SUPPLEMENTAL MATERIAL S2

Choosing and matching food-related stimuli

1. Visual Stimulation

The most frequently employed method for assessing brain response to food is the display of food images on a screen. This approach has several advantages. First, unlike oral and olfactory stimulation, the paradigms are relatively simple to create and require no specialized delivery systems. Second, outside of the scanner the sight of food is an indication of food availability and an important exogenous catalyst for promoting behaviors to acquire the food. Learning about the neural systems supporting these behaviors and the variables influencing these systems is important for understanding food choice, food craving and incentive motivation. However, in the scanning environment it is difficult to visually present actual food items. Food pictures provide a reasonable proxy but it is recommended that the pictures be made relevant to food availability and that the participant be made aware of this association. For example, responses in appetitive circuits (e.g. amygdala, orbitofrontal cortex and striatum) are enhanced when participants understand that the observed items will be made available for consumption after the scan (1, 2). Further, the anticipation of eating may interact with many variables of interest. For example, restrained eaters show increased food intake at a taste test when anticipating eating a subsequent meal (3).

A third advantage of using food pictures is the ease with which variables can be manipulated such as portion size, energy density, macronutrient content etc. This flexibility results from a greater ability to acquire and manipulate the images and from faster trial times, allowing greater number of presentations for inter-trial averaging and consequently the assessment of a greater number of factors. This advantage also promotes the creation of parametric designs and greater generalization because the researcher is not limited to the number of “channels” available in liquid and odor delivery devices (typically between 2 and 10). Ease and speed of image presentation also facilitates more involved designs where behavior is manipulated in the scanner, such as bidding for, or choosing between items.

Fourth, using food pictures avoids complications related to nutrient metabolism, satiation and post-ingestive signals that occur when participants are asked to repeatedly taste and ingest liquid stimuli over the course of the fMRI task. Importantly, many factors that can be manipulated to create advantage can also be disadvantageous if not properly considered and controlled. For example, noise can be introduced by collating images that vary in macronutrient content, portion size, caloric load, familiarity, or healthfulness, because many neural circuits of interest are strongly affected by these variables. Likewise, a researcher might be interested in the influence of liking on brain response and sort responses by liking ratings. However, if all liked images are carbohydrate and all disliked images fat then it is impossible to determine whether macronutrient or liking drives differential brain response (see e.g.(4)) . Care should also be taken to equate images on visual perceptual parameters such as contrast, size, color etc.

Finally, it is imperative to use images of foods that are representative of the participants' diet. This is because the value of foods and their ability to recruit brain circuits is strongly tied to their nutritional properties (5-7), which are conveyed by metabolic signals to the brain. As such, foods that have been previously consumed by participants become calorie/nutrient-predictive stimuli capable of eliciting conditioned brain responses, whereas unfamiliar food images will not.

1.1 What should the control stimulus be?

It is also critical to choose an appropriate visual control stimulus. In comparisons of food with nonfood stimuli, low level visual features, such as luminance and contrast should be matched as should stimulus liking and familiarity. In making comparisons between food stimuli it is also important to consider whether one should match portion size, macronutrient content, actual or estimated energy density, actual or estimated cost and perceived healthiness. The appropriate control stimulus may depend on the research question, but generally contrasting high- versus low-calorie food images would provide the best comparison for studies interested in food reward.

1.2 Online resources for various image sets

There are several (food image) sets available online and it is recommended to use these if possible. Examples are the Food-pics database (http://eat.sbg.ac.at/resources/food-pics, (8)) and the Full4Health Image collection (http://nutritionalneuroscience.eu/index.php/11-resources/32-f4h-image-collection, (9)). A more detailed overview is given at the end of this document in Table S1.

2. Olfactory stimulation

Food aromas are potent cues, as anyone who has passed a French bakery on an empty stomach can attest. A meta-analysis comparing visual, olfactory and oral food-cue paradigms found that visual stimulation led to the most extensive and robust activations, with olfactory and oral stimulation as shared runner-ups (10). Surprisingly few studies have directly compared the impact of visual versus olfactory food stimulation. The olfactory cortex is in the limbic system and highly integrated with regions involved in valuation, interoception, drive and memory (11), and as such may have a privileged role in driving food seeking behavior (12). In addition, there are receptors for gut peptides, such as ghrelin, on neurons in the olfactory bulb and evidence that manipulation of these peptides influences olfactory perception (13-16). Hence, the olfactory system is more tightly integrated with physiology regulating metabolism than the visual system and an important target of investigation in relation to food seeking and consumption.

Another attractive feature of the olfactory system is that odors not only indicate food availability, but also food receipt, as olfaction is an integral part of the flavor percept (17). This means that one can use the same physical stimulus as a distal cue of food availability and a proximal cue of food receipt, which is important given the evidence for distinct circuits for anticipatory versus consummatory food reward (18). Further, unlike food pictures, which provide a representation of a food, food aromas, like the sight of real food, indicate availability. This is important because, while presentation of actual food items in the scanner is difficult, olfactometers enable precise delivery of odorants so that sensation can be time-locked with the BOLD response (19-22). With all of these advantages, the primary reason that aromas are not used more frequently is that odor delivery in the scanner is expensive and requires a significant level of expertise to run and maintain odor delivery devices (i.e. olfactometers). Moreover, the few commercial olfactometers that are available are prohibitively expensive and the assembly of one's own device requires a high level of engineering expertise. However, if one is considering taking on these challenges, olfactometers can be found for purchase here: http://www.burghart-mt.de/en/, http://www.osmicenterprises.com/index.html. There are also several published papers describing the steps and equipment necessary to make your own olfactometer (19-22). Several special considerations for odorant delivery are discussed below.

2.1 To sniff or not to sniff

Olfactory sensation depends upon breathing and sniffing (23). Thus, it is important to instruct subjects to sniff in concert with odorant delivery. This is often accomplished with a “count-down cue” to time the sniff (“three, two, one, sniff”) with the olfactometer programmed to deliver the odorant at the end of countdown (18). Another method is to use an airflow sensor at the nostrils and trigger delivery based on sniff initiation or breath inhalation at the nose (24). Although it has been argued convincingly that sniffing is a necessary part of the olfactory percept (25), sniffing is not strictly necessary for olfactory stimulation. Passive diffusion of volatiles to the olfactory epithelium has also been achieved by asking participants to effectively eliminate airflow from breathing in the nasopharynx by practising velopharyngeal closure (26). However, it has been noted that olfactory stimulation during velopharyngeal closure might not effectively activate all brain areas involved in processing olfactory information. This may be due to the fact that sniffing is an integral part of olfactory perception (7, 8). If sniffing is employed, it is an important factor to control, as sniffing itself results in neural activity in olfactory cortex (27), and may be accompanied by movement (if a participant interprets sniffing as a big inhale of breath, rather than small short inhalation). This can be done by measuring sniff vigor and volume with an olfactory mask coupled to a spirometer (28) and standard MRI equipment for measuring breathing rate.

2.2 Orthonasal versus retronasal stimulation

Orthonasal olfaction is associated with sensing foods at a distance and is dependent upon the odorant entering the external nares and flowing across the olfactory epithelium from front to back. In contrast, retronasal olfaction is associated with sensing foods being consumed and is dependent upon volatiles entering the nasopharynx from the oral cavity and flowing across the olfactory epithelium from back to front (29). This is an important consideration because the direction and dynamics of odorant flow across the epithelium is thought to play a role in olfactory coding (30). In addition, orthonasal and retronasal olfaction map on to different aspects of ingestive behavior (anticipation versus consumption). Direct comparison of ortho and retronasal olfaction is complicated because eating is associated with other sensations (e.g. taste, temperature) and mouth movements. However, Hummel and colleagues created a delivery device where tubes are inserted into the nose with one ending at the external nares and another at the nasopharynx to simulate retronasal delivery (31). In so doing, the same physical stimulus can be used to stimulate both orthonasal and retronasal olfaction and differential BOLD response measured to the same odorant (32).

2.3 Design efficiency

A single presentation of an odor in an event-related design requires, at minimum, about 13 seconds, which limits the total number of events that can be presented. Regardless of the design, odor delivery should be short and inter-trial intervals relatively long (ideally even 30 s) because the uniquely rapid habituation to odors is an important consideration, as noted by Poellinger et al. (33). Block designs have higher power, as inter-stimulus time can be shorter and more presentations can be achieved (compare trial duration of 3 s in an on-off block design (34) to between 13-35 s in event-related designs (28, 35). Here habituation is dealt with by using an on-off design with pauses of no odorant delivery during an odor block. In determining how long each block should be it is also important to keep in mind that different cortical areas show different habituation patterns in response to odors (33).

2.4 What should the control stimulus be?

Since sniffing is associated with activation of many regions of interest, it is important to measure responses to odorless sniffs. Here a critical issue is ensuring that the air stream (or ambient air) is not contaminated. This means that the tubes carrying the air to the participants must be cleaned or replaced frequently. When making comparisons between food and non-food odors it is important to consider whether odorants are purely olfactory, such as phenylethal alcohol or if they contain a trigeminal component. Nonfood odors can also produce taste-like sensations. For example, many floral aromas are described as sweet, and to some may even be edible (36). For this reason, it can be useful to have participants rate odorant edibility. Finally, odors are notoriously difficult to name. Differences in nameability between food and nonfood odors may lead to unanticipated confounds. We therefore recommend familiarizing participants with the odorants, providing their labels and measuring discriminability.

3. Oral stimulation

There are several advantages of using oral, rather than (or in addition to) visual and olfactory stimulation. First, the experience of pleasure derived from eating depends heavily on flavor perception, which results from the integration of distinct oral sensations of taste, retronasal olfaction, oral somatosensation and possibly chemesthesis (37). Individual differences in sensitivity of and preference for particular flavors (e.g. sweet concentration preference) and textures (e.g. fat sensing) play an important role in ingestive behavior. Therefore, examination of oral sensation is critical to understanding the neural circuits regulating feeding.

Second, oral stimulation occurs during food consumption and represents a distinct aspect of ingestive behavior from food acquisition. This is an important point because appetitive learning is driven by the generation of errors between predictions/actions and outcomes (38). Whereas visual and olfactory cues provide information important for prediction and action, oral sensory information provides information about outcome. As such, measuring brain response to both oral and extra-oral stimulation provides a more comprehensive assessment of so-called “food reward circuits” and can be valuable for interpreting findings. For example, response in the dorsal striatum to consuming small drops of milkshake is often negatively associated with body mass index (BMI), which has lead researchers to conclude that these striatal “reward” responses are hypo-responsive in obesity (39-42). However, striatal response to high-calorie food images correlates positively with BMI (43-48). This suggests that a more accurate interpretation is that BMI is associated with amplified prediction signals coupled with blunted outcome signals (49).

A third, and relatively unexplored advantage of assessing oral stimulation is that nutrients can be consumed and metabolized. This process is associated with a cascade of events including gastric secretions, hormone release and gut-to-brain neural signaling (i.e. the generation of vagal afferent signals) that are critical for associating food stimuli with their nutritive value (50-53). This provides the opportunity to study the dynamic gut-brain axis, which is emerging as a major factor in understanding metabolism and ingestive behavior in health and in disease. One major hurdle towards this aim is the lack of information on timing, which makes it impossible to time-lock post-oral or metabolic events with brain response. Moreover, because internal state is changing over the course of the scanning session, it is important to measure variables related to internal state, like hunger, fullness and thirst.

Perhaps the biggest disadvantage of oral stimulation is that, to date, it has only been feasible to deliver liquids in the fMRI scanner. This limitation results because of difficulty with delivery and movement. The logistics of delivering a food item, even as small as a blueberry or an M&M™ to a subject lying in an fMRI scanner bore are not trivial. The bore is narrow and head coils often obscure or bar the mouth area. One could conjure an image of a reverse vacuum-like device, but this would need to be non-magnetic and designed so that it poses no risk of choking. However, even if one could successfully deliver the food item the movement caused by chewing has serious consequences for data quality. A basic assumption in fMRI analysis is that a given voxel corresponds to a given volume of brain tissue across time (54). Even small movements can lead to significant displacement and thereby reduce signal to noise, known as “partial volume effects”. However, more problematic is the fact that the movement associated with chewing is directly related to the event of interest. Thus, the data from a given voxel will be derived from two correlated sources, mouth movement causing displacements and BOLD response related to eating. Solving these issues would bring about a major step forward and is an important direction for research and development.

Notably, early studies that used water bolus methodology to measure regional cerebral blood flow with PET did not have the same magnitude of constraint. Voxels were larger, making small displacements less detrimental to SNR, temporal resolution was poorer, making precisely timed phasic stimulus delivery unnecessary, and participants were only inserted into the PET camera up to their forehead. In one study this allowed experimenters to hand-feed subjects squares of chocolate and measure brain response over a 60-sec window (rather poor temporal resolution compared to the 1-3-sec typical of current fMRI) as participants let the chocolate melt in their mouths (55). This eating experience is arguably more pleasurable than consuming small drops of liquid. Unfortunately, PET fell out of favor because it requires the use of a radioligand, is extremely expensive, and the poor temporal resolution posed significant limitations for studies of rapid cognitive and perceptual operations. While the temporal disadvantage may not be as problematic for feeding research the cost and radiation exposure keep PET beyond the scope of most research programs. Although, MRI may be used to study blood-flow related responses to food with the use of arterial spin labeling techniques (ASL, (56)) delivery of solid food remains challenging. This is not an insignificant limitation given the importance of actions in motivated behavior and habitual responding, and bearing in mind the established literature documenting differences in oral sensation and metabolism in the consumption of liquid versus solid energy sources (57). Although these considerations are important, it is worth noting that liquid delivery is also not akin to drinking since only very small boluses of liquid are delivered at a time. Thus each “food” event is limited primarily to stimulation of oral sensation. Special considerations for oral stimulation are discussed below.

3.1 To swallow or not to swallow

Swallowing is an integral part of the act of eating, but it also introduces movement, which degrades data quality. Therefore, it is worth considering whether measures should be taken to limit swallowing or to de-correlate it from the event of interest. For example, if a researcher is interested in taste intensity perception then they could opt for a design where very small quantities of liquid are sprayed into the mouth negating the need to swallow (58), where the liquids are sucked out of the back of the mouth (59), or where participants are asked to postpone swallowing until a cue is presented, decoupling it from the onset of taste perception (60). One caveat associated with these methods is that taste buds are distributed across the entire oral epithelium, not only on the tongue, including the palate and pharynx (61), therefore taste stimulation is not comprehensive. However, if a researcher wanted to study the act of eating then a swallow is necessary, since only then is a food consumed. In addition, retronasal olfaction is a critical part of flavor (17) and is dependent on a swallow to move volatiles from oral to nasal cavity via the nasophayrnx (58, 62, 63).

3.2 Choosing a taste task

Generally, in fMRI studies there is the risk of participants falling asleep during passive stimulation tasks. This is often counteracted by engaging them with a task, such as making a perceptual rating. With oral stimulation somnolence is less of a risk, as participants are engaged in managing small drops of liquids dripping into the mouth while in a supine position. Moreover, asking participants to engage in a task hinders detection of sensory responses because taste representation is sparse and the insular "taste" cortex is multimodal. More specifically, unlike visual, motor, somatosensory, and auditory cortex where most neurons are engaged by the sensory input or motor output, many neurons in taste cortex do not respond to taste (64). For this reason, this multimodal cortex has been proposed as better defined as ingestive cortex (65). In addition, insular cortex is engaged by attention to body states (66). The combination of sparse taste representation and attentional activation may be equal or higher than sensory activation in gustatory cortex (35, 67, 68). Perceptual judgments (such as rating pleasantness or intensity) also influence the location of activation within gustatory cortex (69-71). There is also evidence that in the absence of a task the flow of stimulus information differs. For example during passive tasting there is stronger connectivity between the amygdala and the insula compared to performing a detection, identification or pleasantness rating task (70). Therefore, if the goal of the experiment is to understand a process related to sensation it is best to deliver the liquids passively.

Another important consideration is whether to deliver a cue to alert the participant to the impeding stimulus delivery. If no cue is provided and several different stimuli are used (e.g. milkshake and tasteless), the stimuli are generally unpredictable and subject to the generation of prediction errors. However, if a cue signals the identity of a forthcoming stimulus (e.g. a picture of a milkshake or water) then no error signal is generated. This is important because dopamine release is integral to error signal generation and individual variance in dopamine signaling may influence the sensory response (72). A similar situation occurs when no cue is used but the timing of delivery is random.

Another consideration is the quality of a cue used. If information about the stimulus is conveyed by the cue this too can have an important influence on the response (73-75).

3.3 What should the control stimulus be?

Early studies made the intuitive choice to use water as a stimulus e.g. (76, 77). However, water has a “taste” (78) and has an important physiological significance. As such, comparison of taste (e.g. sweet, sour, salty, bitter) minus water, may fail to isolate gustatory cortex. Subsequent studies then showed that water activates gustatory cortex as effectively as taste (79, 80). Water can also be a reinforcing stimulus itself, especially under a thirsty state. Two alternatives to water have been proposed. First, Frey and Petrides asked participants to move their mouths and swallow as if they were tasting (79). This method was successful in producing greater response to taste vs. mouth movement in chemosensory cortex. A second option developed by O’Doherty et al. is to administer a solution that contains the main molecular components of saliva (bicarbonate sodium and potassium chloride) (81). Of note, it is important not to describe the solution as “artificial saliva” but rather as “tasteless” or “control” to avoid negative responses. Tasteless solutions have become the gold standard. However, they do not have the typical viscosity associated with saliva and many participants report that they perceive taste. For this reason, it is best to create individualized tasteless solutions based on a “two alternative forced choice” procedure with several concentrations. Here, the subject is asked to “choose the solution that tastes most like nothing, or has the least taste” (see e.g. (82)). The concentration of the chosen tasteless solution may differ between individuals by a factor 8, which means that a single average concentration should not be used, but a determination of each participant’s tasteless is important.

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Supplemental Table S1. Online food image resources

Name	Nr images Food/non-food	Categories	Culture	Ratings/measures	URL	Publication[1]
Databases developed for research						
F4H Image Collection	377/41	Sweet, savory, high and low calorie, non-foods (office utensils)	European (Netherlands, Scotland, Greece, Germany, Sweden, Hungary)	Liking, perceived calories and healthiness	http://nutritionalneuroscience.eu/index.php/resources/f4h-image-collection	Charbonnier et al. 2016 DOI 10.17605/OSF.IO/CX7TP
FRIDa	295/582	Natural, transformed, rotten food + various non-foods	Mediterranean	Valence, arousal, familiarity typicality ambiguity, perceived calorie-content, perceived immediate-edibility, perceived level of transformation	https://foodcast.sissa.it/neuroscience/	Foroni et al. 2013
Food.pics	896/314	sweet and savoury foods, high and low calorie, warm and cold dishes, processed and raw foods	German, North-American	palatability, desire to eat, complexity, recognizability, valence, arousal	http://eat.sbg.ac.at/resources/food-pics	Blechert et al. 2014

Name	Nr images Food/non-food	Categories	Culture	Ratings/measures	URL	Publication[1]
OLAF	96	Sweet high fat, salty high fat, fruit, veggies	Spanish	valence, arousal, dominance craving	https://zenodo.org/record/10202	Miccoli et al. 2014
Databases developed for AI learning[2]						
PFID		Fast food	United States		http://pfid.rit.albany.edu/	
Food-101	101.000	1000 categories			https://www.vision.ee.ethz.ch/datasets_extra/food-101/	
UEC FOOD 256	256	Food	Japanese	N/A	http://foodcam.mobi/dataset256.html	
Food-5K Food-11	2500/16643	Food and non-food	?	N/A	http://mmspg.epfl.ch/food-image-datasets	

[1] Blechert, J., A. Meule, N. A. Busch and K. Ohla (2014). "Food-pics: an image database for experimental research on eating and appetite." Frontiers in Psychology 5(617).
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[2] AI databases contain typical and less typical and noisy images, but may be a good source to select appropriate images from.