that we would require 90 participants (45 per group) to yield 80 % power for two-sided between-group comparisons with an error probability of α = 0.05. Thus, we aimed to collect data until we reached our target of 90 usable datasets for our two main tasks, the food choice task, and the intertemporal choice task. In this thesis, we only focus on the food choice task.

We recruited participants between March 2019 and September 2019 via social media channels, flyers, online advertisement in Bonn at the university and university hospital of Bonn, and advertisement on the local newspaper and local radio.

First, participants filled in an online screening questionnaire via Qualtrics (Qualtrics, Provo, Utah, USA). In this questionnaire, we employed the following exclusion criteria: female gender, age below 20 or above 60, smoking, BMI below 18 or above 34 kg/m^2, left-handedness, diabetes or any other metabolic disease, dietary restrictions (i.e. vegetarian,

vegan, halal, kosher, allergies, intolerances), current or past history of psychiatric or neurological disease, excessive alcohol or drug consumption in the past 12 months, vaccination in the past six weeks, or antibiotic treatment in the past four weeks. Additionally, we applied the standard MRI safety criteria and excluded individuals with large tattoos or any tattoos close to the head, non-removable piercings or other metal in the body, claustrophobia, or any previous surgery on the head or heart.

We decided to only test male participants to avoid that gender-related difference in the gut-microbial composition and its sensitivity to our dietary intervention would introduce noise into the data (Haro et al., 2016; Yoon and Kim, 2021). We excluded left-handed participants because of previously observed functional differences between left- and right-handers in fMRI studies (Cuzzocreo et al., 2009). Moreover, vaccination and antibiotic treatment were exclusion criteria because of their known impact on immunological blood markers and gut microbial composition, respectively (Preidis and Versalovic, 2009).

We tried to keep any information about the purpose and hypotheses of our study as minimal as possible during the recruitment process. With this, we wanted to avoid evoking any selection bias for health-concerned individuals and avoid inducing any motivational biases for healthier eating behaviors. Thus, we informed participants that we aimed to investigate the impact of a dietary supplement on decision making. Participants were informed about the ingredients of the placebo (PLC) and verum (VER) supplements. Only with enrollment in the study, participants received more detailed information in the participant information sheet about the tasks and measures of our study.

In total, 117 participants joined our study. The data of 22 participants had to be excluded from the analysis because of the following reasons: intake of antibiotics (8) or gastrointestinal infection (3) during the study time, other gut-microbiota modulating medication for several days in a row (3), technical problems with the MRI scanner (1), incorrect field of view during scanning (1), dropout before post-experimental testing (1), problems with the response grips (3), more than 30 % missed trials (2).

Thus, we included n = 95 datasets (mean age: 31.7 years, *SD*: 10.8 years, n_{PLC} = 46; n_{VER} = 49) in our analyses.

3.2.3 General experimental procedure

In our between-group interventional study, participants attended three study appointments, scheduled between April and November 2019.

First, after passing the online screening, we invited participants in small groups to an information meeting in the Life&Brain research institute at the University of Bonn. During this information meeting, participants received detailed information about the MRI safety criteria and confirmed with their signature that none of these criteria applied to them. Moreover, we provided a detailed overview of the study procedure, and gave verbal and written instructions about how to conduct the 3-day dietary-record and the stool sampling. We scheduled two study sessions for every participant and collected participant's breakfast wishes for the study days.

Next, a few days or weeks after the information meeting, participants attended the pre-intervention session, followed by the seven-week dietary intervention with either placebo or verum, and a post-intervention session. All experimental sessions and the information meeting were conducted by female experimenters.

The experimental procedure of both sessions is depicted in Fig. 9. All questionnaires, tasks, and measurements of the study that are relevant for this thesis are highlighted in blue in the figure and described in detail in the following sections. Details about other parts of the study not included in this thesis can be found in the pre-registration (https://osf.io/utsn4) and results will be reported elsewhere.

Both sessions were nearly identical with only minor differences in a few tasks that are not included in this thesis. Prior to the lab sessions, participants filled in an online questionnaire at home containing the three-factor eating questionnaire (TFEQ, German Version: Fragebogen zum Essverhalten, FEV) (Pudel and Westenhöfer, 1989; Stunkard and Messick, 1985) and further questionnaires on the irritable bowel syndrome (Roalfe et al., 2008), mood (Bourgeois et al., 2010), sleeping, regular exercise, and demographics.

For the pre- and post-intervention sessions, participants arrived at the lab either at 7:00 am, 8:30 am, or 10:00 am. Arrival time was identical for both sessions of each participant. We instructed participants to bring a 3-day dietary record and a stool sample, to maintain their

regular sleeping time, and to be fasted for 12 hours (i.e. no food, medication, or drinks except water).

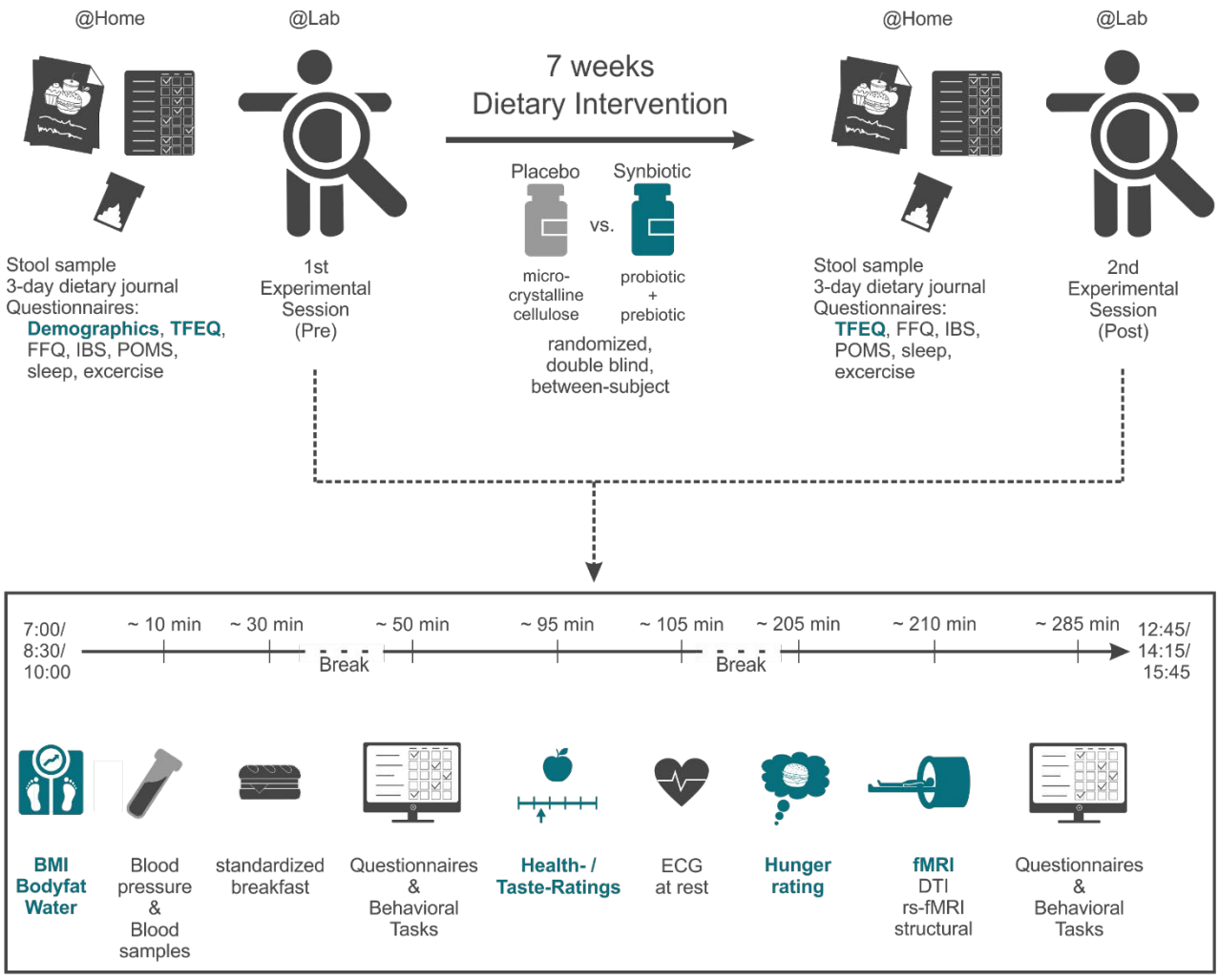

Fig. 9: Experimental procedure of the dietary intervention study. Participants attended two study sessions, one before and one after the 7-week dietary intervention with either a placebo or synbiotic dietary supplement. Additionally, participants filled in questionnaires at home, recorded their eating behavior for three days and collected stool samples. Measures that are relevant in this thesis are highlighted in blue and described in detail in the methods section. BMI, body mass index; DTI, diffusion tensor imaging; ECG, electrocardiogram; FFQ, food frequency questionnaire; fMRI, functional magnetic resonance imaging; IBS, irritable bowel syndrome; POMS, profile of mood states; rs-fMRI resting-state functional magnetic resonance imaging; TFEQ, three-factor eating questionnaire.

Upon arrival, participants filled in questionnaires for checking their sleeping and fasting times, and current positive and negative affect (Watson et al., 1988). Next, we measured participant's body fat content, body weight, BMI, blood pressure, and took fasting blood samples. Blood samples were taken to determine the impact of the dietary intervention on different parameters (e.g. gastrointestinal peptides, inflammatory markers, liver enzymes, blood glucose, insulin, etc.) and the relation of these parameters with behavioral and fMRI measures. However, these analyses are outside the scope of this thesis.

Afterwards, participants had a 20 min breakfast break and received a standardized sandwich (451 - 479 kcal), and either a cup of tea, coffee, or water. Participants had access to water during the whole study, but consumption of food, tea, or coffee was restricted to the breakfast. After the breakfast, participants conducted several behavioral tasks (e.g. assessing risk taking, moral and social decision making, cognitive reflection, etc.) and answered personality questionnaires. For a complete list and details on all tasks and questionnaires, see our pre-registration (https://osf.io/utsn4). Next, participants rated tastiness and healthiness of food items in preparation for the food choice task as described in detail in chapter 3.2.8. After an electrocardiogram at rest for 15 min to measure heart rate variability, participants had a break of around 60 min before the fMRI scanning started. During the break, participants were instructed to not leave the laboratory and not use their phone. Directly before the fMRI scanning, which took place roughly three hours after the last food intake, participants reported their current hunger level. The fMRI scanning lasted around 90 min and included a structural scan, diffusion tensor imaging, resting-state fMRI, an intertemporal choice and a food choice fMRI task. In the post-intervention session, the structural scan and diffusion tensor imaging were replaced by a social WTP fMRI task for food. After the scanning, participants conducted a last task battery. In the pre-intervention session, participants then received the dietary supplement for the upcoming seven weeks together with a detailed written and verbal intake instruction and a calendar to record their regular intake and note down any occurrences (i.e. medication, illness, travel). In the post-intervention session, participants answered a control questionnaire, received a debriefing about the aim of the study and their payment.

The order of tasks and questionnaires was identical for all participants. Both sessions lasted around 5 h 45 min, each.

3.2.4 Stool samples

To investigate changes in gut microbial composition due to the dietary intervention, participants brought stool samples to the pre- and post-intervention sessions. Stool samples were taken with sampling tubes from Sarstedt with screwcaps and sampling spoons. Participants received the sampling material together with verbal and written instructions during the information session. Samples were collected no longer than 24 hours before the experiment and stored at room temperature. At the lab, stool samples were labelled and frozen at - 80 °C until the whole data collection was finished.

Microbial DNA was extracted from the stool samples with the Qiagen QIAamp PowerFecal kit according to the manufacturer's instructions. Afterwards the sequencing of 16s rRNA took place via amplification of the V1V2-region with the Illumina MiSeq-platform for characterizing alpha- and beta-diversity.

The analysis of the stool samples won't be explained in more detail here because in this thesis, we only conducted group comparisons between placebo and verum group. Due to problems with the company, which conducted the DNA analysis and sequencing, the final sequencing data became available too late to be considered in this thesis.

3.2.5 Dietary supplement

We used a randomized, double-blind, placebo-controlled between group design. Participants either received a placebo or a verum dietary supplement. Both supplements were provided in powder form in identical small resealable bottles with 30 g per bottle. The commercially available verum contained a synbiotic, a mixture of 2 x 10^9 probiotic bacteria from five strains (*Bifidobacterium lactis*, *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus salivarius*, *Lactococcus lactis*) together with inulin from the agave as a prebiotic. The placebo contained microcrystalline cellulose.

We handed out four bottles (~ 120 g) to each participant and instructed participants to take 2 g of the powder daily for the seven weeks. Thus, we used a standard dose and intervention duration (John et al., 2018). The powder had to be dissolved in water and consumed at approximately the same time every day. For proper measuring of the exact 2 g, we provided

small measuring spoons together with written and verbal instruction of how much to fill these spoons to yield 2 g. Participants had to bring back the empty bottles and any left-over for the second session. We weighted the returned left-over and participants self-reported how often they forgot to take the supplement. Both measures, weight of left over and self-reports, were used to assess compliance and exclude participants, who took less than 50 % of the intended amount of supplement.

Apart from the dietary supplement, participants were required to not make any major changes to their diet during the seven weeks.

3.2.6 Anthropometric data

We measured anthropometric data, including proportion of body fat, proportion of water, body weight, and BMI with a bioelectrical impedance scale (Tanita® SC-240MA, SkEurope BV, Amsterdam, The Netherlands). Due to technical problems, the proportion of body fat is missing for five participants (remaining n_{PLC} = 44, n_{VER} = 46) and the proportion of water for six participants (remaining n_{PLC} = 43, n_{VER} = 46). The bioelectrical impedance method measures proportion of body fat and water by determining the body's resistance by means of weak electric current flowing through the body (Kushner, 1992).

3.2.7 Questionnaires

Details about all questionnaires used in this study are available in the pre-registration (https://osf.io/utsn4). For this thesis, we used the data from the demographic questionnaire, TFEQ (Pudel and Westenhöfer, 1989; Stunkard and Messick, 1985), hunger ratings before the fMRI scanning, and the control questionnaire at the end of the post-intervention session. Demographics and TFEQ were sampled in the online questionnaire, which participants answered at home.

In the demographic questionnaire, we asked about age, income, education, and current job only before the pre-intervention session. This demographic data was used to characterize the study population and compare the two treatment groups to ensure that our randomization

was successful. Descriptive statistics and results of the group comparisons are summarized in Tab. 4.

The TFEQ was sampled at both time points, pre- and post-intervention. The TFEQ distinguishes three psychological dimensions of eating behavior: i) *Cognitive restraint* as a measure of how much control an individual has over its eating behavior and choice of food. ii) *Disinhibition* is rather the opposite and measures the loss of control and passivity in food choice. iii) *Hunger* describes how easily someone is attracted and influenced by external food cues like advertisement or smell and internal cues like hunger (Löffler et al., 2015).

Participants self-reported their hunger level in each experimental session before the fMRI scanning on a continuous scale ranging from 1 = “not hungry at all” to 7 = “extremely hungry". We sampled hunger levels for three reasons: First, we wanted to compare the two treatment groups at the pre-intervention timepoint to rule out any random differences in hunger levels after a standardized snack and fasting time between the groups. Second, we wanted to analyze whether our synbiotic intervention affects hunger levels in such standardized situation. Third, we used the hunger data as covariate in all our analyses of the food choice data to control for any hunger related effects. Controlling for hunger is relevant because several studies demonstrated that hunger affects various aspects of dietary decision making (Hanssen et al., 2021; Otterbring, 2019; Skrynka and Vincent, 2019).

Lastly, we used control questions that participants answered after the post-intervention session to judge the quality of our data. We asked about participant’s experiences with the dietary supplement and our tasks, and any relevant medical or behavioral occurrences during the intervention time. Based on these questions, we decided whether data sets needed to be excluded from data analysis in accordance with our pre-registered criteria. Moreover, we used the treatment guesses to analyze whether participants became aware of their received treatment (for results see chapter 3.3.1).

3.2.8 Food choice task

We used a food choice task adapted from a previous study (Maier et al., 2015) to investigate dietary decision making. The food choice task is depicted in Fig. 10 and consisted of two

parts: a rating part and a choice part. Both parts of the task were programmed with an in-house software (Scenario Designer).

First, in the ratings, participants rated 52 snack food items for healthiness and tastiness via a 100-point visual analog scale. The scale had the following anchors: 0 = “not tasty at all”/”not healthy at all” and 100 = “extremely tasty”/”extremely healthy”. Participants only saw the anchors but not the individual intermediate points along the scale. Food items were adjusted for equal brightness and size and shown as colored images in the center of a black screen. Food items comprised salty and sweet snacks, fruits, nuts, and cereals (see Fig. 10A). Ratings were self-paced without a time limit. The ratings of taste and health were organized in two separate blocks, each block with the same 52 snack food items but either asking about subjectively perceived taste or health. Order of food items within blocks and order of the two blocks were randomized. Order of the blocks was counterbalanced across treatment groups and kept constant from pre- to post-intervention session within participants.

Individual taste- and health-ratings of each participant were used to construct food pairs for the choice part of the task. The choice task took place in the fMRI and lasted around 21 min. We presented participants with 150 forced choices between two food items and instructed them to choose the item, which they would like to eat in that moment. Moreover, we prompted participants to also consider the healthiness of the food options. This way, we created a challenge in case health and taste were not aligned. Based on the individual taste- and health- ratings, we constructed two types of choice trials: 50 % of the trials were conflict trials and the other 50 % were no-conflict trials. In no-conflict trials, health and taste were aligned such that the healthier item was also tastier. In conflict trials, health and taste were not aligned and the healthier item was less tasty. Choosing healthy in conflict trials requires to forgo the tastier item and is thus challenging. Food combinations were created in such a way that the number of repetitions of each food item was roughly equal for each food item. The position of the individual items on either the left or right side of the screen was randomized.

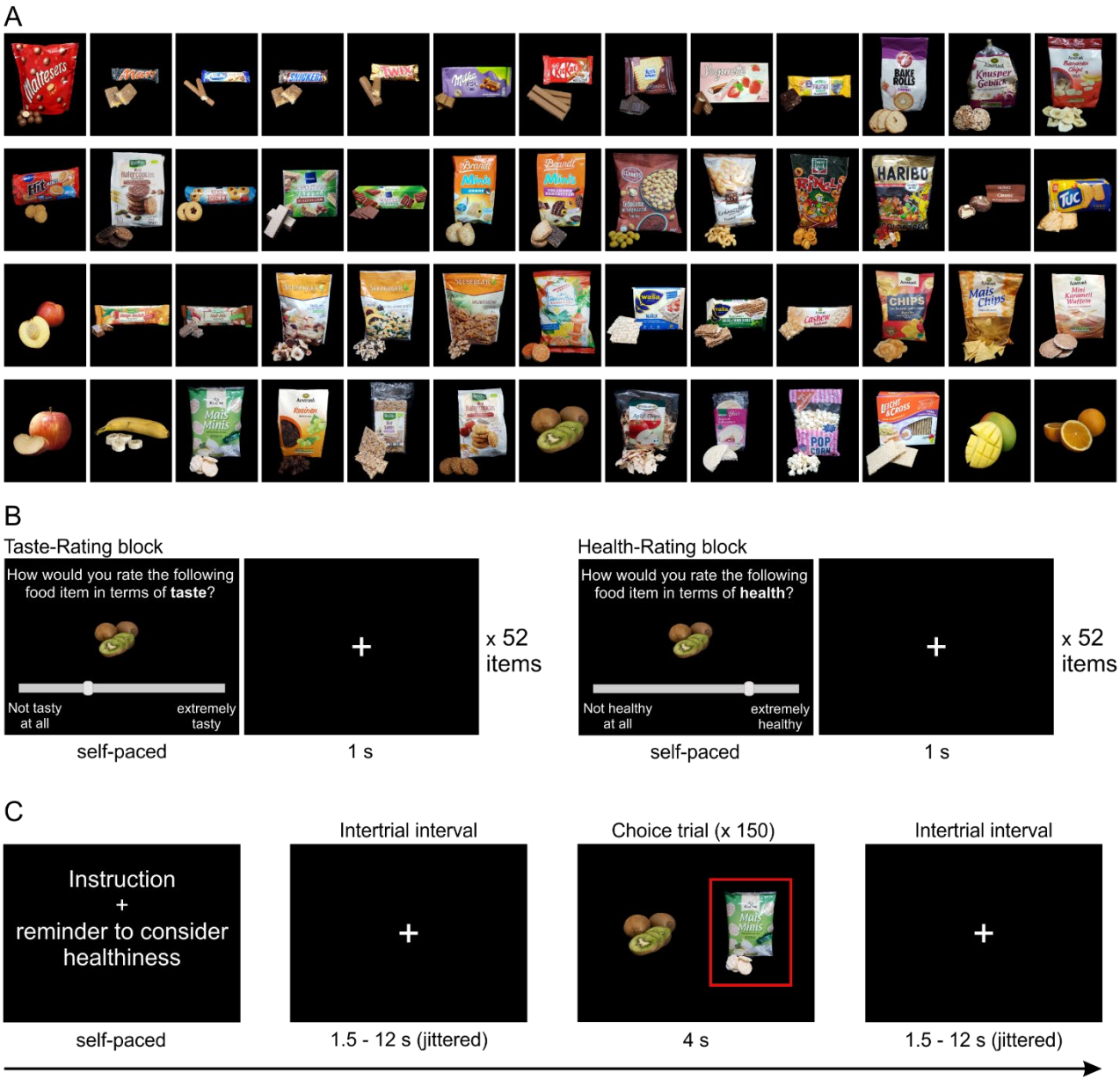

Fig. 10: Task design of the food choice task. (A) Food stimuli for the food choice task consisted of 52 snack food items. (B) In the rating part of the food choice task, participants rated taste and health of all 52 snack food items in two separate blocks with a 100-point visual analog scale in self-paced manner. (C) The food choice task took place in the fMRI scanner. Participants received instructions and a reminder to consider healthiness before the start of the task. 150 choice trials consisted of 50 % conflict and 50 % no-conflict trials (for details see methods section), and participants had 4 s to make their choice via response grips. Their choices were indicated to the participants via a red frame around the chosen item for the remainder of the 4 s. Trials were separated by intertrial intervals with geometrically jittered durations of 1.5 to 12 s.

Participants were told that the food choice task was part of a behavioral task pool from which in the end one task would be randomly chosen and their choice in one of the trials would be implemented. Therefore, each choice should be treated as equally important, and participants should be motivated to choose based on their true preference. Moreover, participants did not eat for three hours prior to the experiment, which should further enhance their eating motivation.

Each choice trial lasted 4 s and participants chose the left or right item via response grips and button presses with their left or right index finger, respectively. After each choice, the chosen item was highlighted by a red frame and the food items, and the red frame remained on the screen until the 4 seconds were over. If participants did not make a choice within 4 seconds, the trial was recorded as *miss* and excluded from analysis. Occurrence of conflict and no-conflict trials was randomized, and trials were separated by intertrial intervals with a geometrically jittered duration of 1.5 to 12 s.

The design of our food choice task allowed to analyze the following behavioral dependent variables: taste- and health-ratings, reaction time during taste- and health-ratings, proportion of healthy food choices, reaction time during food choice, and the relevance of taste and health for food choices.

3.2.9 The principle of functional magnetic resonance imaging

We implemented our food choice task in an fMRI setting to further analyze the neural correlates during dietary decision making. fMRI is a neuroscientific method that uses magnetic fields to visualize brain activity by detecting changes in blood oxygenation related to neural activity (Kwong et al., 1992; Ogawa et al., 1992). Physically, the detection of changes in blood oxygenation relies on the magnetic properties of hemoglobin, the oxygen transporting protein in the red blood cells. While carrying oxygen, and thus being oxygenated, hemoglobin is diamagnetic. After losing oxygen, hemoglobin becomes deoxygenated and paramagnetic. These two magnetic states of hemoglobin affect the magnetic field, which is generated by the MRI machine. These measurable differences in magnetic field homogeneity induced by the blood oxygen level is called BOLD signal (Buxton, 2013). The BOLD signal

serves as indirect marker of neural activity. The time course of the BOLD response is depicted in Fig. 11.

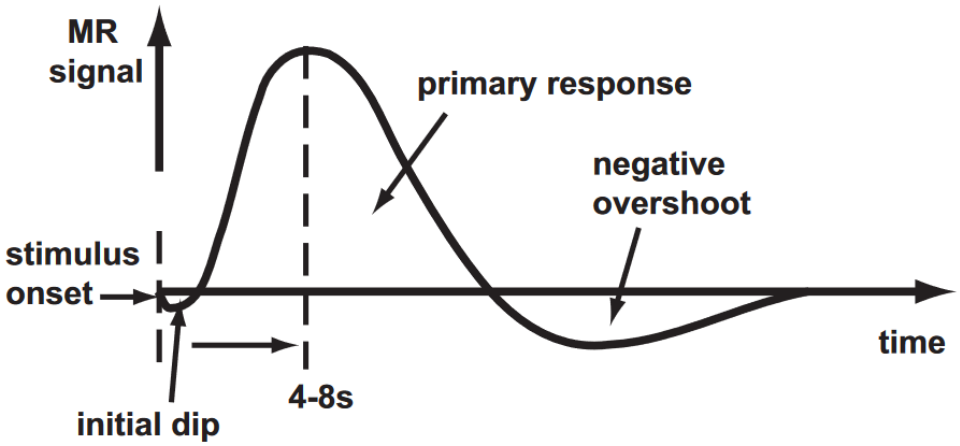

Fig. 11: Schematic representation of the BOLD response. Figure adapted from Kwong et al., 1992, licensed under CC BY-NC 3.0 (https://creativecommons.org/licenses/by-nc/3.0/#).

Increased neural activity leads to an increased energy demand in the active brain regions. Brain cells use glucose as their primary energy source, which is oxidatively metabolized to carbon dioxide. Conclusively, increased neural activity leads to an increase in oxygen demand and thus an increased extraction of oxygen from the blood (Arthurs and Boniface, 2002; Buxton, 2013). The concentration of deoxygenated hemoglobin increases, which leads to an initial dip in the MRI signal (Fig. 11). After a delay of 4 - 8 s, cerebral blood flow increases drastically and delivers more oxygenated blood to the active brain region than is consumed, which is called hemodynamic response. Thus, the ratio of oxygenated to deoxygenated hemoglobin rises and the MRI signal reaches its peak. After this oversupply of oxygenated blood, the hemodynamic response decreases and falls below its baseline level before it returns to baseline (Poser et al., 2011).

To determine brain activity in relation to specific experimental tasks, the BOLD signal is statistically evaluated within three-dimensional voxels (usually with a size of 3 x 3 x 3 mm) in the brain. The software *Statistical Parametric mapping* (SPM) then creates a statistical

parametric map that tests for task-related effects across all voxels of the brain (Friston et al., 1994).

However, noise and artefacts in the fMRI data due to magnetic field inhomogeneities, physiological effects (e.g. heart rate, breathing), or timing of image acquisition lead to variability in the MRI signal that can mask the true task-related BOLD effect. Therefore, proper preprocessing is required to remove unintended variability before the statistical analysis of the fMRI data (Huettel et al., 2014).

Preprocessing

The preprocessing commonly includes motion correction, slice time correction, co-registration, normalization, and temporal and spatial filtering. Preprocessing can be briefly described based on (Huettel et al., 2014) as follows:

The motion correction step improves data quality by correcting for head movements that occur during the scanning process. The individual images of the brain acquired over time are aligned to a reference image such that all brain images and individual voxels of a participant are in the same position. This realignment happens by estimating translational and rotational movement parameters along the *x*, *y*, and *z*-axes.

fMRI data of the brain is acquired sequentially in slice form. However, during data analysis all slices, although not acquired at the same time, are treated as one functional volume. Therefore, slice time correction considers timing differences and aligns all slices to the same reference timepoint via temporal interpolation.

In a co-registration step, the low-resolution functional scan is registered to the high-resolution structural scan of each participant for better localization of brain activity within each participant. Spatial normalization then transforms individual participant's brains into a common stereotaxic space, like from the Montreal Neurological Institute (MNI space). This way, all brains in a sample match in size and shape, and fMRI data can be compared across participants. Lastly, the data is temporally and spatially filtered for artefact removal. Temporal filtering removes low-frequency noise that is caused by physiological processes or the scanner itself. Spatial filtering smoothest the data by averaging the signal of neighboring

voxels, with smoothing diameter and weights defined by the widths of a 3D Gaussian kernel. Spatial filtering increases the signal-to-noise ratio.

Overall, preprocessing is essential to improve data quality for subsequent statistical analyses.

First level analysis

Statistical analysis after the preprocessing can be divided into two steps: First level analysis and second level analysis.

On the first level, a general linear model (GLM) is used for a univariate analysis of the fMRI data of each individual participant. With a GLM, the variation in the BOLD signal time course in each voxel is predicted by a linear combination of several regressors. Regressors represent experimental conditions and are convolved with a hemodynamic response function. Parameter estimates β of each regressor are estimated and define the contribution of the regressor to the BOLD signal time course. Regressors allow to compare BOLD signal time courses between conditions by calculating contrasts. Statistical testing then determines whether β estimates of two regressors differ significantly under the null hypothesis (H_0) of no difference (Huettel et al., 2014; Penny et al., 2007).

Second level analysis

At the second level, a random effects analysis is conducted with the individual contrasts of each participant obtained at the first level. This, way, the second level analysis tests for statistical differences in the contribution of regressors to the BOLD signal time course at a population level.

Different statistical tests allow for example to determine whether the contribution of a regressors differs significantly from zero across all participants (one sample *t*-test) or whether it differs between two groups of participants (two-sample *t*-test). Since test statistics are calculated for each voxel, false-positive rates (Type I error) are highly inflated due to multiple comparisons. Different correction methods are available to control for the false positive rate at a global level across all voxels (Huettel et al., 2014; Penny et al., 2007).

3.2.10 Imaging protocol

Structural and functional MRI data was acquired with a 3T Siemens Trio scanner (Erlangen, Germany) and a 32-channel head coil at the Life&Brain research institute, University Hospital Bonn. All participants received instructions on the task, the appropriate usage of the response grips (Nordic NeuroLab, Bergen, Norway), the use of the emergency ball and were given OHROPAX Classic ear protection (OHROPAX GmbH, Wehrheim, Germany). We used a mirror-system mounted on the head coil and a screen at the back of the scanner for the presentation of the paradigm.

For the functional scans, we obtained T2*-weighted echoplanar images (EPI) with a GRAPPA sequence (TR = 2500 ms, TE = 30 ms, flip angle = 90 °, field of view = 192 x 192 mm, matrix size = 96 x 96). We covered the whole brain with 37 slices in ascending order, a voxel size of 2 x 2 x 3 mm, and an interslice gap of 0.3 mm. We acquired images in an axial direction with an additional 10 ° tilt in relation to the anterior commissure – posterior commissure line for better coverage of prefrontal brain regions. We acquired all volumes within one single run per experimental session.

A structural scan was only collected in the pre-intervention session with a T1 weighted magnetization-prepared rapid acquisition gradient echo (MPRAGE) (TR = 1660 ms, TE = 2.54 ms, TI = 850 ms, flip angle = 9°, field of view = 256 x 256 mm). We acquired 208 slices in a saggital direction with a voxel size of 0.8 x 0.8 x 0.8 mm.

3.2.11 Statistical analyses of behavioral data

General Procedure

We used the R language and environment (version 4.0.3, R Core Team, 2017) and R Studio (version, 1.0.143, RStudio Team, 2016) for all behavioral data analyses. We used the following packages for data cleaning, visualization, and analyses: *arsenal*, *BayesFactor*, *car*, *dplyr*, *ggplot2*, *ggpubr*, *glmmTMB*, *lme4*, *lmerTest*, *pacman*, *patchwork*, *plyr*, *psych*, *readxl*, *Rmisc*, *sjPlot*, *tidyr*.

For statistical analyses, we used linear mixed-effects models for continuous dependent variables (in the same way as already described in detail in chapter 2.2.8 and Equation 1) and logistic mixed-effects models for binary dependent variables.

For the logistic mixed-effects models we used the *glmer* function in R with the bobyqa optimizer and nAGQ set to 10. Similar as for the linear mixed-effects models, all logistic mixed-effects models contain random intercepts for participants: $u_j \sim N(0, \sigma_u^2)$. The error term is assumed to follow a standard logistic distribution: $\varepsilon_{ij} \sim L(0,1)$. Apart from the error term, the structure of the logistic regression equation looks the same as the linear regression equation (Equation 1).

We dummy coded binary IVs (0/1) such that estimates represent simple effects and the intercept represents the reference condition (Schad et al., 2020). Continuous IVs were z-scored across participants and all statistical tests were performed two-tailed with a significance threshold of $\alpha \leq 0.05$. We pre-registered to exclude any behavioral outliers (greater than three standard deviations from the sample mean). However, we had no valid reasons why the observations represented recording errors or spurious behavior, nor did these outliers affect the analysis assumptions. Therefore, we decided to not exclude outliers per se, but to run analyses with and without outliers and report any deviations.

We tested model assumptions and plotted the data in the same way as described in chapter 2.2.8. Additionally, for logistic regression models, we plotted predicted probabilities averaged within quintiles with their 95 % confidence intervals.

First, we compared the placebo and the verum group at the pre-intervention timepoint to rule out any differences between the two groups that would obscure possible intervention effects. We used Kruskal-Wallis tests due to non-normality of the data and compared demographic, anthropometric, and eating behavior variables between the groups. Moreover, we used Chi-squared tests to analyze treatment guesses.

Anthropometrics and self-reported hunger

For the analysis of the anthropometric data, we used two separate linear mixed-effects regression models with BMI and proportion of body fat as dependent variables and the

between-participant variable treatment (PLC = 0, VER = 1), within-participant variable session (pre-intervention = 0, post-intervention = 1), and their two-way interaction as independent variables. We added age (z-scored) as a covariate to the models.

For the analysis of self-reported hunger, we used a similar linear-mixed effects model and regressed hunger ratings (three hours after a standardized snack and immediately before the food choice fMRI task) on treatment (PLC = 0, VER = 1), session (pre-intervention = 0, post-intervention = 1), and their two-way interaction. We added age and proportion of body fat (both z-scored) as covariates to the model.

Self-reported eating behavior

To assess the effect of the synbiotic intervention on self-reported eating behavior, we used three linear mixed-effects regression models and regressed the three dimensions (i.e. cognitive restraint, disinhibition, hunger) separately on treatment (PLC = 0, VER = 1), session (pre-intervention = 0, post-intervention = 1), and their three-way interaction. We added covariates for age and proportion of body fat (both z-scored).

Perception of taste- and health-attributes of food products

Next, we wanted to know whether the synbiotic intervention affected the taste- and health-ratings of snack food items. We regressed mean taste- and health-ratings of each participant in two separate linear mixed-effects regression models on treatment (PLC = 0, VER = 1), session (pre-intervention = 0, post-intervention = 1), their two-way interaction and controlled for age and proportion of body fat (both z-scored). We used the mean taste- and health-ratings of each participant instead of the individual ratings in each trial because assumptions of the model (equal variance and normality of residuals) were not fulfilled with the individual ratings. The overall results of the analyses are the same when using individual ratings or mean ratings.

In an additional control model, we added the Nutri-Score as moderator of the synbiotic intervention effect in a three-way interaction (Nutri-Score x treatment x session).

Ability to make healthy food choices

We quantified the ability to choose healthy by calculating the proportion of healthy choices across all trials (conflict and no-conflict) in our food choice task.

In a first analysis, we tested how the proportion of healthy choices in our task relates to the three psychological dimensions of the self-reported eating behavior in the TFEQ. To avoid that the relation between healthy choice behavior and self-reported eating behavior is contaminated by any repeated exposure or intervention effects, we only used the data from the pre-intervention time point. In a linear model, we regressed the proportion of healthy choice on the three dimensions of the TFEQ and controlled for age and proportion of body fat. All IVs were z-scored in this model.

We further run a bivariate Pearson correlation between the proportion of healthy choices and cognitive restraint paralleling the analysis from Maier and Hare, 2017.

Next, in a linear mixed-effects model, we estimated the effect of the synbiotic intervention, reflected by the interaction of treatment (PLC = 0, VER = 1) and session (pre-intervention = 0, post-intervention = 1), on the proportion of healthy choices while controlling for age, proportion of body fat, hunger, and mean taste- and health-difference (all z-scored). For the mean taste- and health-difference, we subtracted the respective rating of the unhealthier item from the healthier item in every trial and calculated the mean across all trials for each participant. Controlling for the mean taste- and health-differences ensures that inter-individual differences in the proportion of healthy choices cannot be attributed to inter-individual differences in choice difficulty. For example, choosing the healthy food item is more difficult when the choice options differ much in taste as when their taste is nearly identical. Since the choice combinations and the taste- and health-differences depend on the individual ratings, mean choice difficulty might vary across participants.

We repeated the same linear mixed-effects model with the proportion of healthy choices calculated separately for the conflict and no-conflict condition and added conflict-condition (no-conflict = 0, conflict = 1) as moderator in a three-way interaction (treatment x session x conflict-condition). With this analysis, we wanted to rule out that synbiotic intervention effects were specific to one condition only.

The analysis of a potential synbiotic intervention effect on the ability to make healthy choices tested our pre-registered main hypothesis. Therefore, we complemented our frequentist analysis with Bayesian hypothesis testing (for theoretical details about Bayesian hypothesis testing see chapter 2.2.9). We estimated a Bayesian mixed-effects model with the *lmBF* function and its default settings from the *BayesFactor* package (Morey and Rouder, 2018). The Bayesian model paralleled exactly our frequentist analysis with proportion of healthy choices across both conditions regressed on treatment (PLC = 0, VER = 1), session (pre-intervention = 0, post-intervention = 1), their two-way interaction, and all covariates (z-scored). To obtain a Bayes factor for the two-way intervention effect (treatment x session) on proportion of healthy choices, we compared this full model with all predictors to a null model without the two-way interaction. This analysis enabled us to quantify the evidence in favor of an intervention effect on the proportion of healthy choices (BF10).

Responsiveness to taste- and health-attributes

To assess the impact of individual taste- and health-ratings on food choices, we run two logistic mixed-effects models:

First, we used the choice of the left item (binary choice vector, *choice left*: no = 0, yes = 1) across all trials as dependent variable. Second, we used the choice of the healthy item (binary choice vector, *choice healthy*: no = 0, yes = 1) as dependent variable.

In both cases, explanatory variables were treatment (PLC = 0, VER = 1), session (pre-intervention = 0, post-intervention = 1), health-difference, taste-difference, and their two-way and three-way interactions. Health- and taste-differences were z-scored and calculated as left minus right item (for dependent variable = choice of left item) or healthier minus unhealthier item (for dependent variable = choice of healthier item). We added age, proportion of body fat, and hunger (all z-scored) as covariates of no interest to the models.

For extracting participant-specific beta-weights for taste- and health-difference to be used in subsequent analyses, we run the following logistic model separately for each participant:

$$Choice\ left_i = \beta_0 + \beta_1 TasteDifference_i + \beta_2 HealthDifference_i + \varepsilon_i$$

(Equation 5)

The subscript *i* depicts individual observations per participant. Taste- and health-difference were z-scored and calculated as left minus right item.

For calculating participant-specific values of choice options, we run a second logistic model separately for each participant's data and extracted beta-values for TasteRight, TasteLeft HealthRight, HealthLeft:

$$Choice\ left_i = \beta_0 + \beta_1 TasteRight_i + \beta_2 TasteLeft_i + \beta_3 HealthRight_i + \beta_4 HealthLeft_i + \varepsilon_i$$

(Equation 6)

We determined overall decision weights for taste and health for each participant by averaging the absolute right and left beta-weights separately for taste and health.

We computed a value for each food item on participant level by multiplying the taste and health weights with the taste- and health-ratings to yield weighted taste- and health-ratings. The overall value of the choice options is then the addition of the weighted taste- and health-ratings. These values of choice options will be used in later analyses.

Choice time in dietary decisions

With our analysis of the choice times, we first aimed to confirm that choice times reflected choice difficulty. We calculated the value-difference of the two choice options in each trial as a measure of choice difficulty. In a linear mixed-effects model, we used trial-level data and regressed choice time on the value-difference.

Second, we analyzed the impact of the synbiotic intervention on choice time in a linear mixed-effects regression model. We regressed choice time of each trial on health-difference, taste-difference, treatment (PLC = 0, VER = 1), session (pre-intervention = 0, post-intervention = 1), and the two- and three-way-interactions of taste- and health-differences (z-scored) with treatment and session. Health- and taste-difference reflected the difference between the left and the right item (z-scored). Age, proportion of body fat, hunger, and trial number (all z-scored) were included as covariates of no interest.

For control purposes, we repeated the same linear mixed-effects model with choice times and taste- and health-differences averaged across all trials.

Third, we correlated participant specific beta-weights for taste- and health-difference (see Equation 5) with choice times via a Pearson correlation. With this, we wanted to assess whether there is any association between importance of taste and time required to choose a food item.

Rating time of taste- and health-attributes of food products

Due to technical problems, not all rating times were recorded properly (missing observations across all participants: n_{Health} = 802, n_{Taste} = 705). Missing values are spread across participants, but 5 participants miss all their taste- or health-rating times of one experimental session.

To evaluate whether the synbiotic intervention affects taste- and heath rating times, we estimated two linear mixed-effects model with either taste- or health-rating time as dependent variables. We natural log-transformed rating times because the self-paced nature of the ratings led to highly right-skewed data. We used treatment (PLC = 0, VER = 1), session (pre-intervention = 0, post-intervention = 1), and their two-way interaction as explanatory variables and added age and proportion of body fat (z-scored) as covariates of no interest.

Lastly, we used a Pearson correlation to test for an association of mean choice times with median rating times.

3.2.12 Statistical analyses of fMRI data

Matlab R2020b (version 9.9.0.157001, The MathWorks Inc., 2020) and Statistical Parametric Mapping 12 (SPM12, Wellcome Department of Imaging Neuroscience, London, UK) were used for fMRI data analysis. figures for the fMRI results were created with MRICroGL (Rorden and Brett, 2000). Peak coordinates, peak *t*-values, cluster size and cluster *p*-values for the results tables were determined from the statistical parametric maps via the bspmview toolbox (https://www.bobspunt.com/software/bspmview/). Brain regions were labelled with the automatic anatomic labeling (aal) atlas (Rolls et al., 2015; Tzourio-Mazoyer et al., 2002).

Preprocessing

fMRI results included in this thesis come from standardized preprocessing performed using *fMRIPrep* 20.2.1 (Esteban et al., 2018a; 2018b; RRID:SCR_016216), which is based on *Nipype* 1.5.1 (Gorgolewski et al., 2011; 2018; RRID:SCR_002502).

The following description of the preprocessing pipeline is derived from the boilerplate text, which is automatically generated by *fMRIPrep* and intended to be copied into manuscripts unchanged under the CC0 license (https://creativecommons.org/publicdomain/zero/1.0/).

For the anatomical data preprocessing, T1-weighted (T1w) image was corrected for intensity non-uniformity with *N4BiasFieldCorrection* (Tustison et al., 2010), distributed with ANTs 2.3.3 (Avants et al., 2008, RRID:SCR_004757), and used as T1w-reference throughout the workflow. The T1w-reference was then skull-stripped with a *Nipype* implementation of the *antsBrainExtraction.sh* workflow (from ANTs), using OASIS30ANTs as target template. Brain tissue segmentation of CSF, white-matter (WM) and gray-matter (GM) was performed on the brain-extracted T1w using *fast* (FSL 5.0.9, RRID:SCR_002823, Zhang et al., 2001). Volume-based spatial normalization to two standard spaces (MNI152NLin2009cAsym, MNI152NLin6Asym) was performed through nonlinear registration with *antsRegistration* (ANTs 2.3.3), using brain-extracted versions of both T1w reference and the T1w template. The following templates were selected for spatial normalization: *ICBM 152 Nonlinear Asymmetrical template version 2009c* [Fonov et al., 2009, RRID:SCR_008796; TemplateFlow ID: MNI152NLin2009cAsym], *FSL's MNI ICBM 152 non-linear 6th Generation Asymmetric Average Brain Stereotaxic Registration Model* (Evans et al., 2012, RRID:SCR_002823; TemplateFlow ID: MNI152NLin6Asym).

During functional data preprocessing, for each of the 2 BOLD runs found per participant (across all sessions), the following preprocessing was performed. First, a reference volume and its skull-stripped version were generated using a custom methodology of *fMRIPrep*. A B0-nonuniformity map (or *fieldmap*) was estimated based on a phase-difference map calculated with a dual-echo gradient-recall echo sequence, processed with a custom workflow of *SDCFlows* inspired by the epidewarp.fsl script (https://www.nmr.mgh.-

harvard.edu/~greve/fbirn/b0/epidewarp.fsl) and further improvements in HCP Pipelines (Glasser et al., 2013). The *fieldmap* was then co-registered to the target EPI reference run and converted to a displacements field map (amenable to registration tools such as ANTs) with FSL's *fugue* and other *SDCflows* tools. Based on the estimated susceptibility distortion, a corrected EPI reference was calculated for a more accurate co-registration with the anatomical reference. The BOLD reference was then co-registered to the T1w reference using *flirt* (FSL 5.0.9, Jenkinson and Smith, 2001) with the boundary-based registration (Greve and Fischl, 2009) cost-function. Co-registration was configured with nine degrees of freedom to account for distortions remaining in the BOLD reference. Head-motion parameters with respect to the BOLD reference (transformation matrices, and six corresponding rotation and translation parameters) are estimated before any spatiotemporal filtering using *mcflirt* (FSL 5.0.9, Jenkinson et al., 2002). BOLD runs were slice-time corrected using *3dTshift* from AFNI 20160207 (Cox and Hyde, 1997, RRID:SCR_005927). The BOLD time-series (including slice-timing correction when applied) were resampled onto their original, native space by applying a single, composite transform to correct for head-motion and susceptibility distortions. These resampled BOLD time-series will be referred to as *preprocessed BOLD in original space*, or just *preprocessed BOLD*. The BOLD time-series were resampled into standard space, generating a *preprocessed BOLD run in MNI152NLin2009cAsym space*. First, a reference volume and its skull-stripped version were generated using a custom methodology of *fMRIPrep*. Several confounding time-series were calculated based on the *preprocessed BOLD*: framewise displacement (FD), DVARS and three region-wise global signals. FD was computed using two formulations following Power (absolute sum of relative motions, (Power et al., 2014)) and Jenkinson (relative root mean square displacement between affines, (Jenkinson et al., 2002)). FD and DVARS are calculated for each functional run, both using their implementations in *Nipype* (following the definitions by Power et al., 2014). The three global signals are extracted within the CSF, the WM, and the whole-brain masks. Additionally, a set of physiological regressors were extracted to allow for component-based noise correction (*CompCor*, (Behzadi et al., 2007)). Principal components are estimated after high-pass filtering the *preprocessed BOLD* time-series (using a discrete cosine filter with 128s cut-off) for the two *CompCor* variants: temporal (tCompCor) and

anatomical (aCompCor). tCompCor components are then calculated from the top 2% variable voxels within the brain mask. For aCompCor, three probabilistic masks (CSF, WM and combined CSF+WM) are generated in anatomical space. The implementation differs from that of Behzadi et al. in that instead of eroding the masks by 2 pixels on BOLD space, the aCompCor masks subtracted a mask of pixels that likely contain a volume fraction of GM. This mask is obtained by thresholding the corresponding partial volume map at 0.05, and it ensures components are not extracted from voxels containing a minimal fraction of GM. Finally, these masks are resampled into BOLD space and binarized by thresholding at 0.99 (as in the original implementation). Components are also calculated separately within the WM and CSF masks. For each CompCor decomposition, the *k* components with the largest singular values are retained, such that the retained components' time series are sufficient to explain 50 percent of variance across the nuisance mask (CSF, WM, combined, or temporal). The remaining components are dropped from consideration. The head-motion estimates calculated in the correction step were also placed within the corresponding confounds file. The confound time series derived from head motion estimates and global signals were expanded with the inclusion of temporal derivatives and quadratic terms for each (Satterthwaite et al., 2013). Frames that exceeded a threshold of 0.5 mm FD or 1.5 standardized DVARS were annotated as motion outliers. All resamplings can be performed with *a single interpolation step* by composing all the pertinent transformations (i.e. head-motion transform matrices, susceptibility distortion correction when available, and co-registrations to anatomical and output spaces). Gridded (volumetric) resamplings were performed using *antsApplyTransforms* (ANTs), configured with Lanczos interpolation to minimize the smoothing effects of other kernels (Lanczos, 1964). Non-gridded (surface) resamplings were performed using *mri_vol2surf* (FreeSurfer).

After the *fMRIPrep* pipeline, we additionally smoothed the preprocessed data via SPM with a Gaussian kernel with full width at half-maximum (FWHM) of 8 mm.

First Level Analysis

We used a two-stage mass-univariate approach for the fMRI data analysis based on GLMs as implemented in SPM12. On the first level, we modeled participants' individual data with fixed-effects models.

We used three GLMs with the BOLD time series in each voxel as dependent variable and different regressors. Each regressor was modeled by a boxcar function with durations equal to choice time and convolved with a hemodynamic response function (Friston et al. 1994). Moreover, each GLM contained a regressor for missed trials (duration of 4 s) and six movement regressors (3 translation, 3 rotation regressors) as confounds. We added the two pre-intervention and post-intervention sessions as two separate runs into the first-level analysis with separate but identical regressors for both sessions.

GLM1 contained the following regressors twice, once for the pre- and once for the post-intervention session:

1) Choice, 2) Choice parametrically modulated by value of chosen item, 3) Choice parametrically modulated by value-difference of chosen and non-chosen item, 4) missed trials, 5-10) movement regressors.

The parametric modulators value of chosen item and value-difference were obtained from Equation 6 as described in chapter 3.2.11.

We created the following contrast images: i) Choice*Value-chosen$_{pre}$ > baseline (fixation cross) & Choice*Value chosen$_{pre}$ < baseline to assess neural correlates of chosen value pre-intervention and irrespective of the synbiotic intervention for replication of previous findings (Bartra et al., 2013; Hare et al., 2011a; 2009; Maier et al., 2015). To avoid artificial overpowering and a potential intervention-derived bias by including both sessions in this analysis, we only assessed the contrast of the chosen subjective value at the pre-intervention session across both groups. ii) Choice*Value chosen$_{post}$ > Choice*Value-chosen$_{pre}$ to assess changes in the neural correlates of chosen value from pre- to post-intervention.

GLM2 contained the following regressors twice, once for the pre- and once for the post-intervention session:

1) Choice, 2) Choice parametrically modulated by taste of chosen item, 3) Choice parametrically modulated by health of chosen item, 4) Choice parametrically modulated by taste-difference of chosen minus non-chosen item, 5) Choice parametrically modulated by health-difference of chosen minus non-chosen item, 6) missed trials, 7-12) movement regressors.

The parametric modulators taste/health of chosen item and taste-/health-difference of chosen minus non-chosen item were obtained from the individual ratings of each participant.

We created the following contrast images: i) Choice*Taste-chosen$_{pre}$ > baseline (fixation cross) & Choice*Taste-chosen$_{pre}$ < baseline and ii) Choice*Health-chosen$_{pre}$ > baseline & Choice*Health-chosen$_{pre}$ < baseline to assess the neural representation of taste- and health-ratings during food choice irrespective of the synbiotic intervention. To avoid artificial overpowering and a potential intervention-derived bias by including both sessions in this analysis, we only assessed the contrast of the chosen subjective value at the pre-intervention session across both groups. iii) Choice*Taste-chosen$_{post}$ > Choice*Taste-chosen$_{pre}$ and iv) Choice*Health-chosen$_{post}$ > Choice*Health-chosen$_{pre}$ to assess changes in the neural taste- and health-representations from pre- to post-intervention. We decided to focus on the chosen taste and health instead of their differences between the items although this does not exactly parallel the behavioral logistic model (described in chapter 3.2.11). The reason for this decision was that the attribute differences also reflect choice difficulty. By using attribute difference as parametric modulator, we would not be able to clearly distinguish between brain activity linked to choice-difficulty and brain activity that actually arose from the attribute difference.

All parametric modulators of GLM1 and GLM2 were z-scored within participant and not orthogonalized with respect to each other to fully compete for explained variance.

GLM3 contained the following regressors twice, once for the pre- and once for the post-intervention session:

1) Healthy Choice, 2) Unhealthy Choice, 3) Missed trials, 4-9) movement regressors.

We created the following two contrast images: i) $HealthyChoice_{pre}$ > $Unhealthy\ Choice_{pre}$ to assess the neural correlates of healthy choices irrespective of the synbiotic intervention and ii) Healthy Choice > $Unhealthy\ Choice_{pre > post}$ to assess the changes in the neural correlates of healthy choices from pre- to post-intervention.

Second Level Analysis

In the second level analyses, the summary data of each participant was analyzed at the group level with random effects models either via one-sample or two-sample *t*-tests. We conducted one-sample *t*-tests across treatment groups for the analysis of the pre-intervention contrasts from the first-level to confirm previous literature. We conducted two-sample *t*-tests to compare placebo and verum group for the post > pre contrasts as specified on the first level. These two-sample *t*-tests assessed the intervention effect reflected by the interaction of session (post>pre contrast at the first level) and treatment ($PLC_{post>pre}$ </> $VER_{post>pre}$ contrasts at the second level). For the two-sample *t*-tests of GLM2, we changed the default SPM setting “equal variance” to “unequal variance” as recommended by the SPM community. Given the default setting, the F-contrast for non-sphericity estimation did not result in any significant voxels, thus preventing model estimation. When assuming equal variance non-sphericity estimation is not required.

All whole-brain group-level analyses were initially corrected for multiple comparisons via family-wise error (FWE) correction at the cluster level with a cluster-defining uncorrected height threshold of $p<0.001$. Due to the novelty and explorative nature of our analysis of synbiotic intervention effects on brain activity, we also report results at a more liberal threshold ($p_{uncorrected} < 0.001$, $k \geq 20$ or $k \geq 5$) as it is frequently done in fMRI research (Charbonnier et al., 2015; Li et al., 2020). This way, we minimize the risk of false negative findings (type II errors) and increase the chances of exploratory results emerging that could be studied in follow-up projects (Lieberman and Cunningham, 2009).

ROI analyses

In addition to our whole-brain analyses, we conducted ROI analyses for two purposes: First, we wanted to relate BOLD signal during food choice in specific brain regions to

anthropometric data and food choice behavior. Second, we wanted to study potential synbiotic intervention effects in specific anatomically defined brain regions.

For GLM1, we created two ROI masks: To relate proportion of body fat and proportion of healthy choices to BOLD signal in response to chosen food value we created a mask from the overlap of the Bartra vmPFC map (Bartra et al., 2013, Fig. 9) with our significant vmPFC cluster. The vmPFC cluster was obtained from the second level one-sampe *t*-test for the contrast Choice*Value-chosen$_{pre}$ > baseline. From this ROI mask, we extracted average beta values from the Choice*Value-chosen$_{pre}$ > baseline contrast of each participant and correlated them in a Pearson correlation with proportion of body fat and proportion of healthy choices.

To study a synbiotic intervention effect on vmPFC BOLD signal in response to chosen value, we created a similar ROI. For this ROI mask we used an overlap of the Bartra vmPFC map (Bartra et al., 2013, Fig. 9) with the significant vmPFC cluster from the second level one-sample *t*-test for the contrast Choice*Value-chosen$_{pre\&post}$ > baseline. Note, that we used the value-related vmPFC cluster derived from both sessions and groups, as opposed to the cluster of the pre-intervention data only, to have a more independent mask for testing the intervention effect. From this ROI mask, we then extracted average betas from each individual participant's two first-level contrasts for Choice*Value-chosen$_{pre}$ > baseline and Choice*Value-chosen$_{post}$ > baseline. In a linear mixed-effects regression model in RStudio (version, 1.0.143, RStudio Team, 2016b), we then regressed the average extracted beta-values on treatment (PLC = 0, VER = 1), session (pre-intervention = 0, post-intervention = 1) and their two-way interaction. We further added participant-specific random intercepts.

For GLM2, we created two ROI masks: A valuation ROI as a combination of the vmPFC and vStr masks from Fig. 9 in Bartra et al., 2013 and an anatomically defined emotional/salience mask. The emotional/salience ROI mask encompassed the parahippocampus, hippocampus, amygdala, insula and ACC (and was defined via the aal atlas as implemented in the Wake Forest University (wfu) pick atlas (Maldjian et al., 2003). We extracted participants' individual beta-values for taste- and health-related activity at before the synbiotic intervention (first level

contrasts: Choice*Taste/Health-chosen$_{pre}$ > baseline) from both ROI masks. In a Pearson correlation, we correlated proportion of body fat and proportion of healthy choices with these extracted beta-values from both ROI masks.

We further extracted average betas from both ROI masks for each individual participant's four first-level contrasts (Choice*Taste/Health-chosen$_{pre}$ > baseline and Choice*Taste/Health-chosen$_{post}$ > baseline). A potential synbiotic intervention effect on extracted average betas of each ROI mask was tested with two separate linear-mixed effects models for Taste-chosen and Health-chosen as described above for the ROI analysis of GLM1.

3.2.13 Deviations from pre-registration

We did not deviate from our pre-registered study design, but we made adjustments to our pre-registered main behavioral and fMRI analyses of the food choice task, which we outline in the following.

Deviations in the behavioral analyses

First, we decided to add covariates for proportion of body fat, age, and hunger to all models as recommended by Smeets et al. for behavioral and fMRI nutritional studies (Smeets et al., 2019). Covariates for proportion of body fat, age, and hunger control for previously observed impacts of these variables on food wanting and dietary decision making (Hanssen et al., 2021; van Meer et al., 2016; Skrynka and Vincent, 2019).

Second, we pre-registered that we would use a mixed-effects logistic regression with choice of the left item as dependent variable and healthiness and tastiness ratings of left and right items in interaction with treatment and session as independent variables. However, instead of the absolute left and right ratings, we used health- and taste-differences of the two items as independent variables in interaction with treatment and session. Due to the three-way interactions for testing the synbiotic intervention effects, our logistic model was already quite complex. For the ease of better interpretation of the results, we decided to use taste- and health-difference instead of individual attribute ratings. This is a common analysis approach in the food choice literature (Maier et al., 2015; Rramani et al., 2020a).

Third, we pre-registered to run an additional mixed-effects logistic regression with self-control failure (i.e. unhealthy choice in conflict trials) as dependent variable. This analysis approach was based on a similar analysis from Maier et al., 2015. However, we later noticed that for our main hypothesis of the synbiotic intervention leading to more healthy choices, a different analysis approach would be more suitable to test this hypothesis. Therefore, instead of unhealthy choices in conflict-trials, we analyzed healthy choices across all trials as dependent variable.

Fourth, we added a linear mixed-model analysis of the proportion of healthy choices as a straightforward way to test the impact of our synbiotic intervention on the ability to make healthy choices. Moreover, we conducted additional not pre-registered, exploratory analyses for taste- and health-ratings, choice times, and taste- and health-rating times.

Lastly, for the analyses of self-reported hunger and self-reported eating behavior, we did not pre-register a specific analysis approach in advance but also used linear mixed-effects models as we did for our other analyses.

Deviations in the fMRI analyses

We did not conduct the preprocessing of our fMRI data via SPM12 but instead used the *fMRIPrep* pipeline (Esteban et al., 2018a; 2018b). The *fMRIPrep* pipeline is superior and preferred over custom-made scripts in SPM as it is highly standardized and better reproducible.

We need to emphasize that our fMRI analyses differ in many aspects from our pre-registered analysis approach. These deviations resulted from the fact that we could not confirm our hypothesized effect of the synbiotic intervention on healthy choice behavior. Our behavioral analyses suggested that a potential synbiotic intervention effect might be more subtle and diverse than we initially hypothesized. To better reflect our behavioral results on taste responsiveness and explore further neural correlates of dietary decision making, we decided to adopt the pre-registered GLMs in several ways. Therefore, the analyses described in this thesis rather serve an explanatory purpose and are only loosely based on the pre-registration. Deviations to the pre-registered fMRI analyses are summarized briefly in the following:

First, in GLM1, we replaced the planned parametric modulator for the value of the non-chosen item by a parametric modulator for the value-difference between the chosen and the non-chosen item to directly control for the difficulty of the individual decisions.
Second, for GLM2 we used a similar approach as for GLM1 and included parametric modulators for taste and health of the chosen item but replaced the planned parametric modulators for taste and health of the non-chosen item by taste- and health-difference (chosen minus non-chosen). Moreover, we simplified the pre-registered GLM2 and did not include further regressors for healthy and unhealthy choices
Third, in GLM3 we planned to study trials with healthy and unhealthy choices in conflict situations specifically. However, we decided to not specifically focus on conflict situations but study neural correlates of healthy vs. unhealthy choices more broadly across all trials, thus better paralleling our behavioral analyses.
Fourth, in our pre-registration we described to use a second level paired *t*-test for the group-level analysis. A paired *t*-test would, however, not be suitable for our research questions. We were not only interested in changes from pre- to post-intervention within participants. More importantly, we were interested in how differently the placebo and the verum group changed from pre- to post-intervention. Therefore, we created contrasts of pre- and post-intervention measurements within-participants at the first-level and used these for two-sample *t*-tests at the second-level analysis.
Lastly, although not pre-registered, we used several exploratory ROI analyses to study potential synbiotic intervention effects in literature-based brain regions with more power.

3.3 Behavioral Results

3.3.1 Characteristics of study population at the pre-intervention timepoint

We used the data from 95 male participants ($n_{Placebo}$ = 46; n_{Verum} = 49) for our analysis. Mean age of our whole study sample was 31.7 years ($M_{Placebo}$ = 31.14 years, $SD_{Placebo}$ = 10.20 years; M_{Verum} = 32.24 years, SD_{Verum} = 11.42 years). Participants had a BMI between 20.56

kg/m^2 and 33.67 kg/m^2 at the start of the intervention ($M_{Placebo}$ = 25.60 kg/m^2, $SD_{Placebo}$ = 3.11 kg/m^2; M_{Verum} = 25.62 kg/m^2, SD_{Verum} = 2.94 kg/m^2).

Tab. 4: Sociodemographic, anthropometric, and behavioral variables at the pre-intervention timepoint compared between treatment groups via Kruskal-Wallis tests.

Variables	Placebo (*n* = 46)	Verum (*n* = 49)	Total (*n* = 95)	*p*-value
Age [years]	31.15 (10.20)	32.24 (11.42)	31.72 (10.81)	0.811
Income [1]	3.28 (2.50)	4.47 (3.54)	3.86 (3.09)	0.288
n_{Miss}	3	9	12	
Years of Education	14.93 (2.79)	15.78 (2.66)	15.37 (2.74)	0.107
Hunger [2]	3.39 (1.52)	3.35 (1.37)	3.37 (1.43)	0.997
TFEQ - Cognitive Restraint	4.96 (3.39)	5.61 (3.81)	5.29 (3.61)	0.459
TFEQ - Disinhibition	4.85 (2.69)	5.51 (2.73)	5.19 (2.72)	0.339
TFEQ - Hunger	4.59 (3.15)	4.90 (3.10)	4.75 (3.11)	0.552
Body weight [kg]	84.69 (11.66)	83.14 (10.38)	83.89 (10.99)	0.454
BMI [kg/m^2]	25.60 (3.11)	25.62 (2.94)	25.61 (3.01)	0.826
n_{Lean}	22	23	45	
$n_{Overweight}$	18	22	40	
n_{Obese}	6	4	10	
Body fat [%]	19.84 (4.78)	19.27 (5.34)	19.55 (5.05)	0.463
n_{Miss}	2	3	5	
Body water [%]	55.12 (3.10)	55.71 (3.53)	55.43 (3.32)	0.428
n_{Miss}	3	3	6	
Healthy Choices [%]	62.87 (15.19)	63.62 (14.62)	63.26 (14.82)	0.786

Notes: Table depicts means and standard deviation. [1] Yearly household income reported with 12 categories (1: <10.000 €, 2: 10.000 - 19.999 €, 3: 20.000 – 29.999 €, 4: 30.000 – 39.999 €, 5: 40.000 – 49.999 €, 6: 50.000 – 59.999 €, 7: 60.000 – 69.999 €, 8: 70.000 – 79.999 €, 9: 80.000 – 89.999 €, 10: 90.000 – 99.999 €, 11: 100.000 – 149.999 €, 12: >150.000 €). [2] Hunger reported on a continuous scale from 1 = not hungry at all to 7 = extremely hungry. Missing data points for variable income due to voluntary nature of the question; missing data points for proportion of body fat and body water due to technical reasons. TFEQ, Three-Factor-Eating-Questionnaire.

We verified that the placebo and the verum group did not differ by chance before the start of the intervention in any relevant sociodemographic, anthropometric, or behavioral variable. We compared the two treatment groups via Kruskal-Wallis tests and did not find any

significant difference before the start of the intervention (Tab. 4). Thus, the randomization in our double-blind between-group design was successful.

After the intervention, we asked participants to guess which treatment, placebo or verum, they received. With this question we wanted to find out whether participants remained blind to their treatment or whether the verum group felt any difference due to the synbiotic supplement and noticed their treatment. In a Chi-squared test, we did not find a significant difference in the treatment guess from the placebo and the verum group ($\chi^2_{(1)} = 1.48$, $p = 0.225$). Treatment guesses in both groups differed significantly from chance level. Most participants of both groups guessed that they have been in the placebo group (67.3 % wrong placebo guesses in verum group: $\chi^2_{(1)} = 5.90$, $p = 0.015$; 80.0 % correct placebo guesses in placebo group: $\chi^2_{(1)} = 17.04$, $p < 0.001$). Thus, participants did not notice whether they received placebo or verum but predominantly guessed that they received the placebo. Participants probably expected to feel a difference when receiving a synbiotic supplement and thus assumed to be in the placebo group more often.

3.3.2 Anthropometrics and self-reported hunger

To assess whether our seven-week synbiotic intervention had an effect on metabolism and health, we analyzed BMI and proportion of body fat as indices of obesity and metabolic health (Müller et al., 2012). We further analyzed self-reported hunger as indicator of homeostatic and hedonic eating motive (Lowe and Butryn, 2007). After their overnight fast, all participants received a standardized sandwich for breakfast and reported their hunger level around three hours after the breakfast. Note that due to technical reasons, proportion of body fat is missing for five participants, two in the placebo group and three in the verum group. In linear mixed-effects regressions we found that irrespective of the synbiotic intervention, BMI ($\beta = 0.035$, $SE = 0.077$, 95 % CI [-0.12 – 0.18], $t_{(93)} = 0.45$, $p = 0.651$) and proportion of body fat ($\beta = -0.514$, $SE = 0.269$, 95 % CI [-1.04 – 0.01], $t_{(88)} = -1.91$, $p = 0.059$) remained significantly stable from pre- to post-intervention in the placebo group (for model details and results see Tab. A 14). The verum group did not change differently than the placebo group in BMI (interaction treatment x session: $\beta = -0.091$, $SE = 0.107$, 95 % CI [-0.30 – 0.12], $t_{(93)} = 0.85$,

p = 0.397) and proportion of body fat (interaction treatment x session: β = -0.055, SE = 0.376, 95 % CI [-0.79 – 0.68], $t_{(88)}$ = -0.15, p = 0.883). Age significantly predicted BMI (β = 0.645, SE = 0.300, 95 % CI [0.06 – 1.23], $t_{(98)}$ = 2.15, p = 0.034) and proportion of body fat (β = 2.088, SE = 0.480, 95 % CI [1.15 – 3.03], $t_{(93)}$ = 4.35, p < 0.001) such that with higher age both, BMI and proportion of body fat, were significantly higher.

Due to the very similar results for BMI and proportion of body fat and based on the widely discussed limitations of BMI to properly reflect metabolic health and obesity, we decided to use proportion of body fat instead of BMI as proxy of metabolic health in all following analyses (Flegal et al., 2009; Nuttall, 2015; Segal et al., 1987; Strain and Zumoff, 1992; Wellens, 1996).

To test for changes in self-reported hunger we used a similar linear mixed-effects regression model as for BMI (Tab. A 15). Participants reported to be significantly less hungry in the post-intervention measurement than in the pre-intervention measurement (β = -0.413, SE = 0.201, 95 % CI [-0.81 – -0.02], $t_{(92)}$ = 2.05, p = 0.043). Proportion of body fat was not related to reported hunger (β = -0.160, SE = 0.124, 95 % CI [-0.40 – 0.08], $t_{(111)}$ = -1.29, p = 0.198) but age significantly predicted reported hunger such that with increasing age, reported hunger decreased significantly (β = -0.279, SE = 0.128, 95 % CI [-0.53 – -0.03], $t_{(95)}$ = -2.18, p = 0.031). The synbiotic intervention did not show a significant effect on reported hunger levels (interaction treatment x session: β = 0.405, SE = 0.281, 95 % CI [-0.15 – 0.96], $t_{(92)}$ = 1.44, p = 0.153). Hence, hunger levels of placebo and verum group did not change differently from pre- to post-intervention.

3.3.3 Self-reported eating behavior

Although anthropometric measurements and momentary self-reported hunger remained unaffected from the synbiotic intervention, we might still observe changes in behavioral or psychological aspects of eating behavior.

To assess psychological aspects of eating behavior, we used the TFEQ with its three psychological dimensions of eating behavior (i.e. cognitive restraint, disinhibition, hunger).

Age showed a significant, negative correlation with all three domains (all p-values < 0.034) while proportion of body fat only positively correlated with the disinhibition score (β = 1.137,

SE = 0.241, 95 % CI [0.67 – 1.61], $t_{(125)}$ = 4.72, $p < 0.001$). The synbiotic intervention did neither affect cognitive restraint (β = 0.065, *SE* = 0.462, 95 % CI [-0.84 – 0.97], $t_{(88)}$ = 0.14, p = 0.889), disinhibition (β = 0.104, *SE* = 0.404, 95 % CI [-0.69 – 0.89], $t_{(87)}$ = 0.26, p = 0.798), nor hunger (β = -0.894, *SE* = 0.476, 95 % CI [-1.83 – 0.04], $t_{(89)}$ = -1.88, p = 0.063) (see Tab. A 16).

3.3.4 Perception of taste- and health-attributes of food products

The perceived and expected health and taste of food items are major underlying drivers of food choice and eating habits (Rangel, 2013; Sullivan et al., 2015). Changes in food perception due to altered taste sensation or altered processing of food rewards seem to be related to gastrointestinal signals. Bariatric surgery is a weight loss intervention that alters the gastrointestinal tract. In obese participants bariatric surgery led to changes in the gustatory system and the brain's reward circuitry and also affected eating behavior and perception of food healthiness (Behary and Miras, 2015; Cornil et al., 2022; Ochner et al., 2011; Schmidt et al., 2021). These changes might be mediated by bariatric surgery induced effects on body weight, gut microbiota, and metabolic markers (Behary and Miras, 2015; Schmidt et al., 2021). On this basis, we analyzed mean taste- and health-ratings in linear mixed-effects regression models to elucidate whether the synbiotic intervention affected how participants perceived snack food items.

We did not find any significant effect of the synbiotic intervention, neither on taste- (interaction treatment x session: β = 0.446, *SE* = 1.857, 95 % CI [-3.19 – 4.09], $t_{(89)}$ = 0.24, p = 0.811, see Fig. 12A and Tab. A 17), nor on health-ratings (interaction treatment x session: β = 1.052, *SE* = 1.324, 95 % CI [-1.54 – 3.65], $t_{(89)}$ = 0.79, p = 0.429, see Fig. 12B and Tab. A 17). Age and proportion of body fat were also not significantly related to mean taste- and health-ratings (all p-values > 0.241).

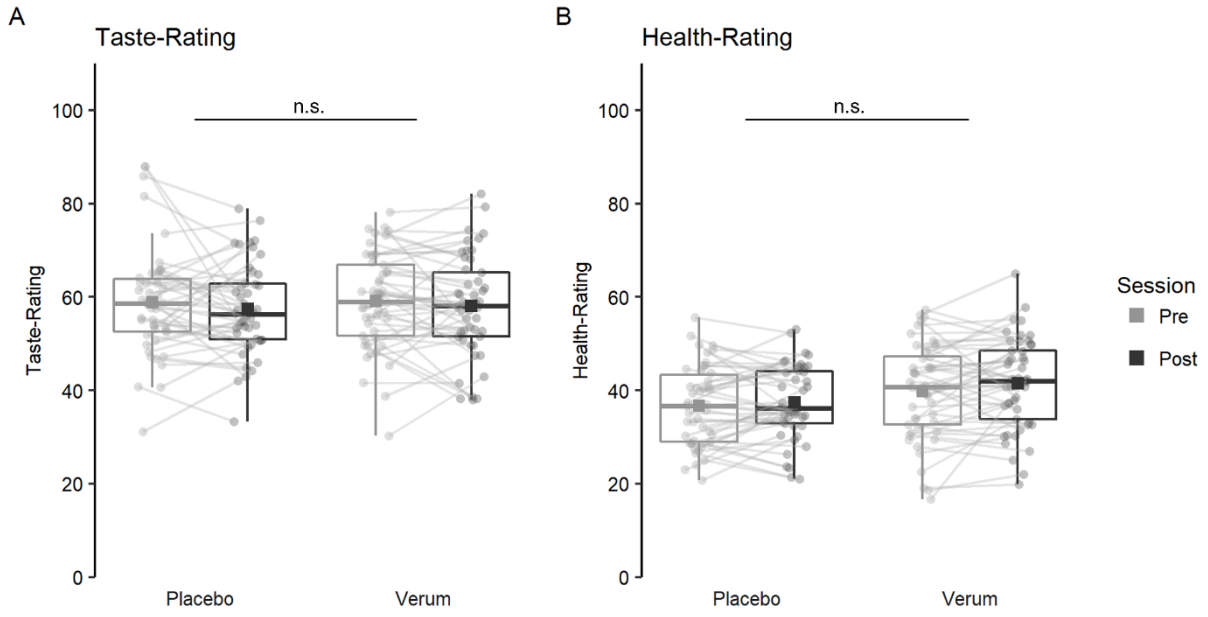

Fig. 12: The synbiotic intervention did not affect taste- and health-ratings of snack food items. Participants rated taste (A) and health (B) of all 52 food items on a 100-point visual analog scale. The order of the taste- and health-rating blocks were randomized and counterbalanced across participants and kept constant across the two sessions of each participant. Mean taste- and health-ratings were calculated for each session of every participant across all 52 food items. The interaction of treatment and session as measure of a synbiotic intervention effect was statistically tested in a linear mixed-effects regression model with the individual ratings of each item as dependent variable. The vertical lines of the boxplots depict the median and the squares show the mean. The individual data points of each participant are shown in in light grey and are connected via lines for the two sessions. n.s., not significant, $p > 0.05$.

In an additional control model, we added the Nutri-Score as moderator of the synbiotic intervention effect. With this control analyses we ruled out that an effect of the synbiotic intervention on food perception depends on the healthiness of the food. In other words, we wanted to make sure that the synbiotic intervention does for example not lead to increased tastiness perception of healthy products specifically. The Nutri-Score did not moderate the synbiotic intervention effect neither on taste- nor on health-ratings (both *p*-values > 0.161, see Tab. A 18).

The relevance of stable taste- and health-ratings is two-fold: First, this null-result suggests that the synbiotic intervention did not modulate the perception of healthiness and tastiness of food items. Second, the null-result rules out that any possibly observed intervention effect on food choice behavior in the following analyses is caused by changes in food perception.

3.3.5 Ability to make healthy food choices

The ability to make healthy food choices is a prerequisite for a metabolically healthy body weight but a huge struggle for most of the population. Preferring calorie-dense and unhealthy food over healthier alternatives is a major driver of obesity (Crino et al., 2015). Therefore, we quantified the ability to make healthy food choices and tested whether the ability to choose healthy is affected by our synbiotic intervention. In our main hypothesis, we suggested that the synbiotic intervention increases the proportion of healthy food choices.

In our incentive-compatible fMRI food choice task, we presented participants with 150 binary food choices and instructed them to consider the food's healthiness in their choice.

The previously provided individual taste- and health-ratings of each food item allowed us to determine whether participants chose the healthier or the unhealthier item on individual trial-level.

First, we tested whether the proportion of healthy choices in our food choice task was related to the self-reported eating behavior from the TFEQ. With this, we wanted to make sure that healthy-choice behavior in our experimental setting reflects psychological aspects of real-life food choices. Of the three dimensions in the TFEQ only cognitive restraint significantly positively correlated with the proportion of healthy choices (β = 4.956, SE = 1.579, 95 % CI [1.82 – 8.10], $t_{(84)}$ = 3.14, p = 0.002, see Tab. A 19). An increase of one standard deviation in self-reported cognitive restraint was associated with roughly 5 % more healthy choices in the food choice task. A bivariate Pearson correlation analysis of the proportion of healthy choices with cognitive restraint ($r(93)$ = 0.296, p = 0.0035, Fig. 13 B) confirmed the result of the linear model and yielded a similar correlation strength as a previous study (Maier and Hare, 2017). This result emphasizes that our food choice task is indeed able to capture aspects of cognitive control in daily food intake.

Next, we analyzed in a linear mixed-effects model, whether the synbiotic intervention affected the proportion of healthy choices.

The model results indicate that the proportion of healthy choices decreased significantly by 3.6 % from pre- to post-intervention (pre: M = 62.87 %, SD = 15.19 %; post: M = 59.29 %, SD = 12.52 %) in the placebo group (β = -3.755, SE = 1.793, 95 % CI -7.27 – -0.24], $t_{(89)}$ = -2.09, p = 0.039). However, the change in the verum group (decrease by 2.8 %, pre: M = 63.62 %, SD = 14.62 %; post: M = 60.84 %, SD = 13.63 %) was not significantly different from the placebo group (reflected by the non-significant interaction treatment x session: β = 1.514, SE = 2.492, 95 % CI [-3.37 – 6.40], $t_{(88)}$ = 0.61, p = 0.545, Fig. 13A, Tab. A 20).

This result does not confirm our main hypothesis, which suggested a positive effect of the synbiotic intervention on the proportion of healthy choices. Thus, we additionally conducted a Bayesian analysis to confirm the result and to further quantify the evidence in favor of the null effect. The Bayes factor BF_{10} of 0.274 indicated that a null-effect of the synbiotic intervention is 3.6 times more likely than an alternative effect and thus supports the null-hypothesis with substantial evidence (Wetzels and Wagenmakers, 2012).

Our food choice task consisted of conflict and no-conflict trials: In half of the trials the healthier item was also tastier than the alternative item (no-conflict). In the other half of the trials the healthier item was less tasty (conflict) and thus choosing healthy was more challenging. To make sure that a potential effect of the synbiotic intervention does not depend on the type of conflict condition, we conducted an additional linear mixed-effects model and included the type of conflict condition as moderator. The conflict condition did not moderate the synbiotic intervention effect as indicated by the non-significant three-way interaction treatment x session x conflict condition (β = -4.360, SE = 5.477, 95 % CI [-15.09 – 6.38], $t_{(263)}$ = -0.80, p = 0.427, see Tab. A 21).

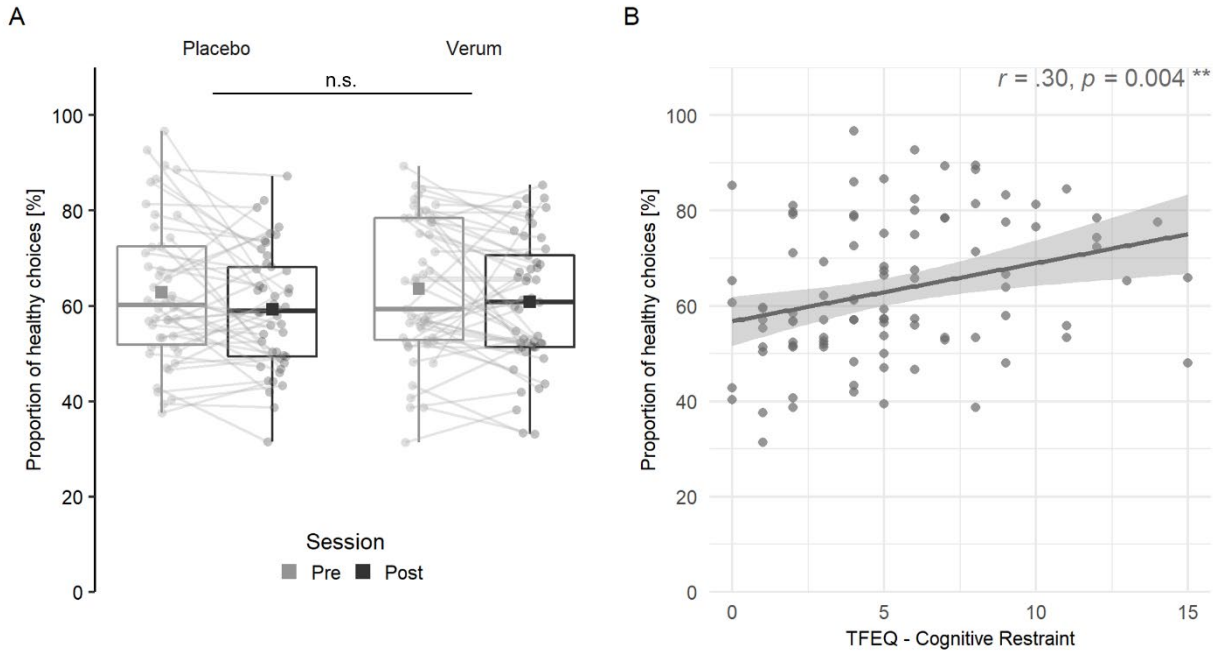

Fig. 13: The proportion of healthy choices is not affected by the synbiotic intervention (A) but correlates with self-reported cognitive restraint in eating behavior before the intervention (B). The proportion of healthy choices was calculated for each participant across all trials (including conflict- and no-conflict condition). (A) The interaction of treatment and session as measure of a synbiotic intervention effect was statistically tested in a linear mixed regression model. The vertical lines of the boxplots depict the median and the squares show the mean. The individual data points of each participant are shown in light grey and are connected via lines for the two sessions. (B) The correlation between self-reported cognitive restraint in the TFEQ and the proportion of healthy choices at the pre-intervention timepoint was tested in a Pearson correlation. The shaded grey area reflects the 95 % confidence interval. ** $p < 0.01$, n.s., not significant, $p > 0.05$. TFEQ, Three-Factor Eating Questionnaire.

3.3.6 Responsiveness to taste- and health-attributes across all food choices

In a next step, we took a closer look at the underlying drivers of food choices and analyzed the relevance of the taste and health attributes for the choices in our task. We wanted to know whether the synbiotic intervention affected the responsiveness to any of the two attributes. Therefore, we used a logistic-mixed effects model with choice of the left item as dependent variable and taste- and health-differences in interaction with treatment and session as explanatory variables (see Tab. A 22).

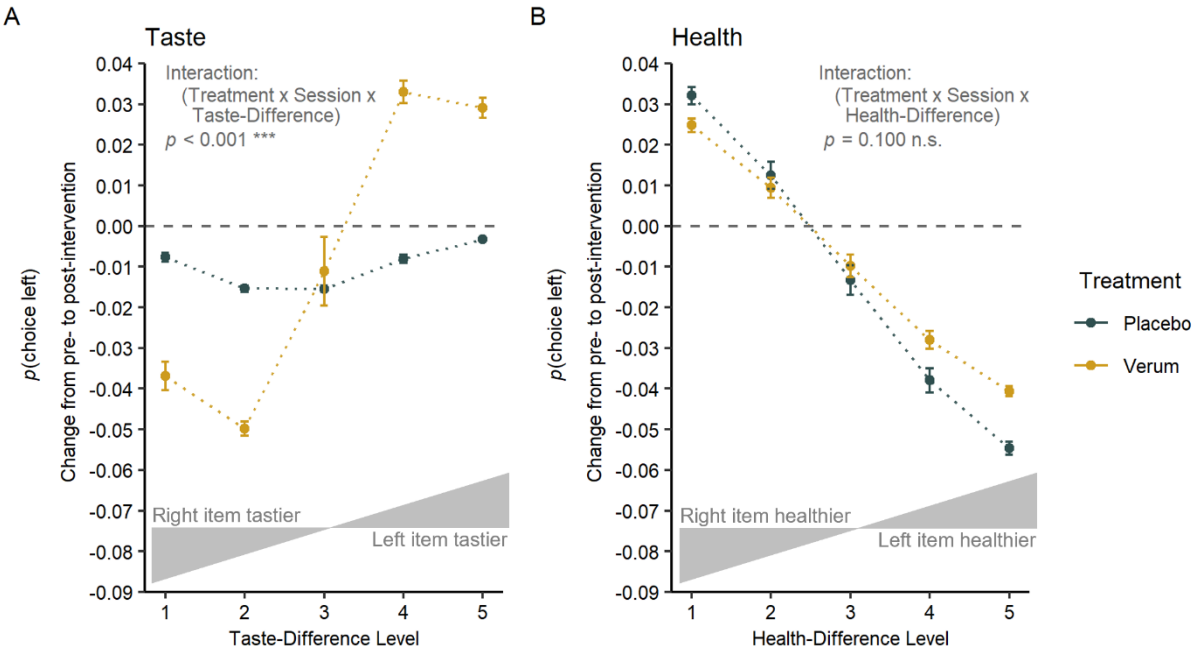

Fig. 14: The synbiotic intervention increases the importance of taste- but not health-difference in food choices across all trials (conflict & no-conflict). The error bar plots depict the change from pre- to post-intervention in the probability of choosing the left item depending on the taste-difference (A) and health-difference (B) (left-right, z-scored) of the choice options. This change is shown separately for the placebo and the verum group. The synbiotic intervention enhanced the impact of taste-difference on food choice. The impact of health-difference on choice decreased similarly strong for both groups from pre- to post-intervention. Probabilities were predicted with logistic regression models based on 100 equidistant taste-/health-differences across the full range of differences. For easier visualization, these 100 taste-/health-differences were divided into quintiles and mean values and 95 % confidence intervals are plotted for each quintile. The dashed lines between the mean values were added for enhancing visualization but do not reflect the actual underlying data between the quintiles. The horizontal dashed line at y = 0 indicates no change from pre- to post-intervention. Note, that some of the confidence intervals are too small to be visible. The interaction of treatment x session x taste-/health-difference reflects the effect that the synbiotic intervention has on the integration of taste/health for food choices. This interaction was statistically tested in a mixed logistic regression model (see Tab. A 22). n.s., not significant, $p > 0.05$; ***, $p < 0.001$.

First, we found that irrespective of our intervention both, taste ($\beta = 1.345$, $SE = 0.039$, $OR = 3.84$, 95 % CI [3.56 – 4.14], $z = 34.68$, $p < 0.001$) and health ($\beta = 0.820$, $SE = 0.035$, $OR = 2.27$, 95 % CI [2.12 – 2.43], $z = 23.27$, $p < 0.001$), significantly explained the variation in choices. In other words, with increasing healthiness and increasing tastiness of one item

in comparison to the alternative, the probability of that item to be chosen increased. Still, as indicated by the larger odds ratio, taste-difference had a stronger relevance for choices than health-difference. Overall, this result confirms that participants made reasonable choices by deciding based on their taste- and health-ratings. Thus, participants followed their own taste preferences but also considered our instruction to choose healthy.

Next, we did not find an effect of the synbiotic intervention on the responsiveness to health-differences (β = 0.111, *SE* = 0.068, *OR* = 1.12, 95 % CI [0.98 – 1.28], z = 1.64, p = 0.100) of food choice options (Tab. A 22, Fig. 13B). However, the synbiotic intervention affected the responsiveness to taste-differences (β = 0.289, *SE* = 0.079, *OR* = 1.34, 95 % CI [1.14 – 1.56], z = 3.68, p < 0.001) during choice such that the responsiveness increased stronger for the verum group than for the placebo group (Tab. A 22, Fig. 14A).

3.3.7 Responsiveness to taste- and health-attributes for healthy food choices

Based on the finding that the synbiotic intervention across all choices increased responsiveness to taste-differences between choice options, we wanted to know how healthy choices were affected specifically. Therefore, we repeated the mixed-effects logistic model, but this time used choice of the healthier item (binary choice vector, *choice healthier*: no = 0, yes = 1), instead of choice of the left item, as dependent variable (see Tab. A 23). Health- and taste-differences were accordingly calculated as the respective rating of the healthier minus the respective rating of the unhealthier item. Similar as for all choices, also healthy choices were significantly predicted by both, taste- (β = 1.516, *SE* = 0.042, *OR* = 4.55, 95 % CI [4.19 – 4.95], z = 35.79, p < 0.001) and health-differences (β = 0.356, *SE* = 0.035, *OR* = 1.43, 95 % CI [1.33 – 1.53], z = 10.18, p < 0.001). Moreover, the observed effect of the synbiotic intervention on the responsiveness to taste-difference but not health-difference across all choices holds true when specifically focusing on healthy choices (taste-difference: β = 0.303, *SE* = 0.083, *OR* = 1.35, 95 % CI [1.15 – 1.59], z = 3.65, p < 0.001, health-difference: β = 0.050, *SE* = 0.067, *OR* = 1.05, 95 % CI [0.92 – 1.20], z = 0.74, p = 0.460, Fig. 15). Thus, the synbiotic intervention increases the impact of tempting taste attributes on food choices also specifically for healthy choices.

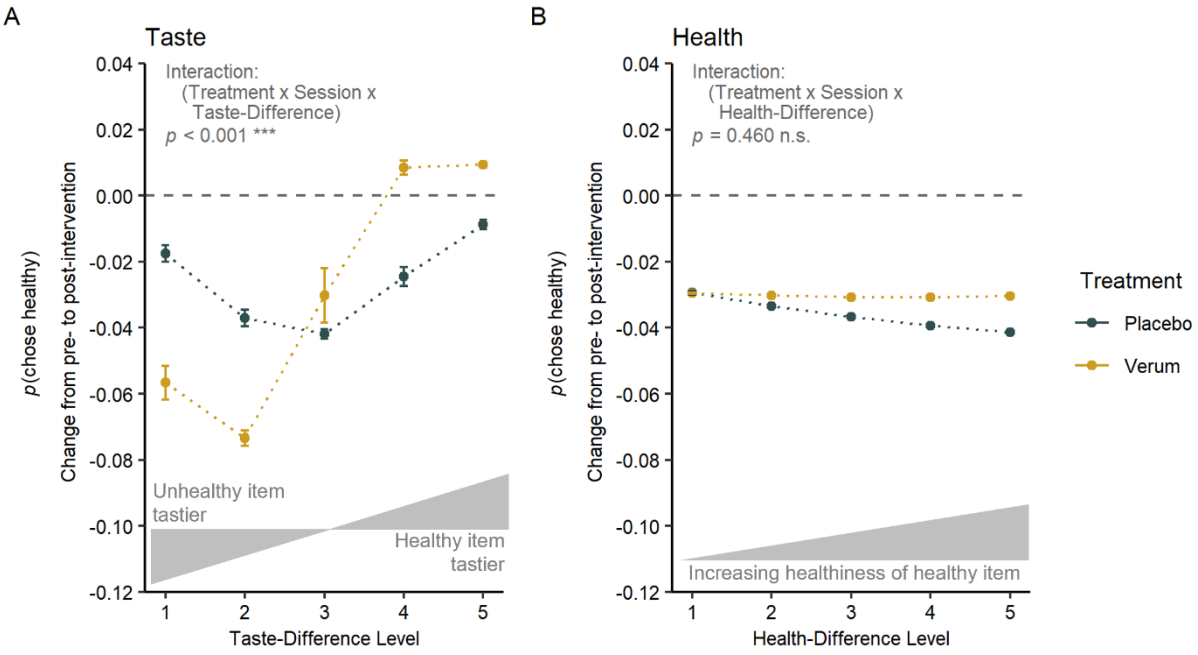

Fig. 15: The synbiotic intervention increases the importance of taste- but not health-difference for making healthy food choices across all trials (conflict & no-conflict). The error bar plots depict the change from pre- to post-intervention in the probability of choosing the healthier item depending on the taste-difference (A) and health-difference (B) (healthier-unhealthier item, z-scored) of the choice options. This change is shown separately for the placebo and the verum group. The synbiotic intervention enhanced the impact of taste-difference when making healthy food choice. The impact of health-difference on healthy choice decreased similarly strong for both groups from pre- to post-intervention. Probabilities were predicted with logistic regression models based on 100 equidistant taste-/health-differences across the full range of differences. For easier visualization, these 100 taste-/health-differences were divided into quintiles and mean values and 95 % confidence intervals are plotted for each quintile. The dashed lines between the mean values were added for enhancing visualization but do not reflect the actual underlying data between the quintiles. The horizontal dashed line at y = 0 indicates no change from pre- to post-intervention. Note, that some of the confidence intervals are too small to be visible. The interaction of treatment x session x taste-/health-difference reflects the effect that the synbiotic intervention has on the integration of taste/health for healthy food choices. This interaction was statistically tested in a mixed logistic regression model (Tab. A 23). n.s., not significant, $p > 0.05$; *** $p < 0.001$.

3.3.8 Choice time in dietary decisions

Previous research demonstrated that the difficulty of food choices is reflected in choice times with more difficult choices having longer choice times (van der Laan et al., 2014; Sullivan and

Huettel, 2021). Therefore, we analyzed choice times to reveal whether the synbiotic intervention had an impact on perceived choice difficulty.

In a first step, we aimed to confirm that independent of the synbiotic intervention choice time increased with increasing choice difficulty. We used the value-difference between the two choice options as a measure of choice difficulty. The more similar the value of two choice options the more difficult is the choice. Hence, choice difficulty is inversely related to value-difference and increases with decreasing value-difference. The value of the choice options is the weighted addition of taste- and health-ratings with the taste- and health-weights derived from beta estimates in individual mixed-effects logistic models for every participant (see detailed description in the statistical methods chapter 3.2.11 and Equation 6).

In a linear mixed-effects model we regressed choice time on value-difference. We indeed found a significant negative association between choice time and value-difference (β = -2.935, SE = 0.066, 95 % CI [-3.07 – -2.80], $t_{(13970)}$ = -44.05, p < 0.001) as illustrated in Fig. 16A.

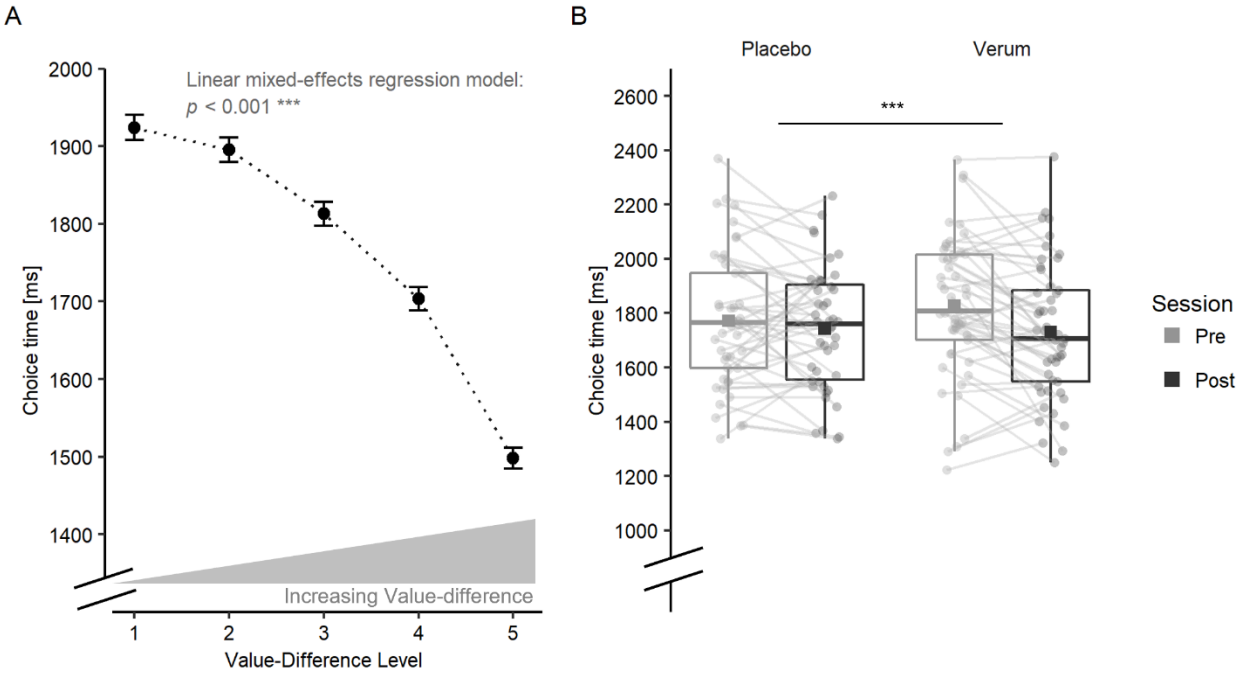

Fig. 16: Food choice time depends on value-difference of choice options and is significantly reduced after the synbiotic intervention. (A) The value of the choice options is the weighted addition of taste- and health-ratings. The weight for taste and health was derived from mixed-effects logistic regression models that were run individually for each participant. In these regression models, Choice of the left item was predicted by taste- and health-ratings from left and right items. The absolute beta-estimates for taste and health were averaged across the left and right item and multiplied with the taste- and health-ratings, respectively, to yield a value for each choice option in every trial. The value-difference is the absolute difference of both choice options. The whole range of value-differences was divided into quintiles and mean values and 95 % confidence intervals are plotted for each quintile. The dashed line between the mean values was added for enhancing visualization but does not reflect the actual underlying data between the quintiles. The choice time decreases significantly with increasing value-difference, indicating that choices become easier and thus quicker with higher value-differences. (B) The synbiotic intervention significantly decreased food choice time. The interaction of treatment and session as measure of a synbiotic intervention effect was statistically tested in a linear mixed regression model (Tab. A 24). The vertical lines of the boxplots depict the median and the squares show the mean. The individual data points of each participant are shown in light grey and are connected via lines for the two sessions. The data points of each participant reflect the mean choice times across all trials. *** $p < 0.001$, * $p < 0.05$.

Next, we focused on the impact of the synbiotic intervention on choice time (see Tab. A 24). Our linear mixed-effects regression showed that, similar as for value-difference, also taste- and health-differences separately negatively correlated with choice times. This relation was significant for health-difference (β = -15.79, SE = 6.807, 95 % CI [-29.13 – -2.45], $t_{(26990)}$ = -2.32, p = 0.020) but not for taste-difference (β = -10.80, SE = 6.571, 95 % CI [-23.68 – 2.08], $t_{(26990)}$ = -1.64, p = 0.100).

Mean choice time across both groups was 1797.35 ms (SD = 610.85 ms) at the pre-intervention timepoint and 1736.17 ms (SD = 585.05 ms) at the post-intervention timepoint.

The synbiotic intervention significantly affected choice times such that in the verum group the decrease in choice time from pre- to post-intervention was significantly stronger than in the placebo group (reflected in the interaction treatment x session: β = -80.90, SE = 13.57, 95 % CI [-107.50 – -54.29], $t_{(27070)}$ = -5.96, p < 0.001). This effect is depicted in Fig. 16B. In the verum group, choice time decreased on average by 5.25 % from pre- to post-intervention (pre: M = 1824.88 ms, SE = 622.75; post: M = 1731.09 ms, SE = 587.45). This was a more than three times larger decrease than in the placebo group (1.62 %, pre: M = 1767.97 ms, SE = 596.54; post: M = 1741.61 ms, SE = 582.47).

This effect of the synbiotic intervention on choice time is stable and still significant when testing it with choice times and taste-/health-differences averaged across all trials per participant and per timepoint (β = -81.3, SE = 38.43, 95 % CI [-153.56, -8.87], $t_{(86)}$ = -2.11, p = 0.038).

At the pre-intervention timepoint, we observed a small, random difference in choice times between the groups with the choice times in the placebo group (M = 1767.97 ms, SD = 596.54 ms) being lower than in the verum group (M = 1824.88 ms, SD = 622.75 ms). However, this difference is not statistically significant as indicated by the simple effect of treatment in the linear mixed-effects model (β = 57.11, SE = 47.74, 95 % CI [-36.46 – 150.67], $t_{(96)}$ = 1.20, p = 0.235, (see Tab. A 24). Due to the dummy coding of the binary variables treatment (placebo = 0, verum = 1) and session (pre-intervention = 0, post-intervention = 1), the estimate for treatment reflects the difference between placebo and verum in the first session.

Health- and taste-differences did not moderate the effect of the synbiotic intervention on choice times (p-values of three-way interactions taste-/health-difference x treatment x

session > 0.26), In other words, the synbiotic intervention affected choice times equally across different levels of choice difficulty.

Lastly, we asked whether the there is any association between the observed effect of the synbiotic intervention on taste responsiveness (chapter 3.3.6) and the effect on choice time. In other words, we wanted to know whether the increase in taste responsiveness after the synbiotic intervention is related to faster choices after the synbiotic intervention. Although such a relation cannot imply causation, it could hint at a potential mechanism via which the synbiotic intervention could affect choice times. Therefore, we correlated the change in choice time from pre- to post intervention with the change in taste responsiveness. Taste responsiveness was determined via individual logistic mixed-effects models on participant-level with *choice left* regressed on health-difference and taste-difference (Equation 5). We extracted the beta-estimate for taste-difference as the measure of taste responsiveness from each participant's model. This analysis did not yield any significant correlation between change in taste-responsiveness and change in choice time ($r(93) = 0.009$, p-value = 0.931).

3.3.9 Rating time of taste- and health-attributes of food products

Based on the above described finding that the synbiotic intervention decreased the time it took to make food choices, we wanted to further elucidate this finding by also analyzing the taste- and health-rating times. We wanted to know, whether the synbiotic intervention specifically affects processing speed in food choices or more generally reaction times across different food-related tasks, including food ratings.

We report median values and interquartile range (IQR) for the descriptive statistics due to right-skewed distribution of rating data.

Median taste-rating time across both groups was 2923.45 ms (*IQR* = 1920.28 ms) at the pre-intervention timepoint and 2382.30 ms (*IQR* = 1360.60 ms) at the post-intervention timepoint. Median health-rating time across both groups was 2951.20 ms (*IQR* = 2193.30 ms) at the pre-intervention timepoint and 2502.20 ms (*IQR* = 1586.80 ms) at the post-intervention timepoint.

Linear mixed-effects models (Tab. A 25) revealed that, independent of the synbiotic intervention, both, taste- and health-rating times, decreased significantly in the placebo group from pre- (taste: *Mdn* = 2928.45 ms, *IQR* = 1966.53 ms; health: *Mdn* = 2835.90 ms, *IQR* = 1921.40 ms) to post-intervention (taste: *Mdn* = 2392.00 ms, *IQR* = 1368.80 ms, β = -0.187, *SE* = 0.013, 95 % CI [-0.21 – -0.16], $t_{(8892)}$ = -14.5, $p < 0.001$; health: *Mdn* = 2468.10 ms , *IQR* = 1457.30 ms, β = -0.130, *SE* = -0.014, 95 % CI [-0.16 – -0.10], $t_{(8789)}$ = -9.2, $p < 0.001$). This significantly quicker rating times can probably be explained by the familiarity with the task and food items.

For health-rating times, placebo and verum group differed significantly in their change from pre- to post-intervention such that the decrease in health-rating time was even stronger in the verum group (reflected by a significant treatment x session interaction: β = -0.074, *SE* = 0.019, 95 % CI [-0.11 – -0.04], $t_{(8805)}$ = -3.8, $p < 0.001$, see Fig. 17B and Tab. A 25). In the placebo group the health-rating time decreased by 13.0 %, while the decrease in verum group was 19.3 % (pre-intervention: *Mdn* = 3125.60 ms, *IQR* = 2429.95 ms; post-intervention: *Mdn* = 2523.65 ms, *IQR* = 1694.58 ms). To test whether changes in health-rating time are associated with changes in choice time, we correlated both changes (post- minus pre-intervention) with each other but did not observe a significant association ($r(88) = 0.263$, *p*-value = 0.127).

For the taste-ratings, we did not find an interaction effect of treatment x session on taste-rating times (β = -0.021, *SE* = 0.018, 95 % CI [-0.06 – 0.01], $t_{(8887)}$ = -1.2, $p = 0.230$, see Fig. 17A and Tab. A 25).

Similar as for the choice time, we also observed a small, random difference in health-rating times between the two groups at the pre-intervention time point with the verum group having a higher health-rating time (*Mdn*: 3125.60ms, *IQR* = 2429.95 ms) than the placebo group (*Mdn*: 2835.90 ms, *IQR* = 1921.40 ms). However, this difference is not statistically significant as indicated by the simple effect of treatment in the linear mixed-effects model (β = 0.09, SE = 0.05, 95 % CI [-0.02, – 0.19], $t_{(97)}$ = 1.7, p = 0.101, see Tab. A 25).

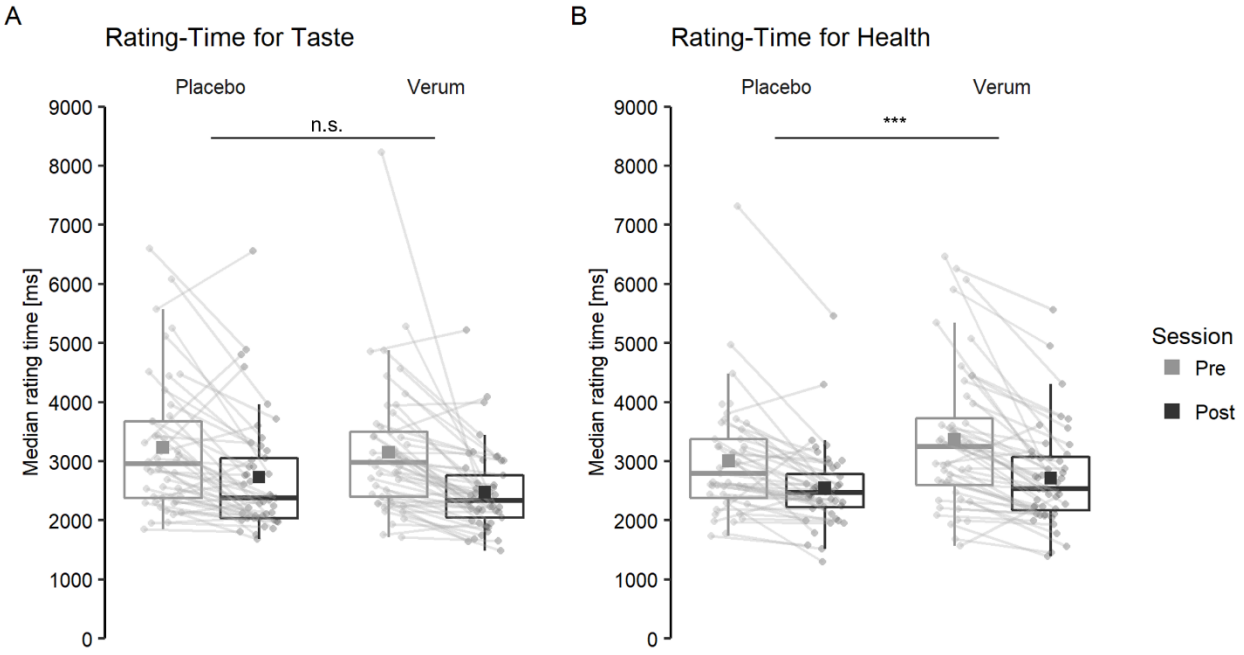

Fig. 17: The synbiotic intervention significantly decreased rating-time for health but not for taste. The individual datapoints depict the median rating-times (instead of mean rating-times due to strong right-skewed data distribution arising from self-paced ratings) for taste (A) and health (B) of each participant across all 52 food items. For each participant, the grey lines connect the paired data of the two sessions. Note, that due to a recording error, not all rating times were recorded properly (missing observations: n_{Health} = 802, n_{Taste} = 705). Five participants miss all the taste- or health-rating times of one session and thus the respective datapoints of the other session do not have a connecting line. The interaction treatment x session as measure of a synbiotic intervention effect was statistically tested in linear mixed-effects regression models across all trials (Tab. A 25). The vertical lines of the boxplots depict the median and the squares show the mean. n.s., not significant, $p > 0.05$; *** $p < 0.001$.

3.4 Neuroimaging Results

At the neural level, we wanted to explore potential brain mechanisms of the observed synbiotic intervention effect on behavioral health and taste assessment and integration into choice. We used fMRI during the food choice task to investigate brain activity reflecting subjective value, taste and health attributes, and healthy choices.

3.4.1 Neural correlates of the subjective value of the chosen food

We assessed the neural correlates of the subjective value of the chosen food with GLM1
First, we tested whether our food choice task implementation was able to confirm the common idea that the subjective valuation during food choice is reflected in the vmPFC (Bartra et al., 2013; Hare et al., 2011a; 2009; Maier et al., 2015).

A whole-brain analysis for regions that negatively correlate with chosen subjective value at the pre-intervention time point did not reveal any significant result (at $p < 0.05$, FWE-corrected at cluster level with cluster-defining uncorrected height-threshold of $p < 0.001$). However, the subjective value of the chosen item showed a significant positive correlation with BOLD signal in several brain regions (Tab. 5, Fig. 18A) including vmPFC, dlPFC, and ACC (all $p < 0.05$, FWE-corrected at cluster level with cluster-defining uncorrected height-threshold of $p < 0.001$).

The vmPFC region representing the chosen subjective value strongly overlapped with the conjunction mask from Fig. 9 in Bartra et al., 2013 (Fig. 18B). This meta-analysis-derived conjunction mask represents modality-independent, positive subjective value effects during both the decision and receipt stage. BOLD signal in the left dlPFC partially overlapped with the dlPFC mask used in Hutcherson et al., 2012 (middle frontal gyrus restricted to Brodmann areas (BA) 9, 10, 46 with a dilation of 3). This overlap was however more dorsal and more caudal (x = -44, y = 14, z = 39) than previously reported activity in dlPFC related to WTP for food and appetitive goal value (Hutcherson et al., 2012; Plassmann et al., 2010; 2007).

We further wanted to know whether this subjective valuation process in the vmPFC during food choices, irrespective of our synbiotic intervention, correlates with individual health related behavioral and metabolic characteristics. Neither proportion of body fat ($r(88) = -0.031$, $p = 0.774$) nor healthy choice behavior ($r(93) = -0.143$, $p = 0.167$) were signficantly associated with the extracted average beta-values for subjective value related BOLD signal in the vmPFC ROI (see chapter 3.2.12 for a description of the ROI mask) at the pre-intervention timepoint.

Tab. 5: Brain regions with a positive correlation of BOLD signal with subjective value of the chosen food item across all trials at the pre-intervention timepoint.

Region, Laterality	Cluster Size (voxel)	Cluster $p_{(FWE)}$-value	Peak *t*-value	Peak MNI Coordinates		
				x	y	z
Inferior temporal gyrus, R	2967	< 0.001	6.826	44	-65	-9
Angular gyrus, R			5.589	34	-69	47
Calcarine fissure, R			5.528	16	-91	1
Inferior parietal gyrus, L	6202	< 0.001	6.424	-51	-41	47
Middle cingulate gyrus, R			6.299	4	-37	34
Middle occipital gyrus, L			6.275	-43	-79	1
Superior frontal gyrus, R	404	0.001	6.078	18	32	53
Middle frontal gyrus, R			4.407	36	18	47
Superior frontal gyrus, L	1234	< 0.001	5.915	-17	40	47
Middle frontal gyrus, L			5.298	-35	18	50
Superior frontal gyrus, medial orbital, L [+]			5.051	-5	42	-9
Postcentral gyrus, R	420	0.001	4.714	56	-21	44
SupraMarginal gyrus, R			4.145	40	-39	44

The results are whole-brain corrected for multiple comparisons at the cluster level (cluster-corrected threshold $p_{FWE} < 0.05$ at an uncorrected voxel-level inclusion threshold of $p < 0.001$). Table shows unique anatomical labels at one laterality of each cluster for all local maxima separated by more than 20 mm. Regions were automatically labelled using the automatic anatomic labeling (aal3) atlas as implemented in the bspmview toolbox. L, left; R, right, MNI, Montreal Neurological Institute. [+] shown in Fig. 18A.

Next, we assessed with a ROI analysis whether the processing of the subjective value in the vmPFC was modulated by our synbiotic intervention. The extracted beta values for the subjective value processsing in the vmPFC did not change significantly differently from pre- to post-intervention for the two groups (Fig. A 2A) (linear mixed-effects regression model, interaction of treatment x session: $\beta = 0.032$, $SE = 0.091$, 95 % CI [-0.15 – 0.21], $t_{(93)} = 0.352$, $p = 0.726$).

In an additional whole-brain analysis we checked for any intervention related changes in subjective value processing outside of the vmPFC. For this, we assessed the difference of the parametric modulator *chosen subjective value* between the two sessions (post minus pre contrast) for each participant at the first level. At the second level, we compared this session difference between placebo and verum group via two-sample t-tests (*chosen subjective*

value: $VER_{post > pre} > PLC_{post > pre}$ and $PLC_{post > pre} > VER_{pos > pre}$). Note, that we did not find any significant results after FWE-correction at the cluster level.

Using a more liberal, exploratory threshold ($p_{uncorrected} < 0.001$, $k \geq 5$) for the synbiotic intervention effect on subjective value related brain activity did not yield any significantly increased BOLD signal in the verum group as compared to the placebo group ($p < 0.001$ uncorrected, cluster extent threshold $k \geq 5$). However, for the contrast $PLC_{post > pre} > VER_{post > pre}$, our analysis yielded significantly increased BOLD signals in the right middle temporal gyrus ($t_{max}(93) = 4.21$, cluster size = 29 (grey matter = 0 voxels), MNI peak: x = 48, y = -45, z = -6) and right rolandic operculum ($t_{max(93)} = 3.81$, cluster size = 33 (grey matter = 9 voxels), MNI peak: x = -54.5, y = -0.5, z = 13.9) (see Fig. 18E, $p < 0.001$ uncorrected, cluster extent threshold $k \geq 20$). The visualisation of the extracted betas from the right rolandic operculum in Fig. 18E reveals that the value-related activity increased for the placebo group while it decreased for the verum group.

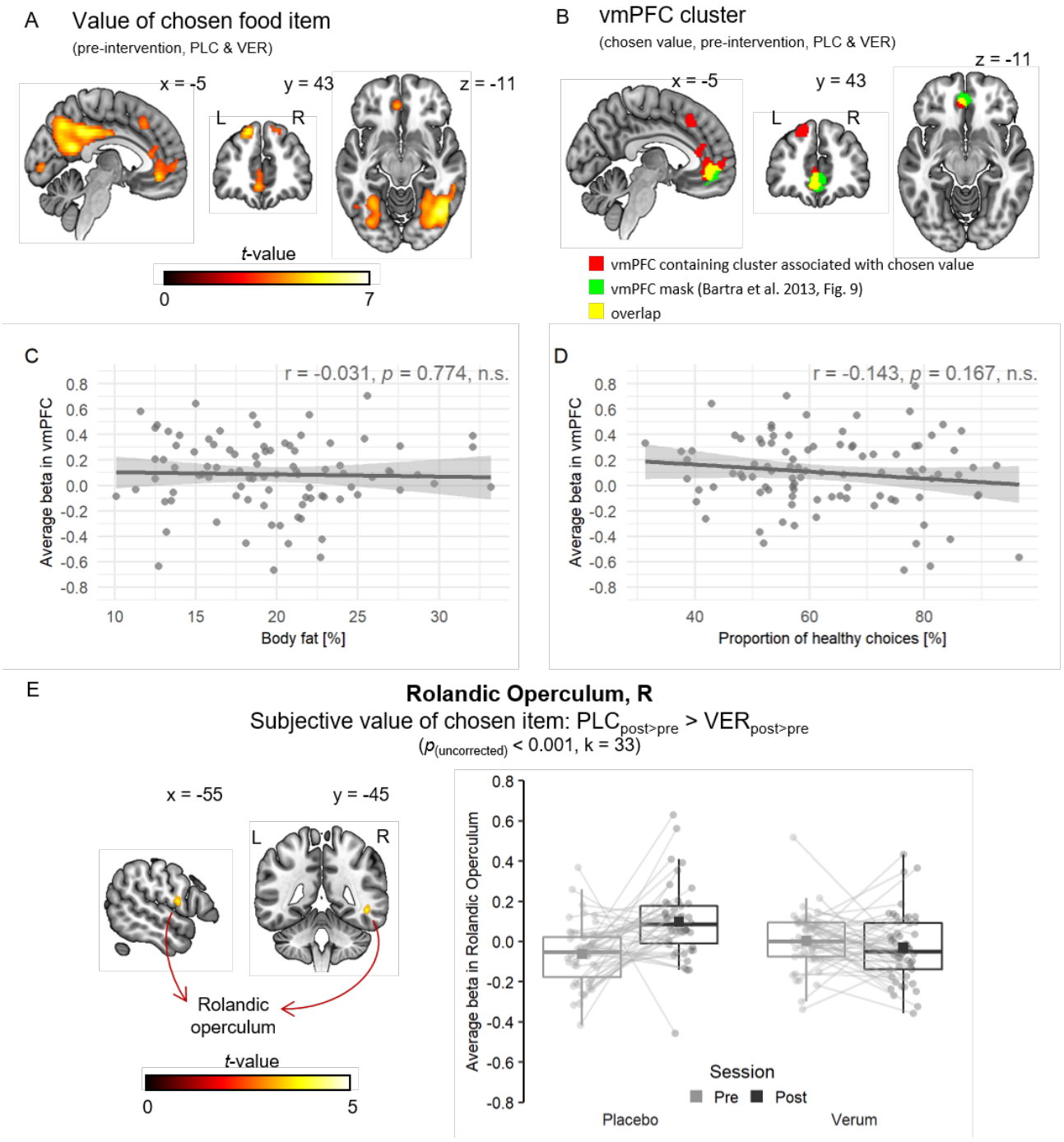

Fig. 18: vmPFC activity reflects subjective value of the chosen food item irrespective of the synbiotic intervention. (A) The statistical parametric map shows the result of the whole-brain analysis for BOLD signal positively correlating with the value of the chosen food item across all trials for all participants at the pre-intervention timepoint (FWE-corrected at the cluster level ($p < 0.05$) with a cluster-defining threshold of $p < 0.001$). (B) The vmPFC-containing cluster (k = 1234) from (A) overlaps with the vmPFC mask from Fig. 9 in Bartra et al., 2013.

(C) The subjective value related vmPFC activity at the pre-intervention timepoint was extracted from the cluster overlay with the Bartra map (shown in (B) in yellow) for every participant but did neither correlate with individual proportion of body fat nor (D) healthy choice behavior. The shaded grey areas reflect the 95 % confidence intervals. (E) An exploratory and uncorrected whole-brain analysis (uncorrected at $p < 0.001$, $k \geq 20$) revealed a significant interaction of treatment and session on the association of the chosen value with the BOLD signal in the right rolandic operculum. The boxplot displays the average beta estimate in the right rolandic operculum for each session and group for visualization purposes only and does not represent a statistical test. The vertical lines of the boxplots depict the median and the squares show the mean. The individual data points of each participant are shown in light grey and are connected via lines for the two sessions. T-maps and ROI masks are overlayed on the MNI152 template brain. L, left; R, right; vmPFC, ventromedial prefrontal cortex; PLC, placebo; VER, verum. n.s., not significant, $p > 0.05$.

3.4.2 Neural correlates of health and taste of the chosen food

As described above, the representation of the subjective value of the chosen food item in the vmPFC remained unchanged after the synbiotic intervention. The subjective value of a food item is composed of both taste- and health-perception of the item as well as the general weight that is put onto each attribute during the decision process. While the synbiotic intervention did not affect the value integration in the vmPFC, it might still modulate the separate representation and integration of taste and health attributes (Lee and Hare, 2021; Maier et al., 2020; 2015). Theoretically, value representation and thus decision-making can be modulated via two routes: either at the integration-level by acting on centralized value integration areas like vmPFC, or at the attribute-level by amplifying or diminishing the representation of individual attributes in specific attribute regions (Tusche and Hutcherson, 2018).

On the behavioral level, the synbiotic intervention increased the impact that taste-difference between the two food items had for the probability one of two food options (chapter 3.3.6) and for the probability of making healthier choices (chapter 3.3.7). Thus, the synbiotic intervention may strengthen the representation of taste, which might also be reflected in the brain.

With GLM2, we first assessed the neural representation of the chosen taste and health the pre-intervention timepoint across all participants. The neural representation of taste-ratings

is of particular interest due to the behavioral findings. Nevertheless, we additionally assessed the parametric regressor for health-ratings throughout all analyses of GLM2 to not miss out on any intervention effects. This first step enables us to validate that our task design can reveal the representation of taste- and health-ratings in the brain and to compare the results to previous literature (Hare et al., 2011a; Maier et al., 2015; Maier and Hare, 2017).

In a whole-brain analysis, we did not find any brain region where BOLD activity negatively correlated with the taste-rating of the chosen food item (at $p < 0.05$, FWE-corrected at cluster level with cluster-defining uncorrected height-threshold of $p < 0.001$). Health-ratings negatively correlated with BOLD signal in the left inferior occipital gyrus (Tab. 6). The taste-rating of the chosen item showed a significant positive correlation with BOLD signal in several brain regions (Tab. 6, Fig. 20A). These regions strongly overlapped with regions for subjective value (see Tab. 5), and included vmPFC, dlPFC (partially overlapping with appetitive goal value signals at x = -44, y = 14, z = 39; reported by Plassmann et al., 2010), bilateral angular gyrus, and bilateral fusiform and lingual gyri ($p < 0.05$, FWE-corrected at cluster level with cluster-defining uncorrected height-threshold of $p < 0.001$). The health-rating of the chosen item showed a significant positive correlation with parts of the left middle occipital and left inferior parietal gyri (Tab. 6, Fig. 21A). We did not find any health-rating related activity in vmPFC or dlPFC as previously reported in a different food choice task by Hare et al., 2011.

Tab. 6: Brain regions with a correlation of BOLD signal with taste and health of the chosen food item across all trials at the pre-intervention timepoint.

Region, Laterality	Cluster Size (voxel)	Cluster $p_{(FWE)}$-value	Peak *t*-value	Peak MNI Coordinates		
				x	y	z
Taste of chosen item: Positive correlation						
Inferior temporal gyrus, R	4208	< 0.001	8.647	42	-65	-9
Middle occipital gyrus, R			6.229	40	-85	7
Angular gyrus, R			6.137	54	-65	27
Superior frontal gyrus, dorsolateral, L	4644	< 0.001	7.265	-19	32	53
Superior frontal gyrus, dorsolateral, R			7.028	20	32	53
Superior frontal gyrus, medial orbital, L			6.805	-9	42	-13
Precuneus, L	2482	< 0.001	7.242	-1	-59	27
Middle cingulate gyrus, R			6.614	4	-37	34
Middle cingulate gyrus, L			4.858	-1	-9	34
Middle occipital gyrus, L	4727	< 0.001	6.930	-43	-79	-3
Inferior parietal gyrus, L			6.639	-51	-43	50
Angular gyrus, L			6.179	-43	-67	44
Superior occipital gyrus, L	177	0.034	5.210	-21	-89	24
Inferior frontal gyrus, triangular part, L	321	0.003	5.027	-45	42	14
Inferior frontal gyrus pars orbitalis, L			3.332	-41	42	-9
Health of chosen item: Positive correlation						
Middle occipital gyrus, L	161	0.047	6.242	-13	-101	4
Inferior parietal gyrus, L	418	0.001	4.574	-33	-71	44
Health of chosen item: Negative correlation						
Inferior occipital gyrus, L	194	0.025	6.031	-29	-93	-9

The results are whole-brain corrected for multiple comparisons at the cluster level (cluster-corrected threshold $p_{FWE} < 0.05$ at an uncorrected voxel-level inclusion threshold of $p < 0.001$). Table shows unique anatomical labels at one laterality of each cluster for all local maxima separated by more than 20 mm. Regions were automatically labelled using the automatic anatomic labeling (aal3) atlas as implemented in the bspmview toolbox. Note that no region showed a negative correlation of the BOLD signal with the taste of the chosen item. L, left; R, right, MNI, Montreal Neurological Institute.

For further, more region-specific, analyses of the neural taste- and health-representations we defined two a priori ROIs (Fig. 19). The choice and combination of brain regions included in the valuation ROI (vmPFC + vStr) and emotional/salience ROI (parahippocampus + hippocampus + amygdala + insula + ACC) was based on previous imaging literature on overall food valuation and valuation of food attributes (Christensen et al., 2021; Gupta et al.,

2020; Maier et al., 2015; Merchant et al., 2020; O'Doherty et al., 2002). Regions included in the two ROI masks have recently been proposed to be relevant for microbiota-gut-brain signaling in the context of eating behavior (Gupta et al., 2020; Plassmann et al., 2021). Especially the salience network with anterior insula and anterior cingulate cortex, and the limbic system with amygdala and hippocampus might be sensitive to changes in gut microbiota (Bagga et al., 2019; Tillisch et al., 2013).

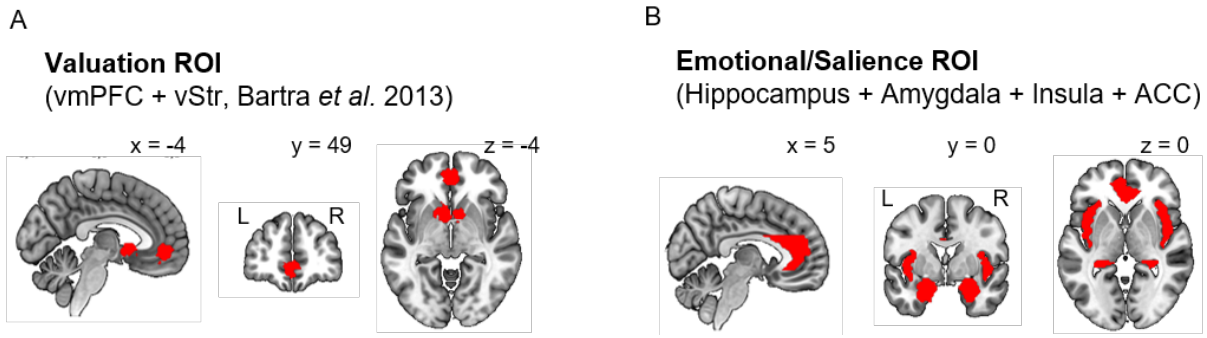

Fig. 19: Masks used for ROI analyses of parametric modulators taste and health. (A) The valuation ROI mask was created from the vmPFC and vStr masks from Fig. 9 in Bartra et al., 2013. (B) Brain regions in the emotional/salience ROI mask were anatomically defined via the aal atlas as implemented in the wfu pick atlas. ROI masks are displayed in red on the MNI152 template brain.

We first investigated whether the taste- and health-related signal in valuation and emotional/salience ROIs, irrespective of our synbiotic intervention, correlated with individual health-related behavioral and metabolic parameters. Proportion of body fat did neither correlate significantly with the average betas for taste nor health related BOLD signal in any of the two ROIs (Taste betas in valuation ROI: $r(88) = -0.025$, $p = 0.818$; Taste betas in emotional/salience ROI: $r(88) = -0.083$, $p = 0.434$; health betas in valuation ROI: $r(88) = 0.013$, $p = 0.902$; health betas in emotional/salience ROI: $r(88) = -0.020$, $p = 0.853$). The proportion of healthy choices across all trials showed a significant positive correlation with the average betas for taste related BOLD signal in the valuation (Fig. 20B, $r(93) = 0.238$, $p = 0.020$) and emotional/salience ROI (Fig. 20C, $r(93) = 0.238$, $p = 0.020$). In other words, the brain's emotional/salience and valuation regions reflected the taste of the chosen item

stronger for participants with a healthier choice behavior in our task as compared to participants with less healthy choices. For the average betas of health related BOLD signal, the relation with the proportion of healthy choices was inverse. Average betas were negatively correlated with the proportion of healthy choices; but only significantly in the valuation ROI (Fig. 21B, $r(93) = -0.246$, $p = 0.016$), not in the emotional/salience ROI (Fig. 21C, $r(93) = -0.151$, $p = 0.143$).

Next, and most importantly, we wanted to know whether the synbiotic intervention modulated the representation of taste and health of the chosen food item in the valuation and the emotional/salience ROI. We extracted the average beta estimates from these ROIs from the health- and the taste-contrasts for each participant and each session. We tested for the synbiotic intervention effect on these betas via the interaction of treatment x session in a linear mixed-effects model. The synbiotic intervention did not affect the average betas of the taste contrast, neither in the valuation ROI (Fig. A 2B, interaction of treatment x session: $\beta = 0.061$, $SE = 0.071$, 95 % CI [-0.079 – 0.201], $t_{(93)} = 0.857$, $p = 0.394$) nor in the emotional/salience ROI (Fig. A 2C, interaction of treatment x session: $\beta = -0.008$, $SE = 0.051$, 95 % CI [-0.108 – 0.092], $t_{(93)} = -0.164$, $p = 0.870$). Similarily, also the average betas of the health contrast remained unchanged after the synbiotic intervention in the valuation (Fig. A 2D, interaction of treatment x session: $\beta = -0.130$, $SE = 0.086$, 95 % CI [-0.298 – 0.039], $t_{(93)} = -1.507$, $p = 0.135$) and emotional/salience ROI (Fig. A 2E, interaction of treatment x session: $\beta = -0.085$, $SE = 0.069$, 95 % CI [-0.220 – 0.049], $t_{(186)} = -1.235$, $p = 0.218$).

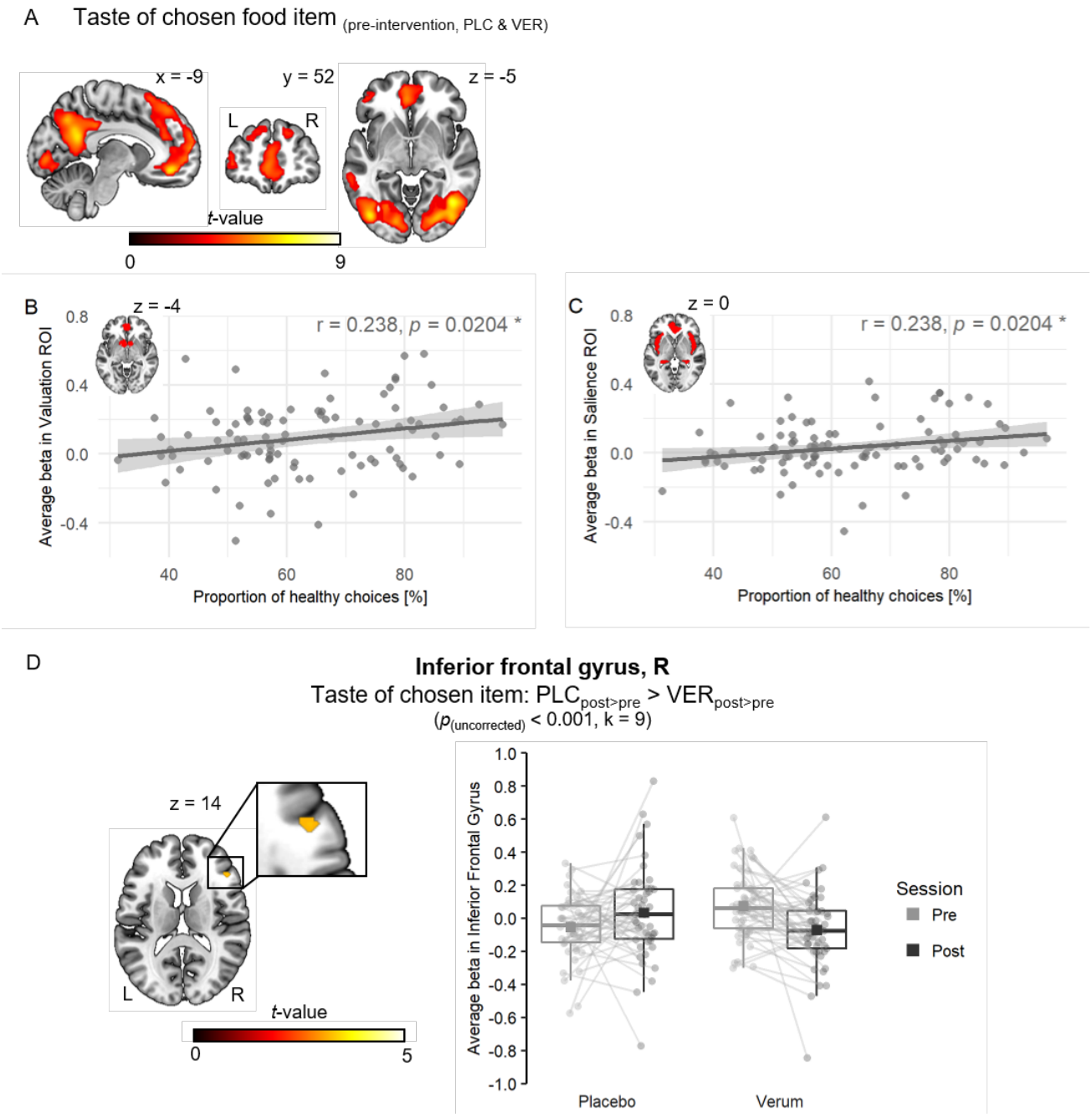

Fig. 20: Parametric modulation of BOLD signal by taste of chosen food item. The statistical parametric map shows the result of the whole-brain analysis for BOLD signal positively correlating with the taste of the chosen food item across all trials for all participants at the pre-intervention timepoint (FWE-corrected at the cluster level (p < 0.05) with a cluster-defining threshold of p < 0.001). Average beta values related to the taste of the chosen item were extracted from the valuation (B) and emotional/salience ROI masks (C) (see Fig. 19 for ROI masks) for every participant from pre-intervention statistical maps. Both, betas in

valuation and salience ROIs showed a significant positive correlation with the proportion of healthy choice. The shaded grey areas reflect the 95 % confidence intervals. (D) An exploratory and uncorrected whole-brain analysis (uncorrected at $p < 0.001$) revealed a significant interaction of treatment and session on the association of chosen taste with the BOLD signal in the right inferior frontal gyrus. The boxplot displays the average beta estimate in the right inferior frontal gyrus for each session and group for visualization purposes only and does not represent a statistical test. The vertical lines of the boxplots depict the median and the squares show the mean. The individual data points of each participant are shown in light grey and are connected via lines for the two sessions. T-maps and ROI masks are overlayed on the MNI152 template brain. L, left; R, right; PLC, placebo; VER, verum. * $p < 0.05$.

In an additional exploratory whole-brain analysis we checked for any intervention related changes in taste and health representation outside of the valuation and emotional/salience ROIs. In the first level analysis, we assessed the difference of each parametric modulator (i.e chosen taste or chosen health) between the two sessions (post minus pre contrast) for each participant. At the second level, we compared these session differences between placebo and verum group via two-sample t-tests (Chosen taste/chosen health: $VER_{post > pre} > PLC_{post > pre}$ and $PLC_{post > pre} > VER_{pos > pre}$). Note, that we did not find any significant results after FWE-correction at the cluster level.

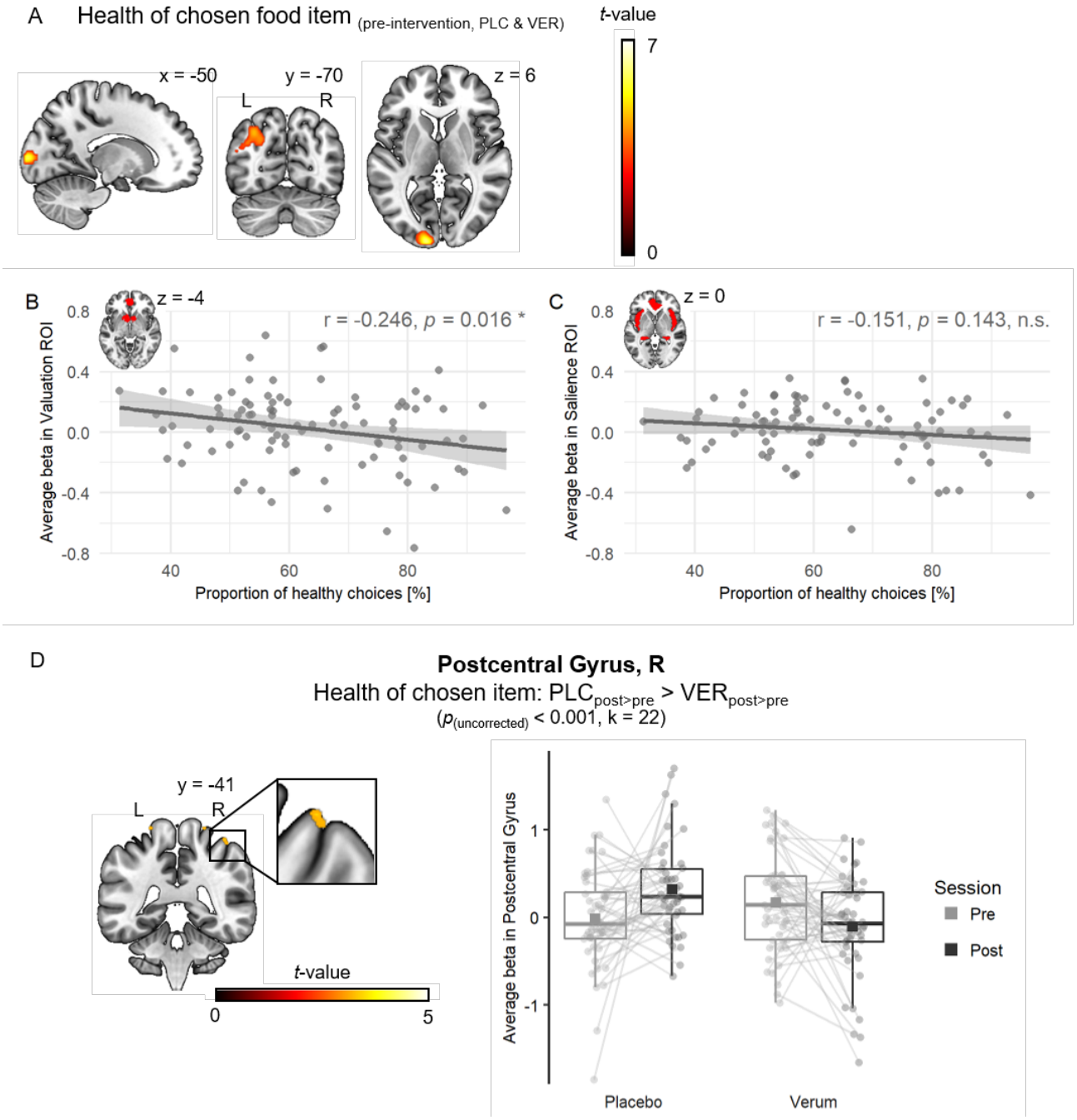

Fig. 21: Parametric modulation of BOLD signal by health of chosen food item. (A) The statistical parametric map shows the result of the whole-brain analysis for BOLD signal positively correlating with the heath of the chosen food item across all trials for all participants at the pre-intervention timepoint (FWE-corrected at the cluster level ($p < 0.05$) with a cluster-defining threshold of $p < 0.001$). Average beta values related to the health of the chosen item were extracted from the valuation (B) and emotional/salience ROI masks(C) (see Fig. 19 for ROI masks) for every participant from pre-intervention statistical maps. Only betas in

valuation ROI showed a significant negative correlation with the proportion of healthy choice. The shaded grey areas reflect the 95 % confidence intervals. (D) An exploratory and uncorrected whole-brain analysis (uncorrected at $p < 0.001$, $k \geq 20$) revealed a significant interaction of treatment and session on the association of chosen health with the BOLD signal in the right postcentral gyrus. The boxplot displays the average beta estimate in the right postcentral gyrus for each session and group for visualization purposes only and does not represent a statistical test. The vertical lines of the boxplots depict the median and the squares show the mean. The individual data points of each participant are shown in light grey and are connected via lines for the two sessions. T-maps and ROI masks are overlayed on the MNI152 template brain. L, left; R, right; PLC, placebo; VER, verum. n.s., not significant, $p > 0.05$; * $p < 0.05$.

For the taste of the chosen item and the contrast $VER_{post > pre} > PLC_{post > pre}$, our analysis with a more liberal, exploratory threshold (puncorrected < 0.001, k ≥ 5) only yielded significantly increased BOLD signal ($p_{uncorrected} < 0.001$ at peak-level) in two clusters (all k < 8) that solely or predominantely covered white matter. However, for the contrast $PLC_{post > pre} > VER_{post > pre}$, we found a cluster of nine voxels ($k_{grey\ matter} = 5$) in the right inferior frontal gyrus (IFG) ($t_{max(93)} = 3.48$, MNI peak: x = 48, y = 32, z = 14, $p_{uncorrected} < 0.001$, k ≥ 5, Fig. 20D).

For the health of the chosen item and the contrast $VER_{post > pre} > PLC_{post > pre}$, we did not find any significant BOLD signal ($p_{uncorrected} < 0.001$, cluster extend threshold k ≥ 5). The contrast $PLC_{post > pre} > VER_{post > pre}$ for health of the chosen item reveald significant resuls in several brain regions (Tab. 7 + Fig. 21D), including ACC, bilateral middle occipital gyrus, and bilateral postcentral gyrus ($p_{uncorrected} < 0.001$, cluster extent threshold k ≥ 20). This finding shows that brain activity related to the health of chosen food items changed significantly differently for the verum group as compared to the placebo group. The examplary visualisation of this interaction for the right postcentral gyrus in the boxplot of Fig. 21D illustrates that health-related activity increased for the placebo group while it decreased for the verum group.

Tab. 7: Brain regions with a negative impact of the synbiotic intervention ($PLC_{post > pre} > VER_{post > pre}$) on the correlation of BOLD signal with health of the chosen food item.

Region, Laterality	Cluster Size (voxel)	Voxel in grey matter	Peak *t*-value	Peak MNI Coordinates		
				x	y	z
Anterior cingulate cortex, supracallosal, L	24	16	3.923	-7	16	24
Middle occipital gyrus, R	43	39	3.707	30	-71	37
Postcentral Gyrus, R +	22	16	3.706	44	-41	63
Postcentral Gyrus, L	31	15	3.677	-63	-1	17
Middle occipital Gyrus, L	25	15	3.388	-31	-81	24

The whole-brain results are uncorrected for multiple comparisons ($p_{uncorrected} < 0.001$, $k \geq 20$). Table shows unique anatomical labels at one laterality of each cluster for all local maxima separated by more than 20 mm. Regions were automatically labelled using the automatic anatomic labeling (aal3) atlas as implemented in the bspmview toolbox. L, left; R, right, MNI, Montreal Neurological Institute. + this cluster is illustrated in Fig. 21D.

3.4.3 Neural correlates of healthy food choices

Lastly, we wanted to know how the overall neural processing during healthy choices, irrespective of taste, health, or value of the chosen item, was reflected in the brain and modulated by the synbiotic intervention. On the behavioral level, the synbiotic intervention did not increase the number of healthy choices (see chapter 3.3.5). Nevertheless, it modulated the relevance of taste for healthy choices (see chapter 3.3.7) and decreased the time to make food choices – both unhealthy and healthy ones (see chapter 3.3.8). Thus, the neural correlates of healthy choices might be specifically modulated by the synbiotic intervention irrespective of individual food attributes.

We set up a third GLM, GLM3, with regressors for healthy and unhealthy choices. For a first overview of brain regions related to healthy choices, we conducted a whole-brain analysis for the contrast healthy choices vs. unhealthy choices irrespective of our synbiotic intervention at the pre-intervention timepoint. This analysis revealed significantly increased activity during healthy choices as compared to unhealthy choices in several brain regions (Tab. 8, Fig. 22A), including parts of the right inferior temporal gyrus, bilateral fusiform gyri and right lingual gyrus ($p < 0.05$, FWE-corrected at cluster level with cluster-defining uncorrected height-threshold of $p < 0.001$). However, we did not find any BOLD signal in response to healthy choices in

the prefrontal cortex. Previously, Harding et al., 2018 used a different beverage choice paradigm but observed activity for healthy choices compared to unhealthy choices in vmPFC and dlPFC. Similarly, research also demonstrated the relevance of the dlPFC for healthy choices particularly in conflict trials (healthier option is less tasty) (Hare et al., 2009; Maier et al., 2015; Schmidt et al., 2018).

Tab. 8: Brain regions with BOLD signal during healthy choices vs. unhealthy choices across all trials pre-intervention.

Region, Laterality	Cluster Size (voxel)	Cluster $p_{(FWE)}$-value	Peak *t*-value	Peak MNI Coordinates		
				x	y	z
Inferior temporal gyrus, R	2900	< 0.001	5.806	46	-73	-6
Fusiform gyrus, R			4.978	36	-55	-16
Lingual Gyrus, R			4.829	22	-73	-3
Middle occipital, L	1328	< 0.001	5.402	-45	-73	14
Superior occipital gyrus, L			4.751	-17	-93	34
Inferior parietal gyrus, L	1019	< 0.001	4.861	-51	-37	53
SupraMarginal gyrus, L			4.634	-61	-27	37
Superior parietal gyrus, L			3.690	-31	-53	63
Calcarine Fissure, L	317	0.001	4.559	-13	-93	1
Inferior occipital gyrus, L			3.648	-31	-79	-9
Postcentral gyrus, R	475	< 0.001	4.551	36	-47	63
Superior parietal gyrus, R			4.133	26	-65	57
Fusiform gyrus, L	423	< 0.001	4.481	-33	-45	-16
Lobule VI of cerebellar hemisphere, L			3.552	-17	-69	-22

The results are whole-brain corrected for multiple comparisons at the cluster level (cluster-corrected threshold *p*FWE < 0.05 at an uncorrected voxel-level inclusion threshold of $p < 0.001$). Table shows unique anatomical labels at one laterality of each cluster for all local maxima separated by more than 20 mm. Regions were automatically labelled using the automatic anatomic labeling (aal3) atlas as implemented in the bspmview toolbox L, left; R, right, MNI, Montreal Neurological Institute.

In a second step, we explored a potential impact of the synbiotic intervention on the neural correlates of healthy choices in a whole-brain analysis. We assessed the difference of the contrast *Healthy choice vs. unhealthy choice* between the two sessions (healthy choice > unhealthy choice$_{post > pre}$) for each participant at the first level. At the second level, we

compared this session difference between placebo and verum group via two-sample t-tests (HealthyChoice > UnhealthyChoice: $VER_{post > pre} > PLC_{post > pre}$ and $PLC_{post > pre} > VER_{pos > pre}$). Note, that we did not find any significant results after FWE-correction at the cluster level.
In a more exploratory analysis with a liberal threshold ($p_{uncorrected} < 0.001$, $k \geq 5$), we did also not find any region with a significant BOLD signal for HealthyChoice > UnhealthyChoice in the contrast $PLC_{post > pre} > VER_{pos > pre}$. For the inverse contrast $VER_{post > pre} > PLC_{pos > pre}$, we found a significant cluster of 7 voxels ($k_{grey\ matter} = 6$) in the left ACC ($t_{max(93)} = 3.33$, MNI peak: x = -9, y = 36, z = -6, $p_{uncorrected} < 0.001$, $k \geq 5$, Fig. 22B). This ACC cluster does not overlap with the vmPFC map from Bartra et al. as depicted in Fig. 18B. For illustration purposes we plotted the extracted betas from this ACC cluster (Fig. 22B). The boxplot shows that the average beta in the ACC decreased for the placebo group, while it increased in the verum group from pre to post intervention.

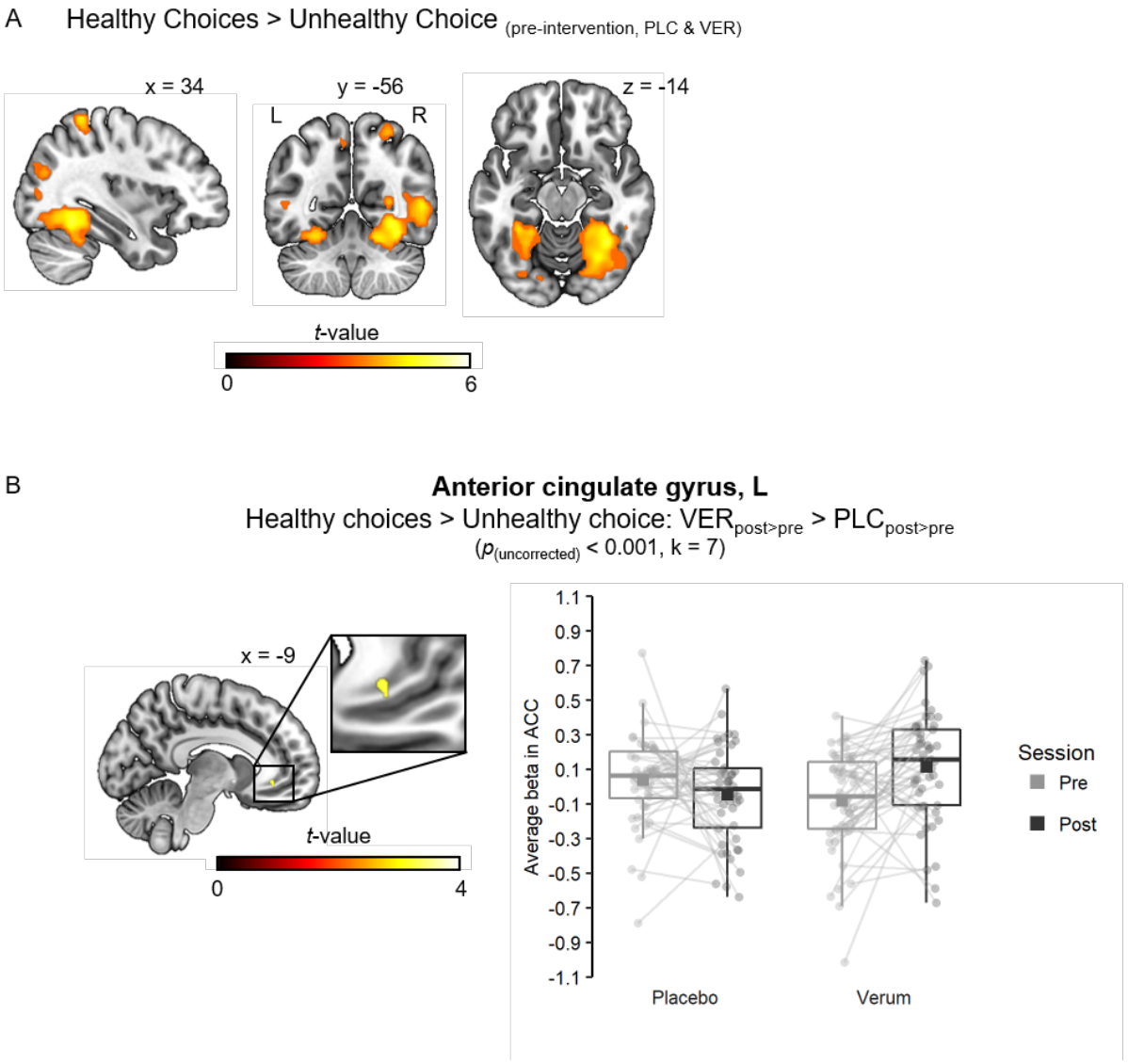

Fig. 22: BOLD signal for Healthy vs. Unhealthy Choices. (A) The statistical parametric map shows the result of the whole-brain analysis for BOLD signal associated with healthy vs. unhealthy choices across all trials and participants at the pre-intervention timepoint (FWE-corrected at the cluster level ($p < 0.05$) with a cluster-defining threshold of $p < 0.001$). (B) An exploratory and uncorrected whole-brain analysis (uncorrected at $p < 0.001$) revealed a significant interaction of treatment and session for the contrast Heathy Choice vs Unhealthy Choice. The boxplot displays the average beta estimate in the left anterior cingulate gyrus for each session and group for visualization purposes only and does not represent a statistical test. The vertical lines of the boxplots depict the median and the squares show the mean. The individual data points of each participant are shown in light grey and are connected via lines for the two sessions. T-maps are overlayed on the MNI152 template brain. L, left; R, right; PLC, placebo; VER, verum.

3.5 Discussion

3.5.1 Food Choice Behavior and the impact of the synbiotic intervention

We hypothesized that a seven-week synbiotic intervention affects eating behavior by leading to healthier food choices, which may in turn be beneficial for a healthy body weight. Our behavioral findings did not confirm this hypothesis. The proportion of healthy choices in our experimental food choice task did not change differently for the placebo and the verum group from pre- to post-intervention. We confirmed this null-result with a Bayesian analysis, which yielded substantial evidence in favor of the null-hypothesis. Moreover, we did not find any effect of the synbiotic intervention on self-reported cognitive restraint, disinhibition, or hunger assessed via the TFEQ.

To be able to reliably interpret the relevance of these findings, we need to highlight two methodological aspects of the food choice task:

First, our food choice paradigm is well suited to repeatedly assess choice behavior in intervention studies. Previous research demonstrated a high test-retest reliability across several task repetitions for up to one month irrespective of whether participants could chose naturally or were cued to make healthy choices (Barakchian et al., 2021; Foerde et al., 2018). In these studies, proportion of healthy choices, the effect of attribute-differences (health and taste) on choice, as well as taste- and health-ratings remained stable over time.

Second, independent of the synbiotic intervention, we found a significant, positive correlation between the proportion of healthy choices and self-reported cognitive restraint in the TFEQ. This correlation nicely parallels a previous result by Maier & Hare (2017). Cognitive restraint is a widely used measure for the ability to withstand the temptation of tasteful food stimuli (Laessle et al., 1989; Maier and Hare, 2017; Williamson et al., 2007). In line with this, a previous study also showed a negative correlation of the WTP for unhealthy food items and healthy eating behavior during daily life (Merchant et al., 2020). Studies on patients in a behavioral weight-loss program showed that higher cognitive restraint was associated with lower energy intake and with the ability to maintain weight loss (Keränen et al., 2011; 2009).

All together, these methodological aspects back up the construct validity and the ability of our task to measure meaningful changes in habitual eating behavior.

Therefore, our above-mentioned results conclusively suggest that the synbiotic intervention did not lead to a healthier eating behavior that could either be capture in self-reports or in our experimental paradigm. This conclusion is further supported by the participant's dietary records of the 3 days before each experimental session. The analysis of the dietary records is part of another sub-project of our study and detailed results are outside of the scope of this thesis. However, results from the dietary records showed that the synbiotic intervention did not lead to significant changes in energy, carbohydrate, protein, or fat intake (Köhlmoos, 2020).

In line with the stable eating behavior, we did also not find any effect of the synbiotic intervention on BMI and proportion of body fat. On the one hand, the stable BMI and proportion of body fat confirm that the synbiotic intervention did not lead to any substantial changes in eating behavior that remained undetected in our tasks. On the other hand, the null effect on BMI and proportion of body fat suggests that the synbiotic intervention did not have any profound effects on metabolism that affected body composition and health independent of eating behavior.

There is extensive research in animals and humans showing that gut microbial composition affects body weight and health (Brahe et al., 2016; Le Chatelier et al., 2013; Turnbaugh et al., 2009; 2006). However, positive findings from interventions in humans, such as probiotics, prebiotics, or synbiotics, are scarce and heterogeneous (Boscaini et al., 2021; John et al., 2018; Koutnikova et al., 2019). According to two recent meta-analyses, we can not necessarily expect measurable changes in body weight, BMI, or proportion of body fat after a few weeks (John et al., 2018; Koutnikova et al., 2019). Such effects rather strongly depend on dose, intervention duration, species included in the supplementation, as well as BMI and metabolic status of participants at the start of the intervention (John et al., 2018; Koutnikova et al., 2019). We can also not rule out that the duration of our intervention was too short for any subtle effects to be already reflected in anthropometric measures.

Nevertheless, the synbiotic intervention might induce changes in food valuation that are not immediately manifested in measurable eating behavior or anthropometrics. Therefore, we

analyzed different aspects of food valuation that were shown to be relevant for a healthy dieting behavior (Demos et al., 2017; Hare et al., 2011a; Sullivan and Huettel, 2021). These aspects included taste- and health-ratings, responsiveness to taste and health attributes during decision-making, and reaction time during food choices.

First, we did not find any effect of the synbiotic intervention on subjective taste- and health-ratings of snack food items. Average taste- and health-ratings across all snack food items remained unchanged. Moreover, the synbiotic intervention did also not affect ratings of healthy and unhealthy food items differently. These findings on the one hand suggest that the synbiotic intervention did not change common, intuitive beliefs about healthy food to be less tasty (Mai and Hoffmann, 2015; Raghunathan et al., 2006). On the other hand, our findings suggest that the synbiotic intervention did not lead to changes in expected subjective liking of snack food items. We cannot draw any conclusions about the sensory perception of food as the participants did not taste the products. Taste-ratings were purely based on visual and thus exteroceptive food cues (Piqueras-Fiszman and Spence, 2015). Studying the effects of a synbiotic intervention on sensory perception of food during actual consumption and its relevance for dietary choices would though be interesting for future studies. There is emerging evidence that gut microbes can affect the sensory properties of taste receptors via different mechanisms including immunological, hormonal, and metabolic pathways (Leung and Covasa, 2021).

Next, we focused on taste- and health-ratings as essential drivers of dietary choices. Independent of the synbiotic intervention we found that difference in taste and health attributes between the two choice options significantly explained food choices. This result parallels previous studies and shows that participants made reasonable choices based on their preferences. Moreover, participants considered our instruction to choose healthy because without such a health cue, only taste but not health attributes would strongly impact choice (Barakchian et al., 2021; Hare et al., 2011a; Rramani et al., 2020b).

Interestingly, the synbiotic intervention increased the responsiveness to taste-differences but not health-differences between choice options. Taste responsiveness means how strongly the taste-difference between the two choice options affects the probability of choosing one option over the other. In the verum group, the impact of taste-difference on choice increased

stronger from pre- to post-intervention than in the placebo group. This increased impact of taste occurred across all choices but also specifically when making healthy choices. We did not observe any differences between the placebo and the verum group in health responsiveness.

Similarly, previous research demonstrated that stressed participants had a higher responsiveness to immediately rewarding taste of food items. This way, stress also increased the probability of making unhealthy choices (Maier et al., 2015). On the other side, a clinical behavioral weight-loss intervention led to a decrease in the impact of taste on food choices and at the same time increased the impact of health leading to more healthy choices (Demos et al., 2017). Cueing participants to consider the healthiness of their choices instead of letting them choose naturally also decreased taste responsiveness and increased health responsiveness (Hare et al., 2011a). On this basis, we propose that our synbiotic intervention selectively enhanced reward sensitivity for immediate taste temptations but left long-term health considerations unaffected.

Puzzlingly, although the synbiotic intervention increased taste responsiveness this did not affect the ability to make healthy choices as the proportion of healthy choices remained stable. The increased responsiveness to taste was thus too subtle to translate into unhealthier choices. Participants were probably still able to regulate their choices sufficiently by cognitive inhibition mechanisms (Appelhans et al., 2011; Hare et al., 2009; Maier et al., 2015). For this line of reasoning, we would assume that the synbiotic intervention did not (negatively) affect cognitive control mechanisms. This is in accordance with a recent study showing that self-control assessed via a questionnaire did not change after a 28-day probiotic intervention (Dantas et al., 2021). Interestingly, in the same study they found a significant decrease in delay-discounting and thus more future-oriented monetary choices after the probiotic intervention. Similarly, a pilot trial in fibromyalgia patients showed a significant decrease in impulsive behavior after an 8-week probiotic treatment (Roman et al., 2018).

We initially hypothesized that the synbiotic intervention would facilitate healthier choices, which makes sense in the light of the previously reported increased future-orientation and cognitive control (Dantas et al., 2021; Roman et al., 2018). Now, that we did not observe healthier choices but instead a higher taste responsiveness, one could wonder whether this

contradicts the previous findings on increased future-orientation and cognitive control. However, considering the vast amount of communication pathways of the Gut-Brain axis, we rather think that there might be different microbial mechanisms at play in parallel (Cryan et al., 2019; Plassmann et al., 2021). These mechanisms might independently from each other affect taste responsiveness and cognitive control and do not necessarily need to be beneficial for a healthy eating behavior. The microbial mechanisms might not even be specifically targeted to manipulate the host's eating behavior in favor of microbial survival, as it is discussed in literature (Alcock et al., 2014; Stilling et al., 2016). Effects on dieting-related behaviors might rather be by-products of local microbial competition (Johnson and Foster, 2018). Effects on taste responsiveness could for example arise from microbiota induced homeostatic changes that signal specific nutritional and metabolic needs or directly act on reward processing pathways (Ezra-Nevo et al., 2020; García-Cabrerizo et al., 2021; Gupta et al., 2020; Leitão-Gonçalves et al., 2017; Morrison et al., 2012).

If probiotic and synbiotic treatments positively affect behavioral control mechanisms while at the same time enhancing responsiveness to taste rewards, both effects could balance each other out when making food choices. Our instruction to consider the healthiness of the food during choices might have even extrinsically increased participants effort to regulate their responsiveness to taste reward. Thus, this balance would explain why we do not observe any significant change in healthy choice behavior.

We next investigated the effect of the synbiotic intervention on choice times. First, we found that with increasing choice difficulty due to higher similarity between the choice options, choice times increased. We observed this link between the similarity of choice options and choice times consistently for similarity measured as value-difference and health-difference and to a weaker and not significant extend also for taste-difference. These observations exactly parallel previous findings and highlight that participants made reasonable choices (Maier et al., 2015; Sullivan and Huettel, 2021).

Moreover, irrespective of the synbiotic intervention, we observed that choice times decreased from pre- to post-measurement in the placebo group. However, this trend was only significant when excluding choice time outliers. Decreased choice times in repeated measurements

have been observed before and are to be expected as the experience with the task increases (Barakchian et al., 2021).

Interestingly, choice times in the verum group decreased significantly stronger from pre- to post-intervention than in the placebo group. Hence, our synbiotic intervention led to quicker food choice while the overall healthiness of the choices remained stable.

As previously mentioned, Maier et al. (2015) reported that stress increased taste responsiveness. At the same time, stress also increased the impact of taste on choice time. For stressed participants choice times increased even stronger with increasing taste-difference than for non-stressed participants (Maier et al., 2015). While our synbiotic intervention also increased taste responsiveness, we did not find such a specific effect of the synbiotic intervention on choice times in response to taste-differences. The decrease in choice times due to the synbiotic intervention was similar across different levels of taste- and health-differences. Moreover, individual changes in choice time (from pre- to post-intervention) did not correlate with changes in individual beta weights for taste-difference. Together, this suggests that the faster choice times do not simply reflect the increased taste responsiveness due to the synbiotic treatment. Instead, faster choice times might be indicative of another independent effect of the synbiotic intervention on decision-making. It is conceivable that the synbiotic intervention might have decreased deliberation and cognitive effort or increased choice certainty or confidence (Alós-Ferrer and Buckenmaier, 2021; Clairis and Pessiglione, 2021; Uggeldahl et al., 2016). Theoretically, decreased choice times could also be an indicator of decreased motivational effort and less interest in the task. However, this is an unlikely explanation since the choices remained equally reasonable.

We also looked at the taste- and health-rating times to see whether participants became consistently faster not only when choosing between foods but also when rating different food attributes. We found that health-rating times decreased significantly stronger in the verum group as compared to the placebo group while taste-rating times did not change differently for the two groups. As taste-rating times were not affected by the synbiotic intervention, it is unlikely that a decrease in motivation is the cause of the faster choices and faster health-ratings. We would expect motivational changes to occur consistently across all tasks and not only specifically for choices and health-ratings.

Nevertheless, we can only speculate why the synbiotic intervention facilitated quicker health-ratings but not taste-ratings. Health-ratings are more objective and knowledge-based than taste-ratings. When asked repeatedly, taste-ratings vary stronger from one assessment to the next and depend on context, satiety, and past consumption experiences (Barakchian et al., 2021; Polanía et al., 2019). On this basis it is conceivable that the synbiotic intervention enhanced the ability to confidently retrieve objective information but not the ability to subjectively assess momentary taste preferences. Feeling more easily confident about the healthiness of food items might also enable faster food choices as it increases the feeling that all relevant information for choice is available. This might not necessarily mean that the health information also sufficiently contributed to the choice process and enabled more healthy choices. In contrast, shorter choice times have rather been associated with a lower impact of health attributes on the decision (Sullivan and Huettel, 2021). Note however, that this suggested causal link of faster health-rating times leading to faster choice times is highly speculative. Our study design does not allow to test for a causal relationship. Although a correlation analysis showed a positive association between the changes in health-rating times and the changes in choice time, this trend did also not become significant.

Overall, our findings on choice and ratings times are of rather exploratory nature as we did not pre-register to analyze them and did not have any prior hypothesis. Therefore, these results and their interpretation need to be considered with caution and a replication is highly advisable. Based on our data, we can also not make any statement about whether the synbiotic intervention effects on choice and rating times occur specifically for dietary decision-making or also affect other decisions.

3.5.2 Neural correlates of dietary decision-making and the impact of the synbiotic intervention

With our fMRI analysis we sought to investigate the neuronal mechanisms of attribute- and value-guided food choices and in particular the impact of the synbiotic intervention on these neuronal mechanisms. We aimed at finding complement evidence in the brain data that

support and mechanistically explain the behaviorally observed increased relevance of taste in food choices after the synbiotic intervention.

First, to better understand key neuronal mechanisms of food choices and potential targets for the synbiotic intervention, one needs to briefly take a closer look at the theoretical framework of food choices:
As food choices are multi-attribute decision-making problems, they require the assessment of the two attributes health and taste (Maier et al., 2020; Sullivan et al., 2015; Sullivan and Huettel, 2021). A decision maker first needs to assess and subjectively weigh each attribute separately before integrating the individual attribute-weights into an overall subjective value of each item (Lim et al., 2013). Thus, the overall subjective value of each food item considers both immediate (taste) as well as long-term (health) consequence (Rangel, 2013). By comparing the overall subjective value of both food items, the option with the highest overall goal-directed value can be chosen to maximize satisfaction (Kable and Glimcher, 2009; Rangel, 2013; Rangel and Hare, 2010).
The synbiotic intervention could theoretically alter the neuronal mechanisms of food choices at two distinct levels of this framework: (i) at the integration-level by affecting the formation of an overall goal-directed value of each item and/or (ii) at the individual attribute level by modulating attribute specific representations and valuations.
We used two different GLMs to assess potential changes after the synbiotic intervention at both levels. Before specifically looking at the impact of the synbiotic intervention on brain activity we will first, for both GLMs, discuss neural correlates of food choice independent of our intervention for task validation and theoretical context. Moreover, we will discuss the relation of these neural correlates with metabolic status and healthy choice behavior to identify potential relevant inter-individual differences.

Neural correlates of chosen value

First, with GLM1, we focused on (i) the formation of an overall goal-directed value. Irrespective of our intervention, we were able to confirm the well-established idea that the overall integrated decision value is reflected in the vmPFC (Bartra et al., 2013; Hare et al.,

2009; Litt et al., 2011; Maier et al., 2015; Plassmann et al., 2010; 2007). The overall value of the chosen item positively correlated with activity in the vmPFC. This value-related vmPFC activity completely overlapped with a meta-analysis derived vmPFC mask from Bartra *et al.*, 2013. This vmPFC mask represents a brain region that was consistently activated by modality-independent (i.e. monetary and primary) subjective value across several studies. This strong overlap of our value-related vmPFC signal with observations in literature clearly validates that our implementation of the food choice task can elicit robust neuronal valuation processes. The modality-spanning nature of valuation processes in this vmPFC area (often termed "common currency") emphasizes the neuronal similarity between different valuation processes (Levy and Glimcher, 2012). Therefore, this vmPFC area is highly relevant for decision-making in general and might be a key region along the Gut-Brain axis for gut-derived effects on decision-making.

The 1234 voxel cluster containing the vmPFC also spanned dorsally and partially overlapped with the dlPFC mask used in Hutcherson et al., 2012. The small overlap with the dlPFC confirms previous literature suggesting that vmPFC and dlPFC act in concert for modality-independent valuation and value comparison (Litt et al., 2011; Morris et al., 2014; Plassmann et al., 2010; 2007; Sokol-Hessner et al., 2012). Note however, that our dlPFC cluster did not cover the peak-voxels that were previously shown to correlate with WTP and goal value (Plassmann et al., 2010; 2007). This discrepancy supports the notion that activity in dlPFC correlates less consistently with the decision value than activity in the vmPFC (Sokol-Hessner et al., 2012). In our whole-brain analysis, we did not find any activity correlating with the chosen value in the amygdala or vStr. Amygdala and vStr. have been linked to subjective valuation processes (Bartra et al., 2013; Maier et al., 2015), but apparently less consistently as it is the case for the vmPFC (Christensen et al., 2021; Hare et al., 2009). Therefore, not finding any correlation of the chosen value with activity in vStr. or amygdala might be explained by differences in task design, instructions, or study population.

In a next step we wanted to further describe the valuation processes in the vmPFC and determined whether inter-individual differences in health-related characteristics relate to differences in vmPFC activity. Such a correlation would by no means imply causation in any direction but could be a starting point to better understand the complex construct of unhealthy

eating behaviors in the context of Gut-Brain communication. We decided to focus on (i) proportion of body fat as a proxy of metabolic health (Grundy et al., 2008; Zhu et al., 2003) and (ii) the proportion of healthy choices in our food choice task as a proxy of health-awareness and healthy choice behavior (Foerde et al., 2020). Neither proportion of body fat nor the proportion of healthy choices in the food choice task correlated with the average beta in the vmPFC. Thus, the metabolic status and healthy choice behavior of a person seems not to be associated with value signals in the vmPFC. This null finding corroborates recent observations from Merchant et al., 2020 in a sample of middle-aged (35-45 years) adults with an overweight to extremely obese BMI (25 - 40 kg/m^2). Instead of proportion of body fat as metabolic health marker and proportion of healthy choices as proxy of healthy behavior, Merchant et al., 2020 used BMI and a Healthy Eating Index (HEI) from a Dietary Assessment tool, respectively. They did not find any relationship of valuation in vmPFC with BMI and the HEI. As the HEI index was assessed during several days prior to the experiment, it is even a much stronger representation of daily eating behavior and more ecologically valid than the healthy choices in our laboratory task. Still, a modulatory effect of proportion of body fat or healthy choice behavior on the impact of the synbiotic intervention on neuronal valuation processes cannot be excluded at this point.

On the behavioral level, Merchant et al., 2020 did not find a relationship of the self-reported valuation of unhealthy food with BMI. However, when focusing not on the overall item value but the weight that participants put on the taste-difference of items (healthy and unhealthy ones) during their food choices, we found this weight to be negatively correlated with proportion of body fat (see chapter 3.3.6). Thus, on the behavioral level, not the overall food valuation but rather the importance of individual food attributes, such as taste in our case, seemed to relate to proportion of body fat. Participants with more proportion of body fat weighted the taste-difference of food items less during their food choices. This inverse relation seems to contradict previous observations: For example, obese individuals were more impulsive in general but also specifically towards food (Nederkoorn et al., 2006; Schag et al., 2013; Schiff et al., 2016). Participants, who valued taste or unhealthy items more strongly, showed a less healthy dieting behavior (Kourouniotis et al., 2016; Merchant et al., 2020). This discrepancy between our finding and previous literature might be caused by our

instruction to consider healthiness during the food choices. Shifting attention more towards the healthiness of food items might be more effective in participants with a higher proportion of body fat, who are probably more weight- and health-concerned.

Next, we move on from the more general relation of metabolic and behavioral factors with neuronal valuation to the influence of the gut microbiota in particular. With our study, we wanted to elucidate whether the 7-week synbiotic intervention modulated the overall value formation during food choice in the vmPFC. We conducted a ROI analysis with a mask of the vmPFC and found no intervention-induced differences in the average extracted betas from this vmPFC mask. Neither for the verum group, nor for the placebo group the correlation between chosen value and vmPFC activity changed after the 7-week intervention. We additionally conducted a whole-brain analysis to not overlook any changes due to the synbiotic intervention outside of the vmPFC. Note, that we did not add covariates for BMI, age, or hunger, as recommended by Smeets et al., 2019, in any whole-brain analysis discussed in the following. Our whole-brain analysis did not yield any brain areas where the synbiotic intervention significantly changed the correlation of the BOLD signal with the chosen food value in any direction after correcting for multiple comparisons at the cluster level. Due to our study being the first to investigate the impact of a synbiotic intervention on neural correlates of food choices, we decided to additionally examine the results at a statistical threshold of $p < 0.001$ uncorrected. We based this decision on the following reasons: Especially for novel research questions without prior effect size estimates, it is important to offset Type I and Type II error rates in univariate whole-brain analyses (Lieberman and Cunningham, 2009). Focusing only on avoiding Type II errors (false positive results) by employing a stringent correction threshold might leave very small but still meaningful effects unrecognized due to a higher risk of Type I errors (false negative results). By applying a more lenient threshold, any emerging possibly true or false positive effect should be follow-up by a replication attempt. In case of a successful replication, the possibility for a more targeted investigation of the effect is granted. Moreover, any impact of a dietary interventions, particularly in neuroimaging, is expected to be highly reliant on thus far largely unknown inter-individual baseline differences in behavior and metabolism (Healey et al., 2017). These inter-individual variability in intervention responsiveness might obscure a potential true positive

effect of the synbiotic intervention in case of a too stringent threshold and calls for explorative analyses with an uncorrected threshold. Still, due to the non-replicated and thus unconfirmed nature of our explorative whole-brain findings, all uncorrected results need to be considered and discussed with caution. Clusters that only or predominantly consisted of voxels in white matter, as indicated in the results section, are not further discussed here.

The explorative whole-brain analysis for the interaction effect of treatment x session on the correlation of BOLD signal with the chosen value revealed a cluster in the right rolandic operculum. In this cluster, the value-related activity increased for the placebo group from pre- to post-measurement while it seemed to be attenuated by the 7-week synbiotic intake. To our knowledge, the rolandic operculum is not described in the (food) valuation literature. However, previous meta-analyses and reviews have pointed at a role of the rolandic operculum for gustatory processing during the anticipation of food and for action planning when overriding temptations (Ha et al., 2020; Han et al., 2018a; Veldhuizen et al., 2011). Thus, one could speculate that the weakened coupling between rolandic operculum activity and chosen value in the verum group, as opposed to the placebo group, could reflect less processing of the anticipated gustatory stimuli or a mitigated regulation of cravings for food items of high value. However, these theories would not explain the behaviorally observed increased relevance of taste while the proportion of healthy choices remained stable. Moreover, this kind of reverse inference from the observed brain activity to the engaged mental process underlying this activity, is critical at this point and purely speculative (Poldrack, 2011; Smeets et al., 2019). This applies in the same way to the following discussion of the results from the other GLMs.

From the analyses of GLM1 we can mainly conclude that the synbiotic intervention did not alter food valuation at (i) the integration level. The synbiotic intervention did not affect the overall goal-directed value formation in the vmPFC or any other brain regions implicated in subjective valuation (i.e. amygdala, dlPFC, vStr.). Interestingly, this finding echoes prior work, which established that neither stress (Maier et al. 2015), attention cues (Hare et al., 2011a), nor cognitive regulation (Tusche and Hutcherson 2018) affected the valuation processes in the vmPFC but rather the individual attribute representation. These consistent observations

suggest that the overall value formation in the vmPFC might be more robust to modulations by external or internal environment than the representation of individual attributes.

Neural representation of taste and health attributes

In the next step, we used a second GLM, to focus on (ii) the individual attribute representations in the brain. GLM2 contained a regressor for all choice trials with two parametric modulators, one for the taste-rating and one for the health-rating of the chosen food item, while controlling for taste- and health-difference (chosen – non-chosen). Our approach allowed us to examine the relevance of health and taste attributes for the overall value formation of the chosen item (Medic et al., 2016). We investigated the potential impact of metabolism, healthy behavior and synbiotic intervention on this attribute integration.

Independent from our intervention, the taste of the chosen food item positively correlated with activity in broad clusters encompassing vmPFC, dlPFC, left precuneus, and ACC, which confirms previous data (Hare et al., 2011a; van der Laan et al., 2021; van Meer et al., 2017). Activity in vmPFC and dlPFC largely overlapped with clusters related to the chosen value from GLM1. These overlaps support the idea that the vmPFC signals both, taste- and health-ratings as well as the integrated value of food items (Hare et al., 2011a).

In contrast to some previous studies (Hare et al., 2011a; 2009; Londerée and Wagner, 2020; van Meer et al., 2017), health of the chosen item did not correlate with BOLD signal in vmPFC or dlPFC but only with signal in the left middle occipital gyrus and left inferior parietal gyrus. As already discussed by van der Laan et al., 2021, who also did not find a correlation of health-ratings with vmPFC or dlPFC activity, this discrepancy might arise from differences in participant instructions or analyses. Unlike studies that found health to be correlated with dlPFC or vmPFC activity, we instructed our participants to make healthy choices instead of simply choosing naturally and we did not exclusively focus on participants with high levels of self-control (Hare et al., 2011a; 2009).

Medic *et al.* also found that not the health of foods but only the taste significantly contributed to the value signal in the vmPFC. Interestingly, they observed a larger inter-individual variability for the influence of health than the influence of taste for the vmPFC signal. This

inter-individual variability might explain why health attributes are only inconsistently reflected in vmPFC activity across different studies and different study populations.

Therefore, a next interesting step is to characterize taste- and health-related BOLD signal in GLM2 further regarding individual differences in proportion of body fat and health choice behavior. We built two ROI masks encompassing several brain areas relevant for food attribute assessment that were shown to be potential targets for peripheral or metabolic factors (Bagga et al., 2019; Christensen et al., 2021; Gupta et al., 2020; Maier et al., 2015; Merchant et al., 2020; Plassmann et al., 2021; Tillisch et al., 2013). The valuation ROI mask included vmPFC and vStr and the emotional/salience ROI mask included parahippocampus, hippocampus, amygdala, insula, and ACC.

Proportion of body fat was not correlated with the average extracted betas for chosen taste and chosen health, neither in the valuation nor in the emotional/salience ROI. Previous research demonstrated that the processing of taste- and health-attributes, regarding their temporal integration into choice, differed depending on BMI (Lim et al., 2018). Our results could not confirm any BMI-related differences of taste and health integration on the neural level. However, our result agrees with the finding from Medic et al., who showed that the extend with which taste and health attributes contributed to vmPFC activity did not differ between lean and overweight participants (Medic et al., 2016). We extended this finding from the vmPFC to brain regions signalling emotions and salience.

The proportion of healthy choices that participants made in our food choice task positively correlated with the average extracted betas for chosen taste in the valuation as well as the emotional/salience ROI. Participants with more healthy choices had a stronger correlation between taste of the chosen item and BOLD signal in the valuation and emotional/salience ROIs. It seems that a healthier choice behaviour is linked to a stronger neuronal reactivity to taste in a wide range of brain areas involved in signalling salience, motivation, and value. For chosen health, the average extracted betas in the valuation ROI showed a significant negative correlation with the proportion of healthy choices. The negative directionality of the correlation was the same for the emotional/salience ROI, although not large enough to be significant. In other words, making more healthy choices in our food choice task was associated with less reactivity to the chosen health in the valuation ROI. Note, that these

results do not imply any causation. Interestingly, Hare et al., 2009 demonstrated that in self-controllers (a classification which could roughly relate to making many healthy choices in our task) vmPFC activity positively reflected taste- as well as health-ratings, while in non-self-controllers vmPFC activity only reflected the taste-ratings. This result by Hare et al., 2009 conflicts with our observation. This conflict might arise from methodological difference in the choice task or from the possibility that the classification of self-controller vs. non-self-controller catches a different behavioral component as the proportion of healthy choices does. Nevertheless, the ecological validity of the relation of healthy choices/self-control with neural responsiveness to health and taste needs to be considered with caution. The proportion of healthy choices (as well as the classification as self-controller or non-self-controller) is derived from the same choices as is the BOLD signal. Any association of these two might be founded in a causal relation due to the nature of the task itself and must not necessarily reflect neural mechanisms of eating decisions outside of the laboratory. Indeed, when relating the vmPFC health beta from a fMRI food choice task to healthy food consumption at an *ad libitum* buffet, the correlation was the opposite and significantly positive (Medic et al., 2016). To confirm our result and make a better statement about how habitual eating behavior relates to neural representation of food attribute, a validated measure of diet quality, like the healthy eating index (Krebs-Smith et al., 2018), could be used.

In the next step, we focused on the impact of the synbiotic intervention on taste and health representation in the brain. Our behavioral results indicated that the synbiotic intervention enhanced the relevance of taste-difference for food choices on the behavioral level. However, the extracted average betas for chosen taste and chosen health in the valuation and the emotional/salience ROIs were not affected differently after placebo or synbiotic intervention. In other words, the representation of the chosen taste and health, at least in these brain areas, was neither weakened nor strengthened due to the intake of the synbiotic.

We further explored synbiotic intervention effects on the whole-brain level to confirm the ROI analyses and to also investigate unpredicted brain regions outside of our ROIs. This whole-brain analysis did not yield any brain areas where the synbiotic intervention significantly changed the correlation of the BOLD signal with the chosen taste or health after correcting for multiple comparisons at the cluster level. At a more exploratory and uncorrected threshold

of $p < 0.001$ (as justified above), we found a cluster in the IFG (BA 46). In this cluster, the correlation of the BOLD signal with chosen taste was significantly affected by the interaction of treatment x session. More specifically, the correlation of the BOLD signal with the chosen taste was increased after the placebo treatment but decreased after the synbiotic treatment. This could lead to the cautious conclusion - while keeping the explorative nature of this analyses in mind - that the synbiotic intervention attenuated taste responsiveness in the IFG. In a positron emission tomography (PET) study, eating chocolate in a satiated as compared to a hungry state led to increased blood flow in the IFG (Small et al., 2001). Due to IFG and BA46 being known for their role in cognitive control (Aron et al., 2004; Friedman and Robbins, 2022) an increased correlation of chosen taste with BOLD signal in this region might reflect the inhibition of behavior, e.g. the inhibition of the urge to choose based on taste rather than health. Interestingly, Hampshire et al., 2010 found that activity in the right IFG reflected the detection of a relevant salient cue (like taste of a food item) but not necessarily the successful inhibition of a response to that cue. Regarding our synbiotic intervention, we could presume that a decrease of activity in the right IFG in response to the chosen taste means that the saliency of taste is experienced as less critical for a required response inhibition. Put differently, there might be less immediate need for a response inhibition when detecting the taste of the food item. Small et al., 2001 showed that blood flow in the IFG was lower in the hungry state and inferred that there was no need to inhibit feeding when hungry (Small et al., 2001). Similarly, our synbiotic intervention might have also reduced the need to disregard the salient taste aspects of snack food items. This would be in line with the behavioral finding that the taste-difference between the two food items had a stronger impact on the choices. Within our line of reasoning, this could mean that there might be a causal process at play: the synbiotic intervention alleviated the neuronal inhibition in response to taste cues and thus increased the behavioral relevance of taste for food choice. Overall, this increased relevance of taste was though not strong enough to lead to unhealthier choice behavior. However, due to the explorative nature of our analyses, this proposed theory is highly speculative.

In the exploratory whole-brain analysis for the correlation of chosen health with the BOLD signal (uncorrected $p < 0.001$) we found a few regions where the correlation changed differently from pre- to post-intervention for the two groups. These regions included ACC and

bilateral postcentral gyri. Correlations of the chosen health with BOLD signal in these regions became stronger for the placebo group while it weakened for the verum group after the intervention. Activity in ACC has previously been shown to positively correlate with health-ratings in a natural choice condition without any instruction to make healthy choices (Hare et al., 2011a). Hare et al., 2011 concluded that the ACC does not only signal the overall choice value (Bartra et al., 2013; Levy and Glimcher, 2012), but also the individual attribute values. This representation of the health attributes in the ACC seems to get stronger in the placebo group after repeated exposure to the food choice task, while the verum seems to have prevented this strengthening of health representation.

The two significant clusters in the bilateral postcentral gyri are striking because observing clusters at both literalities makes it less likely that it is only a false positive finding. The precentral gyri cover the primary sensory and motor areas of the brain. Past research has shown that viewing food images as opposed to non-food images, perceiving chocolate odor, and exerting mental effort to avoid unpreferred food items elicited, among other, activity in the postcentral gyri (Han et al., 2021; Nakamura et al., 2020; Wegman et al., 2018). Thus, the postcentral gyri seem to be relevant for evaluating visual and olfactory food cues, as well as motor control during food approach. Based on the behavioral finding that the synbiotic intervention decreased the health-rating time (as well as the food choice time), one could speculate that a weakened correlation of health-rating with BOLD signal in the postcentral gyri indicates a less effortful evaluation of the healthiness of the choice options while viewing the images.

Neural correlates of healthy choices

Due to the puzzling observation that the proportion of healthy choices remained unaffected from the synbiotic intervention, we finally also estimated a GLM with two regressors distinguishing the two types of choices: healthy choices and unhealthy choices.

With this GLM3 we wanted to elucidate whether any brain regions react differently to healthy choices as opposed to unhealthy choices after the synbiotic intervention. These do not necessarily need to be brain regions that would make it easy (or difficult) to choose healthy (like cognitive control processes in the dlPFC), as the choice behavior was not changed, but

it could include brain regions that signal conflict, pleasure, or disgust. This could tell us for example, whether choosing healthy caused aversion or came at a higher mental effort.

Independent from our synbiotic intervention, in the data of both groups at the first session, we found several brain regions to be stronger active in healthy choice than unhealthy choices. These areas included, among others, bilateral fusiform gyrus, left inferior parietal gyrus, right inferior temporal gyrus, and bilateral superior parietal gyri. This agrees in large parts with a study by Harding et al., (2018) and other literature on food choice (Hare et al., 2011a; 2009; Medic et al., 2016). However, our results disagree with this literature to some degree as we did not observe any activity for healthy choices in dlPFC, OFC, or cingulate cortex. This may be because we analyzed healthy choices across all trials and did not specifically focus on conflict trials in which the healthier food item is less tasty than the unhealthy food item. This means our analysis also included easier trials where it is directly clear to the participant which item is healthier and at the same time tastier. Thus, less cognitive control and less weighing and value comparison is necessary to make a healthy choice.

In a whole-brain analysis we did not find any brain areas where the synbiotic intervention significantly changed the brain response to healthy choices in any direction after correcting for multiple comparisons at the cluster level. Thus, we again conducted an exploratory whole-brain analysis at an uncorrected statistical threshold of $p < 0.001$. At this exploratory threshold, we found a significant interaction of treatment x session on activity in the left ACC in response to healthy as compared to unhealthy choices. While the activity in this ACC cluster slightly decreased for the placebo group, it increased instead for the verum group after the 7-week intervention. A vast amount of research proposed a role of the ACC in cognitive control, specifically for performance and conflict monitoring in critical situations with a higher risk for errors, including also food choices. (Botvinick et al., 2001; Carter et al., 1998; van der Laan et al., 2014; MacDonald et al., 2000; Mulert et al., 2003; Van Veen et al., 2001). Further, ACC activity reflected conscious mental effort (Mulert et al., 2005) and the selection of less preferred food items (Christensen et al., 2021). Thus, the ACC seems to be relevant for overcoming a mental conflict between preferred and unpreferred items. Based on this literature, it is not too farfetched in our eyes, to suggest that the increased activity in ACC signifies that choosing healthy was a stronger conflict and required more mental effort after

the verum treatment. By employing this increased mental effort and strongly monitoring the choice situation, participants seemed to be able to roughly maintain their level of healthy choices although taste gained stronger impact on their choices.

However, the decreased choice time is still puzzling in this context. Our data as well as prior studies have established that higher response conflict and task difficulty are accompanied by increased rather than decreased reaction times (van der Laan et al., 2014; Panayiotou and Vrana, 2004). We have two ideas that might explain these contradictory results: First, since also health-rating time was decreased significantly, it might have become easier for the participants to assess the health of the two options during the food choices. As already discussed above (see chapter 3.5.1), this might have allowed them to also make quicker choices despite the higher conflict and increased mental effort. Second, the significantly decreased choice time (as well as the health-rating time) in the verum group could stem from the large, although not significant, difference in rating and choice time between placebo and verum group before the intervention already. Due to the repeated conductance of ratings and choices, participants of both groups where familiar with the tasks and became quicker when doing the task for the second time after the intervention. However, the relative decrease in rating and choice time might have been restricted by a physiological lower limit. Thus, we might have observed a floor effect in the placebo group while the verum group, due to their higher starting level, had greater potential for a larger decrease in rating and choice time until they reached a similar physiological lower limit. This would mean that the observed significant impact of the synbiotic intervention on food rating and choice time was only a byproduct of a random difference of both groups before the start of the intervention. Due to our random assignment of participants to the two treatment groups and no significant differences in all other demographic, personality, and metabolic variables this idea seems to be unlikely. Nevertheless, before making hastily conclusions based on the rating and choice time data, future studies should replicate and investigate this finding further.

3.5.3 Limitations & Outlook

Our study has some limitations. The sample size was only determined based on a power-analysis with behavioral data from a pre-test with our food choice task and a previous study about the impact of stress on dietary self-control in a very similar food choice task (Maier et al., 2015). Thus, our power-analysis was not specific for our synbiotic intervention or fMRI data. Given the innovativeness of our study, we could not use any more closely related effect sizes from prior studies on dietary intervention effects on food choice. Therefore, we cannot rule out that our sample size of 95 participants was too small to detect a significant effect of the synbiotic intervention on food choice and its neural correlates. On the other hand, if the effect size would be so small that many more participants would be required, it could be debated, whether such a small effect is still meaningful for clinical practice.

While interpreting the results, it is important to keep in mind that we only did group-comparisons between the placebo and the synbiotic treatment. Based on these group comparisons, we cannot make any conclusions about the relevance of the gut-microbiota and the Gut-Brain-Axis for our findings. For this, we would need to confirm that the synbiotic intervention indeed modulated the gut microbial composition in the stool samples. For a more nuanced view, we could even relate the behavioral and neural results to individual bacterial strains or the beta-diversity (e.g. via Bray-Curtis dissimilarity, Jaccard distance or UniFrac) as a measure of change in microbial composition from pre- to post-intervention (Comin et al., 2021; Lozupone and Knight, 2005; Ricotta and Podani, 2017). Knowledge about the general effect of synbiotic supplements is helpful for developing novel weight-loss interventions. Deepening this knowledge by identifying individual drivers and inter-individual differences in the exact microbial composition would help to pinpoint these interventions to each patient individually.

However, we need to be caution with generalizing our findings to the population. Participant recruitment took place with flyers that informed roughly about our research interest. Due to the complexity of the study, interested individuals received a detailed written participant information and attended an information meeting before their participation. Therefore, it was quite clear to the participants that our study focused on health-related behaviors. We cannot

exclude that this led to a selection bias for participants that are generally more interested in health-topics and more motivated to eat healthy. With 3-day dietary records before each measurement timepoint we controlled however that participants did not have large changes in their eating behavior during the intervention time. Moreover, we only tested male participants. Thus, we cannot rule out that the effects of synbiotic interventions depends on the biological sex and differs for females (Chen et al., 2022; Dietrich et al., 2014).

Additionally, the BMI range in our dataset was quite large (20.6 to 33.7 kg/m^2) but did not include underweight and only few obese participants. Thus, our study might not have been powerful enough to detect synbiotic intervention effects that are more pronounced in a certain clinical BMI range (e.g. underweight or obesity). To make use of our research in clinical practice, future studies should also include females and focus on different BMI groups separately. Moreover, intervention effects could be studied separately for metabolically healthy and unhealthy individuals, classified based on blood parameters, or between individuals with physiological body fat and overfat (Gallagher et al., 2000).

Although we confirmed that our food choice task reflected self-reported cognitive restraint in habitual eating behavior, the ecological validity of our task has a few limitations:

First, we told participants to make healthy choices to create a challenging choice situation for them. This might however at the same time cause experimental demand effects, which we did not measure and control for (Tusche and Hutcherson, 2018). Participants might have made more healthy choices and valued taste and health attributes differently than they would outside of the lab in habitual eating situations. Apart from the experimental demand to choose healthy, we do not know participant's intrinsic motivation to do so and whether they even consider it costly if they do not chose healthy (Vosgerau et al., 2020). Due to potential bidirectional link between gut microbiota and social behavior, one could even speculate that the experimental demand effect might be sensitive to changes in gut microbial composition (Archie and Tung, 2015; Sylvia and Demas, 2018).

Second, we only used a very limited range of snack food items in our task. Choosing between a chocolate bar and an apple is of course a frequent conflict situation for many of us. However, most food choices in everyday life are more complex than this and thus results

from the food choice task can only be transferred to habitual dieting behavior to limited extend. This is a common limit to many food choice paradigms in the lab.
We did not send daily reminders to the participants but compliance and thus daily intake of the placebo or synbiotic was controlled via self-reports and weighing of the returned left-over. The returned weight of the remaining powder varied to some degree between participants (deviations ranged from 25 % less to 24 % more than the theoretical left-over). The daily dose of powder (2 g) had to be measured out by the participants each day with a small measuring spoon, which made it error prone and led to the observed variations. According to the self-reports, no participant forgot the intake more than 20 % of the time. Together with the weight of the returned powder, this suggests that compliance was reliably higher than our pre-registered 50 % cut-off.

Despite all these mentioned limitations, our study is informative for future research.
First of all, future research should especially focus on the characterization of the mechanisms that mediate the impact of the synbiotic intervention on food choice behaviors. Potential mediators are microbial metabolites (e.g. SCFA,), gut peptides, neurotransmitters, or immune modulators that can be measured via blood or stool samples (Plassmann et al., 2021).

Future studies should further build upon our exploratory findings to investigate specific targets of Gut-Brain communication (i.e., taste representation, mental effort, or rating and choice times) more directly. As previous literature implies, food cue reactivity as opposed to food valuation might be more strongly related to metabolic markers (Morys et al., 2020; Tetley et al., 2009) and is positively affected by gastric surgery in obese individuals (Guerrero-Hreins et al., 2021; Ochner et al., 2012; 2011; Scholtz et al., 2014). Hence, food cue reactivity could be a more promising target for studying the relevance of Gut-Brain communication for eating behavior. Alternatively, rather than affecting food choice based on expected taste and health attributes, the choice of food could also be changed by differences in taste perception. Previous studies demonstrated that the gut microbiota can modulate taste receptor expression, including those in the oral cavity as well as in the intestine, both being responsible

for food preferences and choice (Alcock et al., 2014; Duca et al., 2012; Raka et al., 2019; Thanarajah et al., 2019; Turner et al., 2020).

The dlPFC was recently found to be relevant for health- and taste-attribute representation and proposed to act as a domain-spanning mechanism for the representation of attribute goal-values (Tusche and Hutcherson, 2018). Thus, future research should also focus more closely on the impact of dietary interventions on the dlPFC. Additionally, studying functional connectivity via a psychophysiological interaction analysis could shed light on possible regulatory processes and their sensitivity to dietary interventions. Of specific interest might be the regulation of the value signals in the vmPFC by cognitive control mechanisms from the dlPFC (Hare et al., 2009; Maier et al., 2015) or the regulation of action selection mechanisms by valuation processes (Hutcherson et al., 2012). It is also conceivable that the synbiotic intervention primarily affects more basic taste processing and homeostatic brain areas, like the thalamus and hypothalamus. These regions could then act as a mediator to indirectly affect valuation processes. This idea could be tested by using different ROI masks (e.g. a taste-map from Neurosynth's meta-analysis tool, (Yarkoni et al., 2011) and by means of a ROI-based mediation analysis (Atlas et al., 2010).

The specific observed effects on choice time could be followed up by mouse tracking and computational modelling to determine whether the processing of taste, health, or both is accelerated by the intervention. Using other choice or reaction time tasks, like intertemporal choice tasks or impulsivity tasks, could reveal whether the effect is specific to food product evaluation and choice or whether it is a more domain-independent effect.

Moreover, especially for novel and more exploratory analyses, multi-voxel pattern analysis could be a more formal approach for reverse inferring mental states from brain data (Poldrack, 2011).

3.5.4 Overarching discussion of behavioral and fMRI results & conclusion

Overall, there is some evidence across our behavioral and neuronal analyses that the synbiotic intervention led to increased importance of taste attributes, easier and thus quicker determination of food health, and stronger cognitive control to choose healthy. Based on our

behavioral and exploratory fMRI results with uncorrected statistical thresholds, it is difficult, if not impossible, to propose a reliable mechanism of how the synbiotic intervention led to these effects.

Since published literature on the role of the gut microbiota for human food choice and its neural correlates is sparse (Osadchiy et al., 2020), it is difficult to integrate our findings into a broader picture. Previous fMRI studies have thus far focused on the effect of probiotics on emotion processing and resting-state connectivity (Bagga et al., 2019; 2018; Dong et al., 2022; Tillisch et al., 2013). Yet, some recent studies did not specifically investigate dietary interventions that modulate gut microbial composition but focused more indirectly on the relevance of specific microbial metabolites. With this approach, researchers found a causal relation between the colonic levels of propionate (one of many gut microbial metabolites) and different measures of food reward. After artificially increasing propionate levels, they observed reduced energy intake, lower food appeal to high-energy but not low-energy food, and attenuated anticipatory reward responses in the caudate and NAcc (Byrne et al., 2016). Fecal indole levels, a microbiota-derived metabolite of the amino acid tryptophan, were further shown to correlate with functional and anatomical connectivity in the extended reward network of amygdala, anterior insula, and NAcc (Osadchiy et al., 2018).

Our study did not confirm the idea that the synbiotic intervention made unhealthy food less appealing and less chosen. However, when comparing our results with the findings from Byrne *et al.*, we need to point out that our classification of unhealthy and healthy food was not solely based on energy content and that we only focused on snack food items. We also do not know whether our synbiotic intervention had any impact on propionate or indole levels and whether the effects and associations observed by Byrne *et al.* and Osadchiy *et al.* are specific to these metabolites only.

The low number of human causal studies on the gut microbial impact on neural correlates of (dieting) behavior since the first publication by Tillisch et al. might have two reasons: First, the low number of publications might reflect that Gut-Brain communication in the context of eating behavior is still a newly emerging topic of current research (Plassmann et al., 2021). Second, we might observe a file-drawer problem of unpublished inconclusive results or null-findings (Franco et al., 2014; Rosenthal, 1979). Maybe there have been more studies, that

like our project, did not yield clear and conclusive results because gut microbial effects, if they exist, are too subtle and too specific to be observed easily, especially in fMRI.
Irrespective of the reason, this strongly highlights the need to even publish exploratory, null, or inconclusive findings to enable future studies to replicate and follow-up on these findings. With this, our study offers a first interdisciplinary attempt to better understand the impact of Gut-Brain communication for food choices and eating behavior in healthy men. Advancing knowledge about the impact of our gut microbiota on eating behavior and its potential individual moderators could lead to more powerful and better targeted weight loss interventions. Since the gut microbiota fully depends on its host for meeting its energy requirements, our own nutrition could be a powerful tool to manipulate our gut microbiota and via this our own health (Boscaini et al., 2021).

4. General Discussion & Conclusion

The two projects presented in this thesis investigated unconscious external and internal impacts on dietary preferences and dietary decision-making with an interdisciplinary approach.

First, we studied the OXT system in the context of marketing research to shed light on the neurobiological mechanism of MPEs. We focused on placebo effects of food marketing on two distinct domains: subjectively reported taste pleasantness and objectively measured cognitive performance after food consumption.

We showed that expensive (but less so organic) labels and superior packaging of food products are powerful in manipulating and enhancing taste pleasantness. However, these MPEs in the appetitive domain seem to be independent of the OXT system. Moreover, famous brand label and verbal advertisement for a presumable energy drink did not per se enhance cognitive performance after drink consumption. Instead, intranasal OXT seemed to have enhanced performance in response to the advertisement by presumably increasing conformity to the advertised information (but note the contradictory Bayesian result and the explorative nature of this study part).

Second, we studied the neuroeconomics of food choice in the framework of the Microbiome-Gut-Brain axis by means of a 7-week synbiotic intervention. The synbiotic intervention did not lead to healthier food choices but increased the importance of taste attributes for food choice and enabled faster choices.

Together both studies clearly demonstrate that human food choices are a complex process, vulnerable to unconscious and sometimes even uncontrollable influences like marketing, hormones, and gut microbial signals. The relevance of these findings, and research on unconscious determinants of eating behavior in general, is three-fold:

First, in the light of rising obesity rates it is essential to better understand inter-individual differences in the vulnerability to overweight and obesity. Be it due to the responsiveness to marketing, the OXT system, or differences in the gut microbiota. In recent years it became clear that obesity is not simply caused by a lack of willpower manifested in unhealthy eating

and insufficient exercising (Chaput et al., 2010; Grannell et al., 2021; McAllister et al., 2009). Obesity is a rather multi-dimensional problem and thus requires more interdisciplinary research to learn more about individual risk factors.

Second, research like ours helps by fostering awareness for unconscious determinants of eating behavior to reduce weight stigmas and discrimination in the population. Weight stigmas have a tremendous impact on psychological and physiological well-being of affected individuals (Rubino et al., 2020). Importantly however, overweight or obese individuals should not be given an excuse for why they are not in control of their weight. Awareness of unconscious determinants should rather allow individuals to actively render own unconscious drivers visible to make them conscious and thus less powerful. Moreover, the need for stronger awareness of obesity as a multi-dimensional problem to reduce weight stigmas does not only concern affected individuals and the public but also policymakers and health care professionals. Such awareness enables for example more efficient public health-campaigns for obesity prevention and treatment and improved quality of patient care. Only the joint effort by science, policy and health-care system, can improve health and well-being of patients (Rubino et al., 2020).

Finally, the previous two arguments set the stage for the third and most important relevance of an interdisciplinary and integrative perspective on eating behavior: Growing knowledge and awareness about unconscious drivers of food-related behaviors helps developing more targeted health interventions. Such an intervention could for example be a probiotic or synbiotic supplement tailored to the individual microbiota of obese patients for weight-loss. As shown in this thesis and extensively reviewed in the literature, the gut microbiota is involved in the regulation of eating behavior (García-Cabrerizo et al., 2021; Gupta et al., 2020; Plassmann et al., 2021; van de Wouw et al., 2017). Moreover, the gut microbiota fully depends on the host's nutrition to meet its own energy requirements (Boscaini et al., 2021). Together, this could offer a promising possibility to reinforce a healthy eating behavior and a healthy body weight by shaping a "healthy" microbiota with your own nutrition and lifestyle (Boscaini et al., 2021; Fetissov, 2017). Thus, a lifestyle intervention with individualized nutritional protocol based on individual gut microbial composition could help in the prevention of obesity.

Other options for health interventions include marketing campaigns that nudge healthy food choices, or OXT treatment in combination with expert-induced expectation for enhancing objective health outcomes like cognitive abilities in mental disorders.

The goal of future studies should be to continue this interdisciplinary approach to better understand and improve health-related behaviors in the context of food and to ultimately arrive at Thomas Edison's vision:

"The doctor of the future will no longer treat the human frame with drugs, but rather will cure and prevent disease with nutrition."

5. Abstracts

Study I: Manipulated by Marketing and Hormones? The relevance of Oxytocin for Marketing Placebo Effects on Food Product Perception

What consumers expect from food products and how they experience food products strongly depends on product information like premium prices, famous brand names, or organic claims. Many studies demonstrated that these marketing means influence subjective and objective experiences like taste pleasantness and cognitive performance. This phenomenon has been coined marketing placebo effects (MPEs). Still, the neurobiological mechanisms mediating MPEs are unclear. Recent research investigated the neuropeptide oxytocin for its effects on analgesic and cognitive placebo responses. We extend this line of research by testing whether oxytocin boosts marketing induced placebo responses on taste perception and cognitive performance by strengthening the consumer-marketer relationship. We conducted a randomized, double-blind, and pre-registered study with healthy male participants, who either received an oxytocin (24 IU) or sham nasal spray. First, we studied MPEs of price and organic labels on experienced taste pleasantness. Second, in a more exploratory part, we used an energy drink label to study the MPE of brand name and advertisement on cognitive performance. Our results showed no effect of intranasal oxytocin on marketing-induced taste preference. The consumer-marketer relationship, assessed in form of trust and expectations, did also not differ between sham and oxytocin group. Our exploratory analysis suggests a possible role of OXT for MPEs on cognitive performance, which is, however, not supported by a Bayesian analysis. Therefore, this finding needs further confirmation in future research.

Study II: Manipulated by Gut Bacteria? The Impact of a Synbiotic Intervention on Food Choice Behavior and its Neural Correlates

The gut microbiota influences human health and behavior. One behavior, which directly impinges on health, is eating behavior. Recent research on the Microbiota-Gut-Brain axis suggests a bidirectional relationship between eating behavior and gut microbial composition. Not only does human nutrition affect the microbial composition, the microbial composition also affects diet-related behaviors. Yet the neurobiological mechanisms of how the gut microbiota influences eating behavior are unclear. In a double-blind, placebo-controlled study in healthy male participants, we modulated the gut microbial composition with a 7-week synbiotic intervention. We investigated the effects of this synbiotic intervention on anthropometric data, self-reported eating behavior, and subjective taste- and health-ratings. We further collected behavioral and fMRI data while participants made binary food choices between snack food items of varying taste and health. We found that the synbiotic intervention increased the impact of taste attributes on food choice and led to a significant decrease in choice and health-rating times. An fMRI region of interest analysis did not show any impact of the synbiotic intervention on previously described brain regions that reflect subjective food value and food attributes during choice. Exploratory, uncorrected whole-brain analyses revealed subtle synbiotic intervention effects on various other brain regions. However, these exploratory results require further confirmation. Our data suggests that a synbiotic intervention does not per se influence the ability to eat healthy. Instead, a synbiotic intervention might modulate the responsiveness to individual food attributes and the decision speed when subjectively judging food and deciding for a food product.

6. List of Figures

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8. References

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10. Appendix: Supplementary Figures

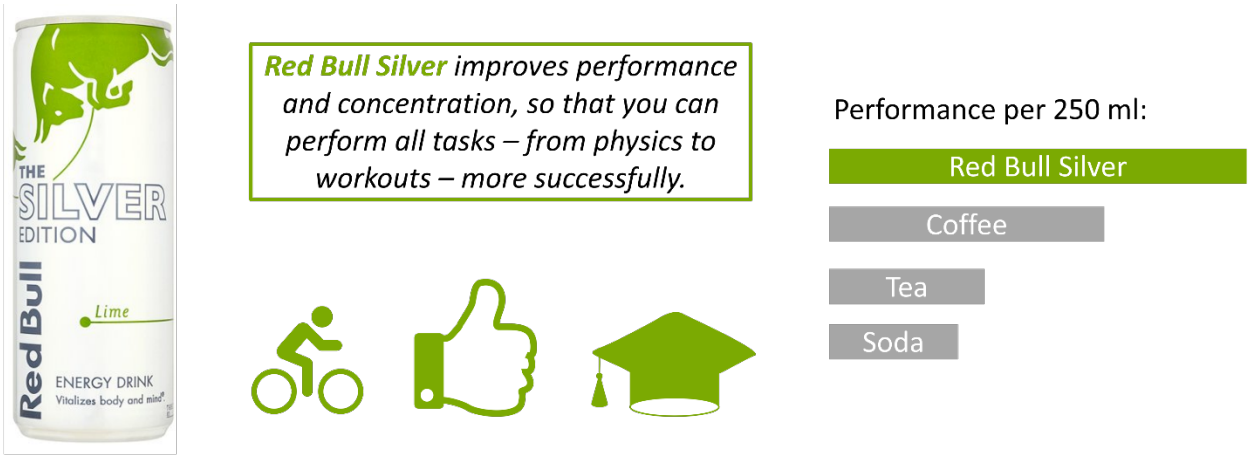

Fig. A 1: Translated version of the poster informing about the energy drink. The poster hung on the wall in the testing room in front of the participant. With this poster we aimed at enhancing the participants' beliefs in the efficacy of the energy drink. Note that the poster was designed by us and is not an official poster.

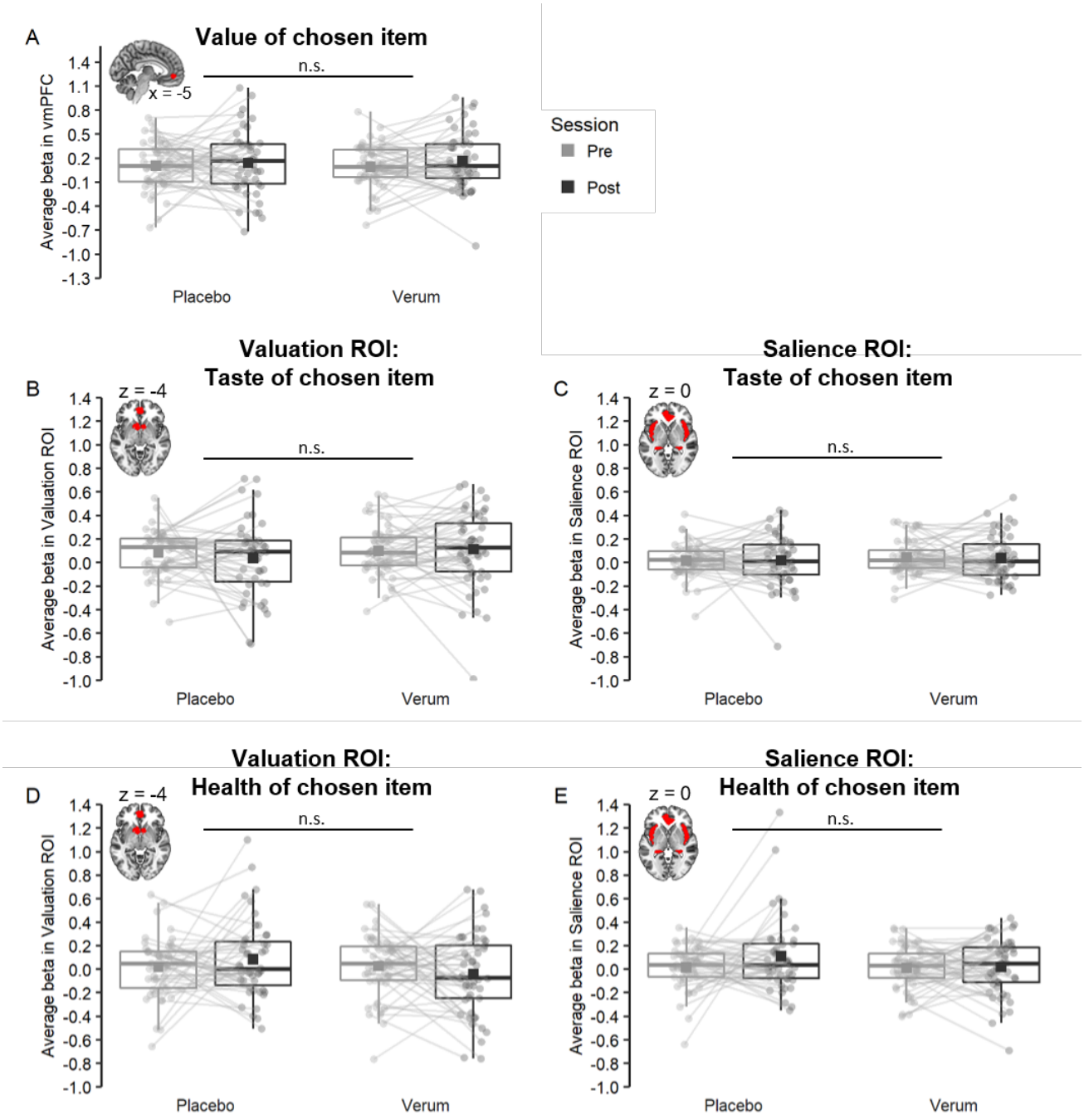

Fig. A 2: No significant effect of synbiotic intervention on the association of choice attributes and brain activity in different food choice related ROIs. (A) The effect of the synbotic intervention on the association of chosen food value with activity in vmPFC by extracting the average betas for the parametric modulator *value of chosen item* from a vmPFC ROI mask. The vmPFC mask was created from the overlay of the Bartra *et al.*, 2013 (Fig 9) vmPFC mask with the vmPFC-containing cluster for value related activity across both sessions and groups. (B + C) The effect of the synbiotic intervention on the association of the chosen taste

with BOLD signal was tested in two different ROIs: a Valuation ROI comprised of vmPFC and ventral striatum (based on maks from Bartra *et al.*, 2013) and an anatomically defined emotional/salience ROI comprised of hippocampus, parahippocampus, amygdala, insula, and anterior cingulate cortex. The choice and combination of brain regions was based on previous literature on the neural correlates of food choice (Bartra *et al.*, 2013, Maier *et al.*, 2015, Gupta *et al.*, 2020, Merchant *et al.*, 2020, Christensen *et al.*, 2021). (D + E) The effect of the synbiotic intervention on the association of the chosen taste with BOLD signal was tested in the sam way as for the taste of the chosen item in B + C. The interactions of treatment x session as measure of a synbiotic intervention effect were statistically tested in a linear mixed-effects regression model. The vertical lines of the boxplots depicit the median and the squares show the mean. The ROIs are overlayed in red on the MNI152 template and are depicted in the inlays.

11. Appendix: Supplementary Tables

Tab. A 1: Linear mixed-effects model for the impact of OXT treatment on positive and negative affect for participants of the taste task.

	Positive Affect				**Negative Affect**			
Explanatory variables	**Estimate (95 % CI)**	***SE***	***t*-value**	***p*-value**	**Estimate (95 % CI)**	***SE***	***t*-value**	***p*-value**
Intercept	30.66 (29.55 – 31.77)	0.6	54.23	**<0.001**	11.53 (11.16 – 11.91)	0.2	60.25	**<0.001**
Treatment (OXT vs. sham)	-0.07 (-1.63 – 1.50)	0.8	-0.09	0.932	0.46 (-0.07 – 0.99)	0.3	1.70	0.090
Time (post vs. pre)	-0.12 (-1.01 – 0.77)	0.5	-0.27	0.785	-0.43 (-0.85 – -0.00)	0.2	-1.96	0.051
Treatment x Time	0.48 (-0.77 – 1.74)	0.6	0.75	0.454	-0.71 (-1.31 – -0.10)	0.3	-2.3	**0.022**
Random Effects								
σ^2	11.35				2.61			
τ_{00}	24.13 $_{ID}$				1.46 $_{ID}$			
N	223 $_{ID}$				223 $_{ID}$			
Observations	444				444			
Marginal R^2/ Conditional R^2	0.001 / 0.680				0.044 / 0.386			

Notes: Positive and negative affect were measured with the positive and negative affect schedule (PANAS). Model contains random intercepts for participants. The variables treatment and time were dummy coded (sham /pre = 0, OXT/post = 1). OXT, oxytocin; *SE*, standard error of the estimate; CI, confidence interval.

Tab. A 2: Linear mixed-effects model for taste pleasantness ratings depending on product label and manipulation type.

Dependent variable: Taste pleasantness				
Explanatory variables	**Estimate (95 % CI)**	***SE***	***t*-value**	***p*-value**
Intercept	6.34 (6.19 – 6.48)	0.07	86.18	**<0.001**
Product appearance (positive vs. neutral)	0.33 (0.15 – 0.52)	0.09	3.51	**<0.001**
Manipulation (organic vs. expensive)	-1.07 (-1.25 – -0.88)	0.09	-11.29	**<0.001**
Product appearance x manipulation	-0.24 (-0.61 – 0.13)	0.19	-1.28	0.201
Random Effects				
σ^2		1.99		
$T_{00\ ID}$		0.71		
N_{ID}		223		
Observations		892		
Marginal R^2 / Conditional R^2		0.105 / 0.340		

Notes: Participants reported their experienced taste pleasantness on a 9-point Likert scale. For the exact product appearance and manipulation see Fig. 3B. Model contains random intercepts for participants. We used effect coding for the variables product appearance and manipulation to get main effects (neutral/expensive = -0.5, positive/organic = +0.5). CI, confidence interval*; SE*, standard error of the estimate.

Tab. A 3: Linear mixed-effects model for the relation of trust in marketers, quality expectations, and taste expectations with MPEs.

Dependent variable: MPE value for both manipulations pooled								
	Model 1				Model 2			
Explanatory variables	**Estimate (95 % CI)**	***SE***	***t*-value**	***p*-value**	**Estimate (95 % CI)**	**SE**	***t*-value**	***p*-value**
Intercept	0.33 (0.17 – 0.49)	0.08	4.14	**<0.001**	0.34 (0.16 – 0.51)	0.09	3.80	**<0.001**
Trust in marketer	0.13 (-0.08 – 0.33)	0.10	1.21	0.226	0.14 (-0.08 – 0.37)	0.11	1.25	0.211
Q. expectation	-0.19 (-0.39 – 0.01)	0.10	-1.86	0.063	-0.21 (-0.43 – 0.01)	0.11	-1.90	0.058
T. expectation	0.17 (-0.02 – 0.36)	0.10	1.79	0.073	0.17 (-0.03 – 0.37)	0.107	1.67	0.095
Manipulation (organic vs. expensive)	-0.20 (-0.52 – 0.11)	0.16	-1.25	0.210	-0.18 (-0.52 – 0.17)	0.17	-1.04	0.299
Trust x Manipulation	0.17 (-0.45 – 0.36)	0.21	-0.20	0.841	-0.02 (-0.03 – 0.37)	0.23	-0.07	0.947
Q. Expectation x Manipulation	0.05 (-0.35 – 0.45)	0.20	0.24	0.810	-0.034 (-0.47 – 0.39)	0.22	-0.19	0.852
T. Expectation x Manipulation	0.01 (-0.37 – 0.39)	0.19	0.04	0.967	0.08 (-0.32 – 0.48)	0.20	0.39	0.699
Positive Affect (post - pre)					-0.08 (-0.26 – 0.09)	0.09	-0.92	0.361
Negative Affect (post-pre)					-0.002 (-0.18 – 0.17)	0.09	-0.02	0.982
Product liking					-0.02 (-0.20 – 0.15)	0.09	-0.26	0.799
Treatment Guess					0.11 (-0.06 – 0.28)	0.09	1.25	0.214
Age					-0.17 (-0.44 – 0.11)	0.14	-1.21	0.229
Income					-0.02 (-0.25 – 0.22)	0.12	-0.13	0.894
AQ					0.01 (-0.17 – 0.19)	0.09	0.11	0.911
General Trust					-0.01 (-0.19 – 0.17)	0.09	-0.10	0.922
Random Effects								
σ^2	2.77				2.73			
τ_{00}	0.00 $_{ID}$				0.00 $_{ID}$			
N	223 $_{ID}$				190 $_{ID}$			
Observations	446				379 [a]			
Marginal R^2 / Conditional R^2	0.020 / NA				0.034 / NA			

Notes: Trust in marketers, quality expectations and taste expectations were assessed via a questionnaire. The MPE value is the difference between the taste pleasantness ratings of the products with positive appearance and the products with neutral appearance (pooled across both manipulation types). Model contains random intercepts for participants. The variable manipulation was effect coded (expensive = -0.5, organic = +0.5) and all other non-binary variables were z-scored. AQ, Autism Spectrum Quotient; MPE, marketing placebo effect; Q. expectation, quality expectation; T. expectation, taste expectation; *SE*, standard error of the estimate; CI, confidence interval. [a] Missing datapoints for variable income due to voluntary nature of this question.

Tab. A 4: Linear mixed-effects model with trust in marketer as dependent variable.

Dependent variable: trust in marketers								
	Model 1				**Model 2**			
Explanatory variables	**Estimate (95 % CI)**	***SE***	***t*-value**	***p*-value**	**Estimate (95 % CI)**	***SE***	***t*-value**	***p*-value**
Intercept	15.66 (15.18 – 16.13)	0.24	64.69	**<0.001**	15.56 (15.06 – 16.07)	0.26	60.08	**<0.001**
Treatment (OXT vs. sham)	-0.14 (-0.81 – 0.53)	0.34	-0.41	0.683	0.03 (-0.69 – 0.74)	0.37	0.08	0.939
Manipulation (organic vs. expensive)	0.88 (0.22 – 1.55)	0.34	2.61	**0.010**	0.77 (0.05 – 1.48)	0.37	2.10	**0.037**
Treatment x Manipulation	-0.35 (-1.29 – 0.58)	0.48	-0.74	0.462	0.19 (-0.82 – 1.20)	0.52	0.37	0.711
Positive Affect (post-pre)					0.57 (0.21 – 0.94)	0.19	3.10	**0.002**
Negative Affect (post-pre)					0.23 (-0.14 – 0.60)	0.19	1.20	0.232
Treatment Guess					0.08 (-0.28 – 0.44)	0.19	0.43	0.666
Age					0.01 (-0.57 – 0.59)	0.29	0.04	0.970
Income					0.09 (-0.41 – 0.59)	0.26	0.34	0.731
AQ					-0.34 (-0.72 – 0.04)	0.20	-1.74	0.083
General Trust					0.53 (0.15 – 0.91)	0.19	2.75	**0.007**
Random Effects								
σ^2		6.34				6.33		
τ_{00}		3.33 $_{ID}$				3.01 $_{ID}$		
N		223 $_{ID}$				190 $_{ID}$		
Observations		446				380 [a]		
Marginal R^2 / Conditional R^2		0.014 / 0.353				0.095 / 0.387		

Notes: Model contains random intercepts for participants. Variable treatment is dummy coded (sham = 0, OXT = 1) and variable manipulation is effect coded (expensive = -0.5, organic = +0.5). All other non-binary variables were z-scored. AQ, Autism Spectrum Quotient; CI, confidence interval; OXT, oxytocin; *SE*, standard error of the estimate. [a] Missing datapoints for variable income due to voluntary nature of this question.

Tab. A 5: Linear mixed-effects model with quality expectation as dependent variable.

Dependent variable: quality expectation								
	Model 1				Model 2			
Explanatory variables	**Estimate (95 % CI)**	***SE***	***t*-value**	***p*-value**	**Estimate (95 % CI)**	***SE***	***t*-value**	***p*-value**
Intercept	4.73 (4.54 – 4.93)	0.1	46.67	**<0.001**	4.25 (2.87 – 5.62)	0.7	6.05	**<0.001**
Treatment (OXT vs. sham)	-0.13 (-0.41 – 0.15)	0.14	-0.92	0.359	-0.15 (-0.45 – 0.16)	0.16	-0.94	0.348
Manipulation (organic vs. expensive)	0.39 (0.11 – 0.66)	0.14	2.74	**0.007**	0.38 (0.07 – 0.68)	0.16	2.44	**0.016**
Treatment x Manipulation	-0.09 (-0.48 – 0.30)	0.2	-0.47	0.642	-0.07 (-0.50 – 0.36)	0.22	-0.34	0.738
Positive Affect (post-pre)					0.17 (0.01 – 0.32)	0.08	2.1	**0.037**
Negative Affect (post-pre)					0.10 (-0.06 – 0.26)	0.08	1.25	0.214
Treatment Guess					0.05 (-0.11 – 0.20)	0.08	0.61	0.544
Age					-0.26 (-0.50 – -0.01)	0.13	-2.06	**0.041**
Income					0.06 (-0.15 – 0.28)	0.11	0.56	0.574
AQ					-0.02 (-0.05 – 0.01)	0.02	-1.12	0.265
General Trust					0.02 (-0.01 – 0.04)	0.01	1.32	0.190
Random Effects								
σ^2		1.11				1.14		
τ_{00}		0.59 $_{ID}$				0.55 $_{ID}$		
N		223 $_{ID}$				190 $_{ID}$		
Observations		446				380 [a]		
Marginal R^2 / Conditional R^2		0.020 / 0.360				0.071 / 0.372		

Notes: Model contains random intercepts for participants. Random intercepts for participants. Variable treatment is dummy coded (sham = 0, OXT = 1) and variable manipulation is effect coded (expensive = -0.5, organic = +0.5). All other non-binary variables were z-scored. AQ, Autism Spectrum Quotient; CI, confidence interval; OXT, oxytocin; SE, standard error of the estimate. [a] Missing datapoints for variable income due to voluntary nature of this question.

Tab. A 6: Linear mixed-effects model with taste expectations as dependent variable.

Dependent variable: taste expectations								
	Model 1				Model 2			
Explanatory variables	**Estimate (95 % CI)**	***SE***	***t*-value**	***p*-value**	**Estimate (95 % CI)**	***SE***	***t*-value**	***p*-value**
Intercept	4.00 (3.80 – 4.20)	0.10	39.58	**<0.001**	3.74 (2.33 – 5.16)	0.72	5.19	**<0.001**
Treatment (OXT vs. sham)	-0.18 (-0.46 – 0.10)	0.14	-1.28	0.201	-0.17 (-0.48 – 0.15)	0.16	-1.05	0.295
Manipulation (organic vs. expensive)	-0.09 (-0.42 – 0.24)	0.17	-0.54	0.592	-0.18 (-0.54 – 0.19)	0.19	-0.96	0.337
Treatment x Manipulation	-0.12 (-0.58 – 0.35)	0.24	-0.49	0.627	0.05 (-0.46 – 0.57)	0.26	0.2	0.841
Positive Affect (post-pre)					0.14 (-0.02 – 0.30)	0.08	1.72	0.087
Negative Affect (post-pre)					0.08 (-0.09 – 0.24)	0.08	0.92	0.359
Treatment Guess					-0.05 (-0.21 – 0.11)	0.08	-0.58	0.56
Age					-0.12 (-0.37 – 0.14)	0.13	-0.91	0.364
Income					-0.03 (-0.25 – 0.20)	0.11	-0.22	0.823
AQ					0.001 (-0.03 – 0.03)	0.02	0.06	0.951
General Trust					0.005 (-0.02 – 0.03)	0.01	0.41	0.68
Random Effects								
σ^2	1.56				1.64			
τ_{00}	0.35 $_{ID}$				0.37 $_{ID}$			
N	223 $_{ID}$				190 $_{ID}$			
Observations	446				380 [a]			
Marginal R^2 / Conditional R^2	0.008 / 0.190				0.026 / 0.203			

Notes: Model contains random intercepts for participants. Variable treatment is dummy coded (sham = 0, OXT = 1) and variable manipulation is effect coded (expensive = -0.5, organic = +0.5). All other non-binary variables were z-scored. AQ, Autism Spectrum Quotient; CI, confidence interval; OXT, oxytocin; SE, standard error of the estimate. [a] Missing datapoints for variable income due to voluntary nature of this question.

Tab. A 7: Linear mixed-effects model for the impact of OXT treatment on taste perception independent of marketing.

Dependent variable: Taste pleasantness of control products

Explanatory variables	**Estimate (95 % CI)**	***SE***	***t*-value**	***p*-value**
Intercept	6.53 (6.29 – 6.76)	0.12	53.89	**<0.001**
Treatment (OXT vs. sham)	0.02 (-0.31 – 0.36)	0.17	0.13	0.897
Product type (applesauce vs. chocolate)	-0.12 (-0.56 – 0.33)	0.23	-0.51	0.608
Treatment x Manipulation	0.11 (-0.52 – 0.74)	0.32	0.34	0.737
Random Effects				
σ^2		2.89		
$T_{00\ ID}$		0.18		
N_{ID}		223		
Observations		446		
Marginal R^2 / Conditional R^2		0.001 / 0.061		

Notes: Participants rated taste pleasantness of the distractor products on a 9-point Likert scale. The distractor products differed from the neutral and positive marketing products. Model contains random intercepts for participants. Variable treatment is dummy coded (sham = 0, OXT = 1) and variable manipulation is effect coded (expensive = -0.5, organic = +0.5). CI, confidence interval; OXT, oxytocin; *SE*, standard error of the estimate.

Tab. A 8: Linear mixed-effects model with MPE as dependent variable.

Dependent variable: MPE value for both manipulations pooled

	Model 1				Model 2			
Explanatory variables	**Estimate (95 % CI)**	***SE***	***t*-value**	***p*-value**	**Estimate (95 % CI)**	***SE***	***t*-value**	***p*-value**
Intercept	0.29 (0.07 – 0.51)	0.11	2.57	**0.010**	0.24 (0.00 – 0.48)	0.12	1.97	**0.049**
Treatment (OXT vs. sham)	0.09 (-0.22 – 0.40)	0.16	0.55	0.584	0.18 (-0.15 – 0.52)	0.17	1.07	0.285
Manipulation (organic vs. expensive)	-0.2 (-0.64 – 0.24)	0.22	-0.88	0.377	-0.21 (-0.69 – 0.26)	0.24	-0.88	0.380
Treatment x Manipulation	-0.09 (-0.71 – 0.53)	0.32	-0.28	0.782	0.004 (-0.66 – 0.67)	0.34	0.01	0.990
Positive Affect (post-pre)					-0.07 (-0.24 – 0.10)	0.09	-0.79	0.430
Negative Affect (post-pre)					0.01 (-0.16 – 0.19)	0.09	0.15	0.879
Product Liking					-0.02 (-0.19 – 0.16)	0.09	-0.2	0.841
Treatment Guess					0.10 (-0.07 – 0.27)	0.09	1.13	0.259
Age					-0.15 (-0.42 – 0.13)	0.14	-1.06	0.290
Income					-0.02 (-0.25 – 0.22)	0.12	-0.13	0.897
AQ					0.01 (-0.17 – 0.19)	0.09	0.13	0.894
General Trust					0.004 (-0.18 – 0.18)	0.09	0.04	0.967
Random Effects								
σ^2		2.79				2.75		
τ_{00}		0.00 $_{ID}$				0.00 $_{ID}$		
N		223 $_{ID}$				190 $_{ID}$		
Observations		446				379 [a]		
Marginal R^2 / Conditional R^2		0.006 / NA				0.019 / NA		

Notes: Model contains random intercepts for participants. Variable treatment is dummy coded (sham = 0, OXT = 1) and variable manipulation is effect coded (expensive = -0.5, organic = +0.5). All other non-binary variables were z-scored. AQ, Autism Spectrum Quotient; CI, confidence interval; OXT, oxytocin; SE, standard error of the estimate. [a] Missing datapoints for variable income due to voluntary nature of this question.

Tab. A 9: Linear mixed-effects model for the impact of OXT treatment on positive and negative affect for participants of the cognitive performance task.

	Positive Affect				**Negative Affect**			
Explanatory variables	**Estimate (95 % CI)**	***SE***	***t*-value**	***p*-value**	**Estimate (95 % CI)**	***SE***	***t*-value**	***p*-value**
Intercept	30.41 (29.32 – 31.51)	0.56	54.5	**<0.001**	11.53 (11.06 – 12.00)	0.24	48.07	**<0.001**
Treatment (OXT vs. sham)	0.31 (-1.22 – 1.85)	0.78	0.40	0.688	0.87 (0.21 – 1.53)	0.34	2.60	**0.010**
Time (post vs. pre)	0.66 (-0.25 – 1.57)	0.46	1.43	0.154	-0.35 (-0.86 – 0.16)	0.26	-1.33	0.186
Treatment x Time	0.19 (-1.08 – 1.47)	0.65	0.30	0.765	-0.93 (-1.64 – -0.21)	0.36	-2.55	**0.012**
Random Effects								
σ^2		10.57				3.32		
τ_{00}		20.26 $_{ID}$				2.37 $_{ID}$		
N		202 $_{ID}$				202 $_{ID}$		
Observations		402				402		
Marginal R^2/ Conditional R^2		0.006 / 0.659				0.044 / 0.442		

Notes: Positive and negative affect were measured with the positive and negative affect schedule (PANAS). Model contains random intercepts for participants. Variables treatment and time were dummy coded (sham /pre = 0, OXT/post = 1). CI, confidence interval; OXT, oxytocin; *SE*, standard error of the estimate.

Tab. A 10: Linear mixed-effects model with cognitive performance in the numerical stroop task as dependent variable.

Dependent variable: cognitive performance of each trial								
	Model 1				Model 2			
Explanatory variables	**Estimate (95 % CI)**	***SE***	***t*-value**	***p*-value**	**Estimate (95 % CI)**	***SE***	***t*-value**	***p*-value**
Intercept	6.06 (5.87 – 6.25)	0.10	63.10	**<0.001**	6.09 (5.89 – 6.29)	0.10	59.81	**<0.001**
Treatment (OXT vs. sham)	0.01 (-0.25 – 0.28)	0.13	0.11	0.916	-0.01 (-0.30 – 0.28)	0.15	-0.07	0.946
Label (Energy Drink vs. Soft Drink)	0.01 (-0.05 – 0.06)	0.03	0.26	0.795	0.01 (-0.05 – 0.07)	0.03	0.26	0.795
Trial	-0.01 (-0.01 – -0.00)	0.0007	-7.02	**<0.001**	-0.01 (-0.01 – -0.00)	0.006	-7.24	**<0.001**
Run (second vs. first)	0.93 (0.85 – 1.01)	0.04	23.36	**<0.001**	0.93 (0.85 – 1.02)	0.04	21.53	**<0.001**
Reward (10 vs. 1)	0.08 (0.02 – 0.14)	0.03	2.80	**0.005**	0.07 (0.01 – 0.12)	0.03	2.15	**0.032**
Order (Energy Drink first vs. Energy Drink second)	0.15 (-0.11 – 0.41)	0.13	1.10	0.273	0.06 (-0.23 – 0.34)	0.14	0.40	0.693
Difficulty (difficult vs. easy)	-2.33 (-2.39 – -2.28)	0.03	-82.23	**<0.001**	-2.34 (-2.40 – -2.28)	0.03	-76.93	**<0.001**
Treatment x Label	0.1 (0.02 – 0.17)	0.04	2.40	**0.016**	0.11 (0.02 – 0.19)	0.04	2.44	**0.015**
Treatment x Reward	-0.04 (-0.11 – 0.04)	0.04	-0.90	0.368	-0.01 (-0.10 – 0.07)	0.04	-0.26	0.794
Treatment x Difficulty	-0.12 (-0.19 – -0.04)	0.04	-2.90	**0.004**	-0.12 (-0.21 – -0.04)	0.04	-2.79	**0.005**
AQ					0.08 (-0.07 – 0.23)	0.08	1.00	0.317
General Trust					0.1 (-0.06 – 0.25)	0.08	1.26	0.211
Positive Affect (post - pre)					-0.01 (-0.15 – 0.13)	0.07	-0.11	0.913
Negative Affect (post - pre)					-0.08 (-0.22 – 0.06)	0.07	-1.09	0.278
Age					-0.17 (-0.36 – 0.03)	0.10	-1.70	0.091
Treatment Guess					0.03 (-0.11 – 0.17)	0.07	0.39	0.699
Income					-0.17 (-0.34 – 0.01)	0.09	-1.85	0.066
Hours of sleep					0.03 (-0.11 – 0.17)	0.07	0.42	0.678
Time since waking up					0.08 (-0.07 – 0.22)	0.07	1.04	0.302
Energy drink consume					-0.07 (-0.23 – 0.08)	0.08	-0.94	0.350

Belief in Energy Drink effects		0.11 (-0.05 – 0.27)	0.08	1.36	0.175
Random Effects					
σ^2	1.91		1.89		
T_{00}	0.87 $_{ID}$		0.79 $_{ID}$		
N	202 $_{ID}$		168 $_{ID}$		
Observations	19392		16128 [a]		
Marginal R^2 / Conditional R^2	0.359 / 0.560		0.386 / 0.566		

Note: Model contains random intercepts for participants. Treatment and label were dummy coded (sham/soft drink = 0, OXT/energy drink = 1), all other binary variables were effect coded (-0.5 and +0.5), treatment guess and trial are mean centered, and all other non-binary variables were z-scored. AQ, Autism Spectrum Quotient; CI, confidence interval; OXT, oxytocin; *SE*, standard error of the estimate. [a] missing data points for variable income due to voluntary nature of this question.

Tab. A 11: Linear model for the impact of treatment and label on anticipated performance.

Dependent variable: anticipated performance								
	Model 1				Model 2			
Explanatory variables	**Estimate (95 % CI)**	***SE***	***t*-value**	***p*-value**	**Estimate (95 % CI)**	***SE***	***t*-value**	***p*-value**
Intercept	5.55 (4.94 – 6.17)	0.31	17.78	**<0.001**	5.47 (4.80 – 6.15)	0.34	15.97	**<0.001**
Treatment (OXT vs. sham)	0.42 (-1.27 – 0.44)	0.43	-0.97	0.335	-0.34 (-1.31 – 0.62)	0.49	-0.70	0.485
Label (Energy Drink vs. Soft Drink)	0.21 (-0.66 – 1.08)	0.44	0.48	0.635	0.51 (-0.43 – 1.45)	0.48	1.08	0.281
Treatment x Label	0.18 (-1.03 – 1.39)	0.62	0.29	0.772	-0.09 (-1.44 – 1.26)	0.68	-0.13	0.894
AQ					-0.17 (-0.52 – 0.19)	0.18	-0.91	0.365
General Trust					0.06 (-0.31 – 0.42)	0.18	0.30	0.762
Positive Affect (post - pre)					0.16 (-0.17 – 0.49)	0.17	0.98	0.328
Negative Affect (post - pre)					-0.19 (-0.52 – 0.15)	0.17	-1.10	0.272
Age					-0.27 (-0.72 – 0.18)	0.23	-1.18	0.238
Treatment Guess					-0.11 (-0.44 – 0.22)	0.17	-0.65	0.515
Income					0.16 (-0.27 – 0.58)	0.21	0.73	0.465
Hours of sleep					0.07 (-0.26 – 0.40)	0.17	0.43	0.669
Time since waking up					-0.14 (-0.48 – 0.20)	0.17	-0.82	0.412
Energy drink consume					0.01 (-0.36 – 0.38)	0.19	0.04	0.967
Belief in Energy Drink effects					0.08 (-0.30 – 0.45)	0.19	0.41	0.680
Observations	202				168 [a]			
R^2 / R^2adjusted	0.011 / -0.004				0.062 / -0.024			

Note: We measured anticipated performance in form of expectations about performance before the start of the task. Only the data of the first run was used for the analysis because anticipated performance of the second run could be biased by the experienced performance in the first run. The variables treatment and label were dummy coded (sham/Soft Drink = 0, OXT/Energy Drink = 1), treatment guess and trial are mean centered, and all other non-binary variables were z-scored. AQ, Autism Spectrum Quotient; CI, confidence interval; OXT, oxytocin; *SE*, standard error of the estimate. [a] missing data points for variable income due to voluntary nature of this question.

Tab. A 12: Linear mixed-effects model for the impact of treatment and label on confidence in performance.

Dependent variable: confidence in performance								
	Model 1				**Model 2**			
Explanatory variables	**Estimate (95 % CI)**	***SE***	***t*-value**	***p*-value**	**Estimate (95 % CI)**	***SE***	***t*-value**	***p*-value**
Intercept	4.23 (3.86 – 4.60)	0.19	22.2	**<0.001**	4.38 (3.97 – 4.79)	0.21	21.14	**<0.001**
Treatment (OXT vs. sham)	0.18 (-0.33 – 0.70)	0.26	0.70	0.485	0.05 (-0.53 – 0.63)	0.3	0.18	0.858
Label (Energy Drink vs. Soft Drink)	0.3 (-0.22 – 0.83)	0.27	1.12	0.263	0.09 (-0.47 – 0.66)	0.29	0.32	0.748
Trial	0.02 (-0.01 – 0.04)	0.01	1.49	0.137	0.02 (-0.01 – 0.04)	0.01	1.27	0.205
Treatment x Label	-0.29 (-1.03 – 0.44)	0.38	-0.78	0.436	0.0005 (-0.81 – 0.81)	0.41	0	0.999
AQ					-0.08 (-0.30 – 0.14)	0.11	-0.73	0.467
General Trust					0.08 (-0.14 – 0.30)	0.11	0.71	0.48
Positive Affect (post - pre)					0.17 (-0.03 – 0.37)	0.1	1.69	0.093
Negative Affect (post - pre)					-0.11 (-0.32 – 0.09)	0.1	-1.11	0.269
Age					-0.33 (-0.59 – -0.06)	0.14	-2.36	**0.019**
Treatment Guess					0.02 (-0.18 – 0.22)	0.1	0.19	0.846
Income					-0.04 (-0.29 – 0.22)	0.13	-0.3	0.767
Hours of sleep					0.11 (-0.09 – 0.31)	0.1	1.04	0.299
Time since waking up					-0.09 (-0.29 – 0.12)	0.1	-0.84	0.402
Energy drink consume					-0.08 (-0.30 – 0.14)	0.11	-0.68	0.496
Belief in Energy Drink effects					0.08 (-0.14 – 0.31)	0.11	0.73	0.466
Random Effects								
σ^2	0.83				0.76			
T_{00}	1.66 $_{ID}$				1.50 $_{ID}$			
N	202 $_{ID}$				168 $_{ID}$			
Observations	1414				1176 [a]			
Marginal R^2/ Conditional R^2	0.005 / 0.669				0.087 / 0.692			

Note: We measured confidence in performance every 6th trial in form of expectations about performance in the upcoming trial. Only the data of the first run was used for the analysis because confidence in the second run could be biased by the experienced performance in the first run. Model contains random intercepts for participants. The variables treatment and label were dummy coded (sham/Soft Drink = 0, OXT/Energy Drink = 1), treatment guess and trial are mean centered, and all other non-binary variables were z-scored. AQ, Autism Spectrum Quotient; CI, confidence interval; OXT, oxytocin; *SE*, standard error of the estimate. [a] missing data points for variable income due to voluntary nature of this question.

Tab. A 13: Linear regression model with average cognitive performance in the numerical stroop task as dependent variable.

Dependent variable: average cognitive performance				
Explanatory variables	**Estimate (95 % CI)**	***SE***	***t*-value**	***p*-value**
Intercept	5.65 (5.46 – 5.83)	0.09	60.42	**<0.001**
Label (Energy Drink vs. Soft Drink)	0.2 (-0.06 – 0.46)	0.13	1.53	0.129
Trust in brand marketers	-0.09 (-0.26 – 0.09)	0.09	-0.99	0.325
Anticipated performance	0.05 (-0.15 – 0.25)	0.1	0.47	0.636
Label x trust in brand marketers	0.07 (-0.20 – 0.35)	0.14	0.54	0.588
Label x anticipated performance	-0.12 (-0.39 – 0.15)	0.14	-0.86	0.393
Observations	202			
R^2 / R^2 adjusted	0.020 / -0.005			

Note: We measured anticipated performance in form of expectations about performance before the start of the task. Only the data of the first run was used for the analysis because anticipated performance of the second run could be biased by the experienced performance in the first run. The variable label is dummy coded (Soft Drink = 0, Energy Drink = 1) and all other non-binary variables were z-scored. AQ, Autism Spectrum Quotient; CI, confidence interval; SE, standard error of the estimate.

Tab. A 14: Linear mixed-effects regression model for the synbiotic intervention effect on anthropometric data (BMI and proportion of body fat) while controlling for age.

	BMI (kg/m^2)				**Proportion of body fat (%)**			
Explanatory variables	**Estimate (95 % CI)**	***SE***	***t*-value**	***p*-value**	**Estimate (95 % CI)**	***SE***	***t*-value**	***p*-value**
Intercept	25.63 (24.77 – 26.49)	0.44	58.52	**<0.001**	20.19 (18.81 – 21.56)	0.7	28.7	**<0.001**
Treatment (VER vs. PLC)	-0.04 (-1.24 – 1.15)	0.61	-0.07	0.942	-0.8 (-2.72 – 1.12)	0.98	-0.81	0.418
Session (post vs. pre)	0.03 (-0.12 – 0.18)	0.08	0.45	0.651	-0.51 (-1.04 – 0.01)	0.27	-1.91	0.059
Age	0.64 (0.06 – 1.23)	0.3	2.15	**0.034**	2.09 (1.15 – 3.03)	0.48	4.35	**<0.001**
Treatment x Session	-0.09 (-0.30 – 0.12)	0.11	-0.85	0.397	-0.06 (-0.79 – 0.68)	0.38	-0.15	0.883
Random Effects								
σ^2	0.13				1.59			
T_{00}	8.68 $_{Participant}$				20.99 $_{Participant}$			
N	95 $_{Participant}$				95 $_{Participant}$			
Observations	190				185			
Marginal R^2 / Conditional R^2	0.045 / 0.985				0.165 / 0.941			

Notes: Proportion of body fat and weight were determined via bioelectrical impedance analysis with a body composition scale (TANITA®). Model contains random intercepts for participants. The continuous variable age is z-scored, and treatment and session were dummy coded (PLC/pre = 0, VER/post = 1). BMI, Body mass index; CI, confidence interval; PLC, Placebo; *SE*, standard error of the estimate; VER, verum.

Tab. A 15: Linear mixed-effects regression model for the synbiotic intervention effect on reported hunger while controlling for proportion of body fat and age.

Dependent variable: hunger				
Explanatory variables	**Estimate (95 % CI)**	***SE***	***t*-value**	***p*-value**
Intercept	3.41 (3.02 – 3.80)	0.20	17.23	**<0.001**
Treatment (VER vs. PLC)	-0.08 (-0.62 – 0.46)	0.28	-0.28	0.782
Session (post vs. pre)	-0.41 (-0.81 – -0.02)	0.20	-2.05	**0.043**
Fat	-0.16 (-0.40 – 0.08)	0.12	-1.29	0.198
Age	-0.28 (-0.53 – -0.03)	0.13	-2.18	**0.031**
Treatment x Session	0.41 (-0.15 – 0.96)	0.28	1.44	0.153
Random Effects				
σ^2		0.9		
$T_{00\ Participant}$		0.82		
$N_{\ Participant}$		95		
Observations		185		
Marginal R^2 / Conditional R^2		0.086 / 0.523		

Notes: Participants reported their hunger level on a continuous scale from 1 = not hungry at all to 7 = extremely hungry around 3 hours after a standardized snack and immediately before the fMRI scanning session. Proportion of body fat was determined via bioelectrical impedance analysis with a body composition scale (TANITA®). Model contains random intercepts for participants. Continuous variables age and proportion of body fat were z-scored, treatment and session were dummy coded (PLC/pre = 0, VER/post = 1). CI, confidence interval; PLC, Placebo; SE, standard error of the estimate; VER, verum.

Tab. A 16: Linear mixed-effects regression model for the synbiotic intervention effect on self-reported eating behavior in the Three Factor Eating Questionnaire.

	TFEQ - Cognitive Restraint				TFEQ - Disinhibition			
Explanatory variables	**Estimate (95 % CI)**	***SE***	***t*-value**	***p*-value**	**Estimate (95 % CI)**	***SE***	***t*-value**	***p*-value**
Intercept	4.89 (3.76 – 6.03)	0.58	8.48	**<0.001**	4.73 (4.00 – 5.47)	0.37	12.63	**<0.001**
Treatment (VER vs. PLC)	0.86 (-0.71 – 2.44)	0.80	1.08	0.284	0.92 (-0.11 – 1.94)	0.52	1.76	0.082
Session (post vs. pre)	0.11 (-0.54 – 0.77)	0.33	0.35	0.730	-0.14 (-0.70 – 0.43)	0.29	-0.47	0.639
Fat	0.33 (-0.37 – 1.03)	0.36	0.93	0.353	1.14 (0.67 – 1.61)	0.24	4.72	**<0.001**
Age	-0.88 (-1.68 – -0.08)	0.41	-2.15	**0.034**	-0.79 (-1.29 – -0.28)	0.26	-3.05	**0.003**
Treatment x Session	0.06 (-0.84 – 0.97)	0.46	0.14	0.889	0.10 (-0.69 – 0.89)	0.40	0.26	0.798
Random Effects								
σ^2	2.41				1.85			
τ_{00}	12.54 $_{Participant}$				4.40 $_{Participant}$			
N	95 $_{Participant}$				95 $_{Participant}$			
Observations	185				185			
Marginal R^2 / Conditional R^2	0.051 / 0.847				0.178 / 0.757			

	TFEQ - Hunger			
Explanatory variables	**Estimate (95 % CI)**	***SE***	***t*-value**	***p*-value**
Intercept	4.45 (3.57 – 5.32)	0.45	9.98	**<0.001**
Treatment (VER vs. PLC)	0.62 (-0.59 – 1.84)	0.62	1.00	0.318
Session (post vs. pre)	0.25 (-0.42 – 0.92)	0.34	0.72	0.473
Fat	0.36 (-0.20 – 0.92)	0.29	1.26	0.212
Age	-1.09 (-1.69 – -0.49)	0.31	-3.55	**<0.001**
Treatment x Session	-0.89 (-1.83 – 0.04)	0.48	-1.88	0.063
Random Effects				
σ^2	2.57			
$\tau_{00\ Participant}$	6.28			
$N_{Participant}$	95			
Observations	185			
Marginal R^2 / Conditional R^2	0.108 / 0.741			

Notes: Proportion of body fat was determined via bioelectrical impedance analysis with a body composition scale (TANITA®). Excluding one outlier each for Cognitive Restraint and Disinhibition (-/+ 3 SD) did not substantially change the results. Model contains random

intercepts for participants. Continuous variables age and proportion of body fat were z-scored, treatment and session were dummy coded (PLC/pre = 0, VER/post = 1). CI, confidence interval; TFEQ, Three Factor Eating Questionnaire; PLC, placebo; SE, standard error of the estimate; VER, verum.

Tab. A 17: Linear mixed-effects regression model for the impact of the synbiotic intervention on taste- and health-ratings while controlling for age and proportion of body fat.

	Mean Taste-Rating				**Mean Health-Rating**			
Explanatory variables	**Estimate (95 % CI)**	***SE***	***t*-value**	***p*-value**	**Estimate (95 % CI)**	***SE***	***t*-value**	***p*-value**
Intercept	58.95 (55.80 – 62.10)	1.61	36.72	**<0.001**	37.12 (34.44 – 39.81)	1.37	27.08	**<0.001**
Treatment (VER vs. PLC)	0.32 (-4.06 – 4.71)	2.24	0.14	0.885	2.81 (-0.93 – 6.55)	1.91	1.47	0.144
Session (post vs. pre)	-1.56 (-4.17 – 1.05)	1.33	-1.17	0.245	0.35 (-1.52 – 2.21)	0.95	0.36	0.717
Age	-0.2 (-2.22 – 1.82)	1.03	-0.19	0.848	-0.88 (-2.59 – 0.84)	0.88	-1.00	0.318
Fat	-1.29 (-3.43 – 0.85)	1.09	-1.18	0.241	0.69 (-1.19 – 2.57)	0.96	0.72	0.475
Treatment x Session	0.45 (-3.19 – 4.09)	1.86	0.24	0.811	1.05 (-1.54 – 3.65)	1.32	0.79	0.429
Random Effects								
σ^2	39.12				19.82			
τ_{00}	75.28 $_{Participant}$				64.11 $_{Participant}$			
N	95 $_{Participant}$				95 $_{Participant}$			
Observations	185				185			
Marginal R^2 / Conditional R^2	0.021 / 0.665				0.048 / 0.775			

Notes: Each participant rated 52 food items separately for subjectively expected taste and health on a visual analog scale ranging from 0 to 100. The order of taste and health blocks was randomized and counterbalanced between participants but kept constant across the two sessions within participants. Mean taste- and health-ratings were calculated across all 52 food items for each participant and each session. Proportion of body fat was determined via bioelectrical impedance analysis with a body composition scale (TANITA®). Model contains random intercepts for participants. Continuous variables age and proportion of body fat were z-scored, treatment and session were dummy coded (PLC/pre = 0, VER/post = 1). CI, confidence interval; PLC, placebo; *SE*, standard error of the estimate; VER, verum.

Tab. A 18: Linear mixed-effects regression model for the impact of the synbiotic intervention on taste- and health-ratings moderated by objective health (Nutri Score) of the food items.

	Taste-Rating				Health-Rating			
Explanatory variables	**Estimate (95 % CI)**	***SE***	***t*-value**	***p*-value**	**Estimate (95 % CI)**	***SE***	***t*-value**	***p*-value**
Intercept	58.85 (55.88 – 61.82)	1.52	38.83	**<0.001**	37.11 (34.51 – 39.70)	1.32	28.02	**<0.001**
Nutri-Score	-0.51 (-1.64 – 0.63)	0.58	-0.88	0.381	-23.79 (-24.72 – -22.86)	0.48	-50.05	**<0.001**
Treatment (VER vs. PLC)	0.41 (-3.73 – 4.54)	2.11	0.19	0.846	2.76 (-0.86 – 6.37)	1.84	1.50	0.138
Session (post vs. pre)	-1.48 (-3.09 – 0.13)	0.82	-1.80	0.072	0.36 (-0.96 – 1.69)	0.68	0.53	0.593
Age	0.17 (-1.64 – 1.98)	0.92	0.19	0.852	-0.88 (-2.44 – 0.68)	0.79	-1.11	0.269
Fat	-1.41 (-3.52 – 0.70)	1.08	-1.31	0.192	0.72 (-1.13 – 2.57)	0.94	0.77	0.446
Nutri-Score x Treatment	-0.07 (-1.66 – 1.52)	0.81	-0.09	0.932	0.69 (-0.61 – 2.00)	0.66	1.04	0.297
Nutri-Score x Session	1.05 (-0.53 – 2.64)	0.81	1.30	0.193	1.07 (-0.24 – 2.37)	0.66	1.60	0.109
Treatment x Session	0.42 (-1.82 – 2.66)	1.14	0.37	0.714	1.1 (-0.74 – 2.94)	0.94	1.17	0.240
Nutri-Score x Treatment x Session	-1.59 (-3.80 – 0.63)	1.13	-1.40	0.161	-0.41 (-2.23 – 1.41)	0.93	-0.44	0.660
Random Effects								
σ^2	769.11				516.78			
τ_{00}	88.53 $_{Participant}$				69.10 $_{Participant}$			
N	95 $_{Participant}$				95 $_{Participant}$			
Observations	9620				9620			
Marginal R^2 / Conditional R^2	0.003 / 0.106				0.476 / 0.538			

Notes: Each participant rated 52 food items separately for subjectively expected taste and health on a visual analog scale ranging from 0 to 100. The order of taste and health blocks was randomized and counterbalanced between participants but kept constant across the two sessions within participants. Individual ratings of each session from each participant were used as dependent variable. Proportion of body fat was determined via bioelectrical impedance analysis with a body composition scale (TANITA®). Model contains random intercepts for participants. Continuous variables age and proportion of body fat were z-scored, treatment x session is dummy coded (PLC/pre = 0, VER/post = 1). CI, confidence interval; PLC, placebo; *SE*, standard error of the estimate; VER, verum.

Tab. A 19: Linear regression model for the association of proportion of healthy choices with the three dimensions of the Three Factor Eating Questionnaire at the pre-intervention timepoint, controlling for age and proportion of body fat.

Dependent variable: proportion of healthy choices				
Explanatory variables	**Estimate (95 % CI)**	***SE***	***t*-value**	***p*-value**
Intercept	62.72 (59.81 – 65.62)	1.46	42.91	**<0.001**
TFEQ - Cognitive Restraint	4.96 (1.82 – 8.10)	1.58	3.14	**0.002**
TFEQ - Disinhibition	-3.19 (-7.18 – 0.81)	2.01	-1.59	0.117
TFEQ - Hunger	-1.36 (-5.21 – 2.50)	1.94	-0.7	0.485
Age	0.21 (-3.40 – 3.82)	1.81	0.11	0.909
Fat	1.94 (-1.78 – 5.66)	1.87	1.04	0.302
Observations		90		
R^2 / R^2 adjusted		0.161 / 0.111		

Notes: Proportion of body fat was determined via bioelectrical impedance analysis with a body composition scale (TANITA®). All variables were z-scored. CI, confidence interval; TFEQ, Three Factor Eating Questionnaire; *SE*, standard error of the estimate.

Tab. A 20: Linear mixed-effects regression model for the synbiotic intervention effect on the proportion of healthy choices across all trials while controlling for the mean health- and taste-difference of choice options, proportion of body fat and age.

Dependent variable: proportion of healthy choices				
Explanatory variables	**Estimate (95 % CI)**	***SE***	***t*-value**	***p*-value**
Intercept	63.23 (59.49 – 66.98)	1.91	33.07	**<0.001**
Treatment (VER vs. PLC)	-0.56 (-5.79 – 4.66)	2.66	-0.21	0.833
Session (post vs. pre)	-3.75 (-7.27 – -0.24)	1.79	-2.09	**0.039**
Fat	0.77 (-1.62 – 3.16)	1.22	0.63	0.527
Age	-0.39 (-2.92 – 2.13)	1.29	-0.30	0.762
Hunger	-1.53 (-3.39 – 0.34)	0.95	-1.60	0.111
Mean Health-Difference	2.50 (0.48 – 4.51)	1.03	2.43	**0.016**
Mean Taste-Difference	3.88 (1.87 – 5.89)	1.03	3.78	**<0.001**
Treatment x Session	1.51 (-3.37 – 6.40)	2.49	0.61	0.545
Random Effects				
σ^2		69.27		
$T_{00\ Participant}$		91.31		
$N_{Participant}$		95		
Observations		185		
Marginal R^2 / Conditional R^2		0.166 / 0.640		

Notes: Proportion of body fat was determined via bioelectrical impedance analysis with a body composition scale (TANITA®). Model contains random intercepts for participants. Continuous variables health-/taste-difference, age, hunger, and proportion of body fat were z-scored, treatment and session were dummy coded (PLC/pre = 0, VER/post = 1). Health- and taste-difference were calculated as healthier – unhealthier item based on the individual ratings. CI, confidence interval; TFEQ, Three Factor Eating Questionnaire; PLC, placebo; *SE*, standard error of the estimate; VER, verum.

Tab. A 21: Linear mixed-effects regression model for the synbiotic intervention effect on the proportion of healthy choices depending on conflict-condition while controlling for the mean health- and taste-difference of choice options, proportion of body fat, age, and hunger.

Dependent variable: proportion of healthy choices				
Explanatory variables	**Estimate (95 % CI)**	***SE***	***t*-value**	***p*-value**
Intercept	85.43 (80.53 – 90.32)	2.50	34.2	**<0.001**
Treatment (VER vs. PLC)	-3.18 (-9.98 – 3.62)	3.47	-0.92	0.36
Session (post vs. pre)	-4.18 (-9.68 – 1.31)	2.80	-1.49	0.137
Condition (conflict vs. no-conflict)	-44.73 (-50.41 – -39.06)	2.90	-15.44	**<0.001**
Fat	0.35 (-2.19 – 2.90)	1.30	0.27	0.786
Age	-0.4 (-3.07 – 2.26)	1.36	-0.30	0.766
Hunger	-2.15 (-4.15 – -0.14)	1.02	-2.10	**0.037**
Mean Health-Difference	2.69 (0.55 – 4.83)	1.09	2.46	**0.014**
Mean Taste-Difference	-3.53 (-5.63 – -1.43)	1.07	-3.30	**0.001**
Treatment x Session	3.63 (-4.01 – 11.27)	3.90	0.93	0.352
Treatment x Condition	5.21 (-2.49 – 12.91)	3.93	1.33	0.186
Session x Condition	1.24 (-6.45 – 8.93)	3.92	0.32	0.752
Treatment x Session x Condition	-4.36 (-15.09 – 6.38)	5.48	-0.80	0.427
Random Effects				
σ^2		173.13		
$T_{00\ Participant}$		98		
$N_{\ Participant}$		95		
Observations		370		
Marginal R^2 / Conditional R^2		0.651 / 0.777		

Notes: Proportion of body fat was determined via bioelectrical impedance analysis with a body composition scale (TANITA®). Model contains random intercepts for participants. Continuous variables health-/taste-difference, age, and proportion of body fat were z-scored, treatment, session, and conflict-condition were dummy coded (PLC/pre/no-conflict = 0, VER/post/conflict = 1). Health- and taste-difference were calculated as abs(left – right) item based on the individual ratings. CI, confidence interval; TFEQ, Three Factor Eating Questionnaire; PLC, placebo; SE, standard error of the estimate; VER, verum.

Tab. A 22: Mixed-effects logistic regression model for testing the impact of the synbiotic intervention on the integration of health- and taste-attributes while controlling for proportion of body fat, age, hunger.

Dependent variable: *choice left*				
Explanatory variables	**Odds Ratio (95 % CI)**	***SE***	**z-value**	***p*-value**
Intercept	1.00 (0.94 – 1.07)	0.03	0.09	0.930
Health-Difference	2.27 (2.12 – 2.43)	0.08	23.27	**<0.001**
Taste-Difference	3.84 (3.56 – 4.14)	0.15	34.68	**<0.001**
Treatment (VER vs. PLC)	1.05 (0.96 – 1.15)	0.05	1.04	0.297
Session (post vs. pre)	0.93 (0.86 – 1.01)	0.04	-1.63	0.102
Fat	1.04 (1.00 – 1.08)	0.02	1.90	0.058
Age	0.96 (0.93 – 1.00)	0.02	-1.84	0.065
Hunger	0.99 (0.95 – 1.02)	0.02	-0.67	0.502
Treatment x Session	1.02 (0.91 – 1.15)	0.06	0.39	0.693
Health-Difference x Treatment	0.94 (0.86 – 1.04)	0.05	-1.20	0.231
Health-Difference x Session	0.85 (0.78 – 0.94)	0.04	-3.28	**0.001**
Taste-Difference x Treatment	1.01 (0.91 – 1.13)	0.06	0.22	0.829
Taste-Difference x Session	0.91 (0.82 – 1.01)	0.05	-1.71	0.087
Health-Difference x Treatment x Session	1.12 (0.98 – 1.28)	0.08	1.64	0.100
Taste-Difference x Treatment x Session	1.34 (1.14 – 1.56)	0.10	3.68	**<0.001**
Random Effects				
σ^2		3.29		
$T_{00\ Participant}$		0.01		
$N_{\ Participant}$		95		
Observations		27096		
Marginal R^2 / Conditional R^2		0.445 / 0.447		

Notes: Proportion of body fat was determined via bioelectrical impedance analysis with a body composition scale (TANITA®). Model contains random intercepts for participants. Continuous variables proportion of body fat, age, hunger, taste-, and health-differences were z-scored, treatment and session were dummy coded (PLC/pre = 0, VER/post = 1). Health- and taste-difference were calculated as left-right item based on the individual ratings. CI, confidence interval; PLC, placebo; *SE*, standard error of the estimate; VER, verum.

Tab. A 23: Mixed-effects logistic regression for testing the impact of the synbiotic intervention on the integration of health- and taste-attributes for healthy choices while controlling for proportion of body fat, age, and hunger.

Dependent variable: *choice healthy*				
Explanatory variables	**Odds Ratio (95 % CI)**	***SE***	**z-value**	***p*-value**
Intercept	2.36 (1.89 – 2.93)	0.26	7.66	**<0.001**
Health-Difference	1.43 (1.33 – 1.53)	0.05	10.18	**<0.001**
Taste-Difference	4.55 (4.19 – 4.95)	0.19	35.79	**<0.001**
Treatment (VER vs. PLC)	0.94 (0.70 – 1.28)	0.15	-0.38	0.703
Session (post vs. pre)	0.77 (0.70 – 0.85)	0.04	-5.33	**<0.001**
Fat	1.14 (1.01 – 1.29)	0.07	2.10	**0.036**
Age	0.96 (0.82 – 1.12)	0.08	-0.57	0.566
Hunger	0.91 (0.86 – 0.97)	0.03	-2.92	**0.003**
Treatment x Session	1.16 (1.02 – 1.32)	0.08	2.24	**0.025**
Health-Difference x Treatment	0.98 (0.89 – 1.08)	0.05	-0.36	0.717
Health-Difference x Session	0.96 (0.88 – 1.06)	0.05	-0.82	0.414
Taste-Difference x Treatment	0.95 (0.84 – 1.07)	0.06	-0.87	0.382
Taste-Difference x Session	0.90 (0.81 – 1.00)	0.05	-1.88	0.061
Health-Difference x Treatment x Session	1.05 (0.92 – 1.20)	0.07	0.74	0.460
Taste-Difference x Treatment x Session	1.35 (1.15 – 1.59)	0.11	3.65	**<0.001**
Random Effects				
σ^2		3.29		
$T_{00\ Participant}$		0.51		
$N_{\ Participant}$		95		
Observations		27096		
Marginal R^2 / Conditional R^2		0.406 / 0.486		

Notes: Proportion of body fat was determined via bioelectrical impedance analysis with a body composition scale (TANITA®). Model contains random intercepts for participants. Continuous variables proportion of body fat, age, hunger, taste-, and health-differences were z-scored, treatment and session were dummy coded (PLC/pre = 0, VER/post = 1). Health- and taste-difference were calculated as healthy-unhealthy item based on the individual ratings. CI, confidence interval; PLC, placebo; *SE*, standard error of the estimate; VER, verum.

Tab. A 24: Linear mixed-effects regression model for the impact of the synbiotic intervention on choice times.

Dependent variable: choice time				
Explanatory variables	**Estimate (95 % CI)**	***SE***	***t*-value**	***p*-value**
Intercept	1768.41 (1701.18 – 1835.64)	34.3	51.55	**<0.001**
Health-Difference	-15.79 (-29.13 – -2.45)	6.81	-2.32	**0.020**
Taste-Difference	-10.8 (-23.68 – 2.08)	6.57	-1.64	0.100
Treatment (VER vs. PLC)	57.11 (-36.46 – 150.67)	47.74	1.20	0.235
Session (post vs. pre)	-18.75 (-38.24 – 0.74)	9.94	-1.89	0.059 [2]
Fat	0.96 (-29.39 – 31.31)	15.48	0.06	0.951
Age	48.34 (0.63 – 96.06)	24.35	1.99	**0.050** [1]
Hunger	29.65 (16.66 – 42.63)	6.63	4.47	**<0.001**
Trial	-87.64 (-94.13 – -81.14)	3.32	-26.43	**<0.001**
Treatment x Session	-80.9 (-107.50 – -54.29)	13.57	-5.96	**<0.001**
Health-Difference x Treatment	8.38 (-10.11 – 26.86)	9.43	0.89	0.374
Health-Difference x Session	12.21 (-6.60 – 31.02)	9.60	1.27	0.203
Taste-Difference x Treatment	-0.07 (-18.63 – 18.49)	9.47	-0.01	0.994
Taste-Difference x Session	8.36 (-9.62 – 26.34)	9.18	0.91	0.362
Health-Difference x Treatment x Session	-14.92 (-41.05 – 11.22)	13.34	-1.12	0.263
Taste-Difference x Treatment x Session	-7.12 (-33.22 – 18.98)	13.32	-0.53	0.593
Random Effects				
σ^2	297597.37			
$T_{00\ Participant}$	51537.2			
$N_{\ Participant}$	95			
Observations	27096			
Marginal R^2 / Conditional R^2	0.033 / 0.175			

Notes: [1] Result does not remain significant after excluding choice time outliers (-/+ 3 SD) (excluded observations: *n* = 137). [2] Result becomes significant after excluding choice time outliers (-/+ 3 SD) (excluded observations: *n* = 137, *p* = 0.038). Proportion of body fat was determined via bioelectrical impedance analysis with a body composition scale (TANITA®). Model contains random intercepts for participants. Continuous variables proportion of body fat, age, hunger, taste-, and health-differences were z-scored, treatment and session were dummy coded (PLC/pre = 0, VER/post = 1). Health- and taste-difference were calculated as left-right item based on the individual ratings. CI, confidence interval; PLC, placebo; SE, standard error of the estimate; VER, verum.

Tab. A 25: Linear mixed-effects regression model for the synbiotic intervention effect on rating times for taste and health while controlling for age and proportion of body fat.

	log(Taste-Rating Time)				log(Health-Rating Time)			
Explanatory variables	**Estimate (95 % CI)**	***SE***	***t*-value**	***p*-value**	**Estimate (95 % CI)**	***SE***	***t*-value**	***p*-value**
Intercept	8.08 (8.01 – 8.15)	0.04	230.3	**<0.001**	8.03 (7.95 – 8.10)	0.04	210.2	**<0.001**
Treatment (VER vs. PLC)	-0.04 (-0.14 – 0.05)	0.05	-0.8	0.406	0.09 (-0.02 – 0.19)	0.05	1.7	0.101
Session (post vs. pre)	-0.19 (-0.21 – -0.16)	0.01	-14.5	**<0.001**	-0.13 (-0.16 – -0.10)	0.01	-9.2	**<0.001**
Age	0.09 (0.04 – 0.14)	0.03	3.7	**<0.001**	0.06 (0.002 – 0.11)	0.03	2.0	**0.044**
Fat	-0.04 (-0.08 – 0.0005)	0.02	-1.9	0.054	0.007 (-0.04 – 0.05)	0.02	0.3	0.762
Treatment x Session	-0.02 (-0.06 – 0.01)	0.02	-1.2	0.230	-0.07 (-0.11 – -0.04)	0.02	-3.8	**<0.001**
Random Effects								
σ^2	0.16				0.19			
T_{00}	$0.05_{Participant}$				$0.06_{Participant}$			
N	$95_{Participant}$				$95_{Participant}$			
Observations	8915				8818			
Marginal R^2 / Conditional R^2	0.073 / 0.298				0.042 / 0.278			

Notes: Rating times were natural log-transformed due to a right-skewed data distribution caused by the self-paced rating mode. Proportion of body fat was determined via bioelectrical impedance analysis with a body composition scale (TANITA®). Model contains random intercepts for participants. Continuous variables proportion of body fat and age were z-scored, treatment and session were dummy coded (PLC/pre = 0, VER/post = 1). For taste-ratings 705 observations and for health-ratings 802 observations are missing across different participants due to problems in the recording of reaction times. CI, confidence interval; PLC, placebo; SE, standard error of the estimate; VER, verum.