Mega-Analysis on the Neural Correlates of Food Viewing and its' Association with Gender, Age, BMI and Hunger State

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Abstract

Background: The omnipresence of food cues in our environment stimulates overeating and contributes to the obesity epidemic. The neural response when viewing these food cues could elucidate the mechanism through which they stimulate overconsumption. Heterogeneity between studies conducted so far may have impeded the detection of small effects. These limitations may be overcome by data pooling on the subject-level (i.e., mega-analysis).

Objectives: The objective was to establish a mega-analysis of food viewing. We aim to investigate brain response to food versus non-food viewing (F>NF) and high caloric versus low-caloric food viewing (HC>LC) accounting for gender, age, BMI and hunger state.

Methods: Studies were searched using the database PubMed. Eligibility criteria included: the publication in a peer-reviewed journal, in English, between 2005 and 2021 reporting fMRI brain response using a passive food viewing paradigm.

Results: Data from 1030 individuals (15 studies) were included. Data harmonisation included, reslicing, realignment, masking and outlier exclusion. The main analyses were two multiple regressions investigating brain activation in response F>NF and HC>LC. Both analyses suffered from a large number of missing voxels. For F>NF brain activation in insula was found. Upon food cues, females compared to males demonstrated higher activations in the left inferior temporal gyrus. Hungrier participants showed increased brain response for F>NF in the left calcarine and cerebellum as well as the right inferior temporal gyrus and hippocampus. For HC>LC brain activation in left hippocampus, amygdala, middle frontal gyrus and the hypothalamus was found.

Conclusion: Image quality was found to be suboptimal. Improvement opportunities for fMRI mega-analysis are discussed.

Keywords: fMRI, data pooling, food cue exposure, data harmonisation

Mega-Analysis on The Relationship Between Gender, Age, BMI and the Neural Correlates of Food Viewing

Obesity is one of the most prevalent health threats and has been linked to a number of chronic diseases, including type two diabetes, coronary artery disease and cancer (Mitchell et al., 2011). A higher energy intake than expenditure is an important driver of obesity. This suggests that obesity is preventable in most cases. However, the omnipresence of food cues in the environment stimulate overeating and consequential energy imbalances in the body (Lawrence et al., 2012). Food cues stimulate the quantity of food intake and influence the types of foods consumed. The response to food cues is primarily guided by the visual system. Eye-tracking studies have demonstrated that a longer gaze duration and higher number of fixations are predictive of food choice. Specifically, food cues high in caloric density are looked upon longer and more frequently (Manippa et al., 2018). Similarly, neuroimaging studies demonstrated that food images evoke different brain responses than non-food images (e.g. Burger & Berner, 2014; Dagher, 2012; Pursey et al., 2014; van der Laan et al., 2011). The neural signature could elucidate the mechanisms through which food cues stimulate overconsumption. Heterogeneity between studies conducted so far may and small sample sizes have impeded the detection of small effects. These limitations may be overcome by data pooling on the subject-level (i.e., mega-analysis). The paper at hand, aims at establishing a fMRI mega-analysis to identify the neural signature of food cue exposure.

Neural Correlates of Food Viewing

Functional magnetic resonance imaging (fMRI) studies have demonstrated the involvement of different brain regions in response to food cues. A common fMRI paradigm to measure food cue reactivity involves participants' passive viewing of food images and non-food images. Across studies, the appetitive brain network is most consistently activated upon food cues. This includes the amygdala and hippocampus, the orbitofrontal cortex and

ventromedial prefrontal cortex, the striatum and the insula (Dagher, 2012; Neseliler et al., 2017; Smeets et al., 2012). On the one hand, this network is regulated by the dorsolateral prefrontal cortex and the anterior cingulate gyrus, regions associated with self-regulation. On the other hand, the hypothalamus and ascending dopaminergic projections homeostatic signals regulate the network (Neseliler et al., 2017).

Studies have shown that the brain response to food cues is modulated by different trait and state factors. The three most relevant trait factors are gender, age and Body Mass Index (BMI), while hunger constitutes an important state factor (Smeets et al., 2012).

First, gender modulates the brain response to food cues. In a systematic review Chao et al. (2017) suggest that women demonstrate higher neural activation in the limbic system as well as the frontal and cortical system when viewing food cues compared to men. Anatomically, both the limbic and the frontal cortex are larger in females compared to males (Zaidi, 2010). Functionally these regions are involved in executive functioning, emotion regulation and reward processing. This suggests that females compared to males respond to food cues with increased cognitive and emotional control. Gender difference to food cue reactivity are also driven by biochemical signals (Zaidi, 2010). During the luteal phase compared to the follicular phase of the menstrual cycle, females eat more (Davidsen et al., 2007) and demonstrate altered brain activation upon food cues in reward related brain regions (Frank et al., 2010; Van Vugt, 2010). While most studies report increase food cue reactivity in females (Chao et al., 2017), few studies (Geliebter et al., 2013) reported increased reactivity in the supplementary motor cortex in males compared to females. These studies include people with higher BMIs and it has been suggested that as BMI increases, gender differences in brain response to food cues are attenuated (Chao et al., 2017).

Second, age modulates the brain response to food cues: van Meer et al. (2016) showed that children compared to adults demonstrated different brain responses to food cues. Compared to adults, children viewing unhealthy compared to healthy foods demonstrate stronger activation in the left precentral gyrus. This suggests a higher motivational or motor response to unhealthy foods in younger people. In a food choice task, younger children, and children who were becoming overweight showed less brain activation in the dorsolateral prefrontal cortex, suggesting decreased self-control (van Meer et al., 2019). However in a meta-analysis, differences between children and adults upon food cue exposure diminished, possibly due to high between study variability (van Meer et al., 2015). Moreover, little is known about elderly; one study indicates that as age increases (from 20 to 53), the activation of the dorsolateral prefrontal cortex decreases in response to food versus non-food images (Cheah et al., 2014). This suggests a reduction in self-control with age. However, Charbonnier et al. (2018) found no differences between elderly and adults in response to food cues.

Third, BMI modulates the brain response to food cues: in a meta-analysis, Brooks et al. (2013) found increased activation in the left dorsomedial prefrontal cortex, the right hippocampal and precentral gyrus as well as the right anterior cingulate cortex in people with higher compared to lower BMI in response to food cues. In addition, people with higher BMI demonstrated decreased brain activity in left dorsolateral prefrontal cortex and the left insular. For high caloric foods the reactivity is further amplified (Pursey et al., 2014). The increase in activation in reward related brain areas (i.e. increased positive appraisal) together with the decrease in activation in control related brain areas upon food cues in individuals with higher BMIs suggest a neural mechanisms through which food cues stimulate overconsumption (Neseliler et al., 2017). This effect has been shown to be independent of age (Samara et al., 2018; van Meer et al., 2016) and can be amplified by increased levels of hunger (Pursey et al., 2014). Importantly, intervention studies have shown that higher activations in reward related

brain regions and lower activations in control related brain regions for high caloric versus low caloric food images predict lower weight loss success (e.g., Hermann et al., 2019; Murdaugh et al., 2012; Yokum et al., 2014).

Fourth, hunger state modulates the brain response to food cues: in a meta-analysis, van der Laan et al. (2011) demonstrated greater activation in the right parahippocampal gyrus extending to the amygdala as well as the left lateral orbitofrontal cortex in fasted compared to satiated subjects. This may reflect higher desirability and expected pleasantness of food in hungry compared to satiated subjects. In addition, Charbonnier et al. (2018) demonstrated increased activation in the dorsomedial and dorsolateral prefrontal cortex upon viewing high caloric foods in hungry compared to satiated participants indicating higher valuation of food and increased inhibitory response, respectively.

However, low power in fMRI studies, large flexibility in analyses protocols (Carp, 2012) and a lack of replication (Button et al., 2013; Poldrack et al., 2017) affects nutritional neuroscience just as other areas of neuroscience (Smeets et al., 2019). For example, in a meta-analysis of children's and adolescents' brain response to food cues, van Meer et al. (2015) suggest that low concurrence in some clusters is partly due to large between study variability. Moreover, in a recent reliability study, Yokum et al. (2021) investigated test-retest reliability of the teams' previously published longitudinal studies on brain responses to food cues. The overall test-retest reliability was poor. While some brain regions demonstrated good test-retest reliability within studies, this did not replicate between studies.

Variability between studies ranges from different experimental protocols (Smeets et al., 2012), scanner type and strength (Friedman et al., 2006), subject sample composition (D'Esposito et al., 2003), pre-processing data and statistical analysis implemented (Strother et al., 2004) as well as impreciseness in labelling (Thirion et al., 2007). Thus, a key factor to achieve a better understanding of the neural processing of food cues is fostering comparability

between studies (Smeets et al., 2019). This requires higher standardization of neuroimaging protocols and data analysis which in turn facilitates data pooling. Data pooling refers to the combination of multiple studies such that one can more easily distinguish variation arising from the measure of interest from that arising of noise. Data pooling leads to increased power, higher generalizability through more representative samples and potentially new insights (Costafreda, 2009; Smeets et al., 2012). Yet, there are different ways to pool fMRI data.

Data Pooling Techniques

In neuroimaging, data pooling can be done at two levels: first, meta-analyses pool effect sizes across different studies in a field; Second, mega-analyses pool across subjects of different studies in a field (Costafreda, 2009).

First, the most commonly used pooling methods are fMRI meta-analyses, of which coordinate based meta-analyses are most often employed (Costafreda, 2009). This technique compares the published peak coordinates of activation across different studies employing a similar paradigm. Hence, the resulting coordinates are based on the group means of studies included (Wager et al., 2007). This technique disregards the number of subjects, statistical information including variance and significance as well as the shape and size of significant clusters. Moreover, by comparing group means, statistical power is not improved (Costafreda, 2009). Matthews et al. (2006) demonstrated that small variation of a visual cue can already result in significant differences in visual cortical blood-oxygen-level-dependent (BOLD) response. This emphasises the likelihood of poor convergence across peak activations using coordinate-based meta-analyses.

Second, traditional fMRI mega-analyses compare the raw fMRI time series of individuals across different studies in a field. Raw time series include hundreds of images for each subject. The unprocessed images of subjects across studies are combined and analysed together. This increases statistical power. While this analysis takes within subject variability

into account, the data load is enormous. Other challenges include the reluctance of authors to share their datasets, the quantity of data and platforms available for sharing these files, as well as the complexity of data processing (Costafreda, 2009, 2011). An intermediate pooling technique are designed mega-analyses (sometimes referred to as multi-site studies; Costafreda, 2009): rather than comparing entire fMRI time series, this technique compares the subject-level contrast images and/or corresponding statistical maps (t-maps) across multiple studies. In fMRI research a subject-level contrast image is a subject's average brain response to one condition versus another condition (e.g., a subject's average brain response to food versus non-food images). By subtracting brain response to one type of visual stimuli from another, only the difference in brain response is preserved. The corresponding t-map entails the information about within subject variability for that contrast. By taking the average brain responses of each participant into account, statistical power is increased, and data load is reduced which in turn attenuates data basing and processing. Moreover, authors are no longer required to share their full datasets, which may be more appealing and improve overall data availability (Costafreda, 2009).

Despite these advantages, mega-analyses are rarely used in practice. There are endeavours to use mega-analyses for resting state data in clinical groups (see the ENIGMA consortium; (Adhikari et al., 2019; Thompson et al., 2014). Yet, mega-analyses for task-based fMRI data and non-clinical groups are scarce. Resting state fMRI is used to characterise specialisation and segregation of brain regions or networks and aims to enhance understanding in the brain's organisation and functionality. Task-based fMRI is adopted to explore the involvement of specific brain regions during a cognitive task (Zhang et al., 2016). To the authors knowledge, mega-analyses for fMRI studies employing a food viewing paradigm have not been conducted until now. Yet, such endeavour may substantially improve knowledge about brain responses to food cues and subsequent eating behaviour.

Objectives

In the present paper, we aim to perform a mega-analysis on brain response to food viewing. Specifically, we aim to establish a sensible method to pool subject-level data across studies in nutritional neuroscience. For this, we will explore differences in brain response to food images versus non-food images (F>NF) and high caloric versus low caloric food images (HC>LC). We expect differences in brain response for F>NF and HC>LC. Further, we are interested in exploring the modulating role of gender, age, BMI and hunger state for both contrasts. We expect gender, age, BMI and hunger state to modulate brain response to F>NF and HC>LC.

Methods

Registration

The mega-analysis was pre-registered (https://osf.io/ctdqh). An updated study protocol can be found on the Open Science Framework (https://osf.io/eh795/).

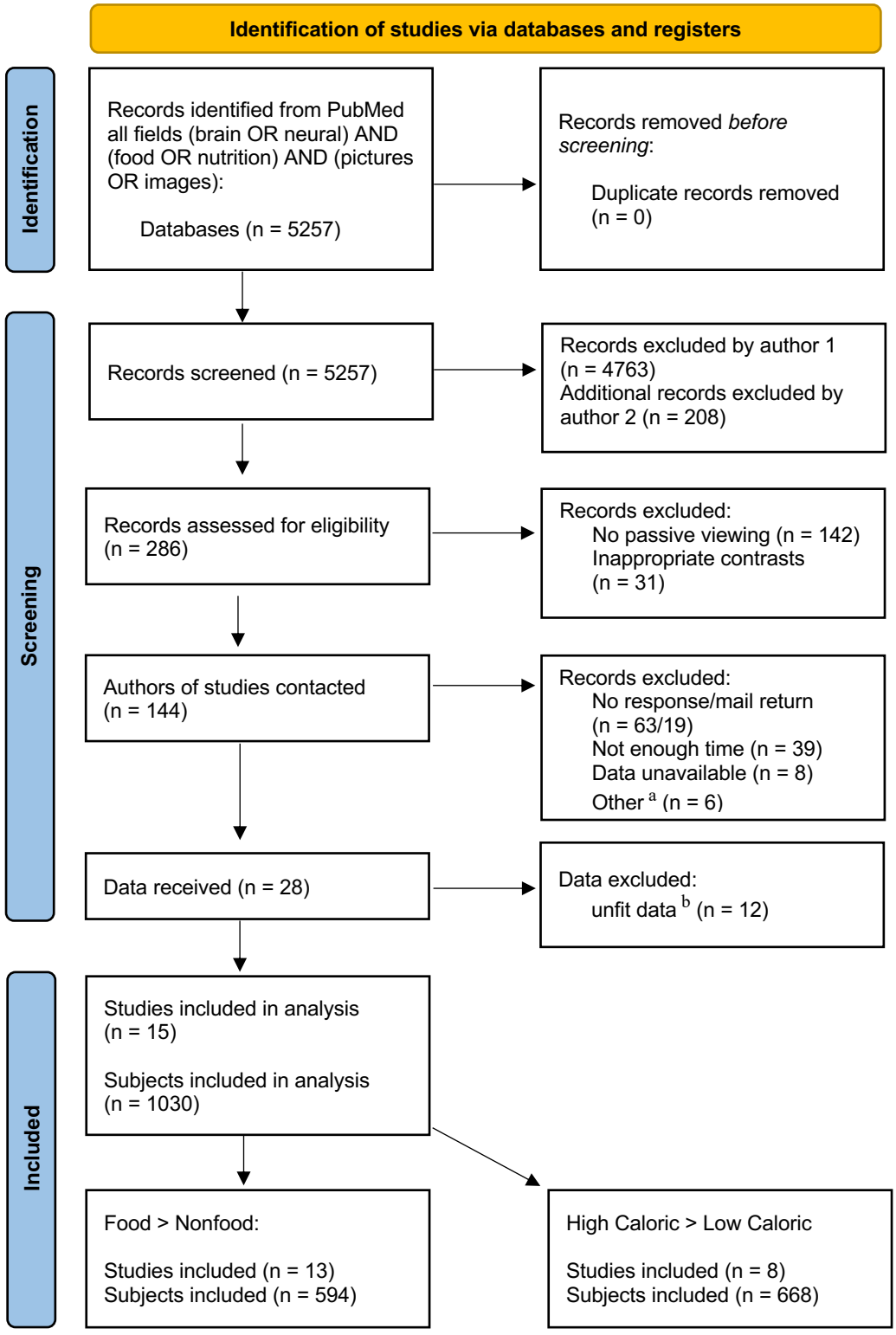
Data Sources and Searches

Studies were searched in the PubMed database (https://pubmed.ncbi.nlm.nih.gov/) using the following keyword search (all fields): (brain OR neural) AND (food OR nutrition) AND (pictures OR images). Additional studies were searched by examining references of relevant articles.

Study Selection

The eligibility criteria for studies included the following: first, studies had to be published in a peer reviewed journal. Second, studies were published in or after 2005. Third, studies involved a visual presentation of pictures of food during fMRI. More specifically, only studies in which participants passively view food pictures were eligible. Fourth, PET, MEG, and fNIR food viewing studies were not eligible for this analysis. Fifth, studies had to include healthy subjects. Based on these criteria we identified 144 eligible studies. The total

number of studies and subjects included relied on the willingness of authors to contribute their data to this project in the short time frame (two months) given. Figure 1 provides a PRISMA flow diagram of the search and selection criteria.



[a] *Note.* Other reasons include author deceased, loved one of author deceased and maternity

[b] *Note*. Unfit data includes the following: group contrasts, rather than subject-level contrasts, ROI-based contrasts, rather than whole brain analysis, t-maps only, missing contrast images; beta-images only, missing t-maps.

Figure 1. PRISMA Flow Chart (adapted from Page et al., 2021)

Data Extraction

Authors of the identified studies were contacted and asked to collaborate in this project. After two weeks a reminder was sent to those who did not respond to the first request. The authors of approximately half of the studies (n = 63)[1] did not respond, partly because their current email address could not be retrieved (n = 19). Other authors could not retrieve the data of requested studies (n = 8), or did not have the time to collaborate in this project (n = 39).

A total of 36 corresponding authors (51 studies) declared their willingness to share their data. These authors were asked to upload participant-level contrast images and t-maps (i.e., F>NF, and/or HC>LC) to the NeuroVault platform (https://neurovault.org/). In addition, they were asked to indicate relevant characteristics of each participant including gender, age, BMI and hunger state in NeuroVault. NeuroVault offers the opportunity to specify such subject-level metadata in a standardized manner, which facilitates the subsequent data analyses.

Overall, data of 28 studies was received. We had to exclude 13 datasets for this analysis because the data was unfit. Unfit data includes group images opposed to subject-level images, region-of-interest images opposed to whole-brain images, t-maps only opposed to contrast images and t-maps, beta-images (i.e., this refers to the averaged subject-level image for one condition) opposed to contrast images. Of the remaining 15 studies, 13 studies included the contrast FNF (amounting to 621 participants) and 8 studies included the contrast HCLC (amounting to 684 participants). An overview of the characteristics of the studies included is summarized in Table 1. It should be emphasised that the studies differed in terms of scanner, site, experimental design and procedure, pre-processing software, pre-processing settings.

[1] It should be noted that the number of studies does not correspond to the number of authors, because some authors published multiple eligible studies.

Table 1

Studies included in the Mega-Analysis (N – number of participants, F -females, SD – Standard deviation, HS - hunger state, numbers indicate hours since last meal)

Study	N (F)	Age (SD)	BMI (SD)	HS (SD)	Design	Food Images	Nonfood Images	Contrasts
Allen et al., 2016	42 (30F)	15,79 (1,87)	31,45 (13,38)	3	Event	High Caloric and Low Caloric Foods	Nonfood Objects Visually Matched	Both
Bach et al., 2021	46 (29F)	41,33 (11,78)	28,88 (8,5)	6	Block	High Caloric and Low Caloric Foods	Scrambled Food Images	Food Images > Nonfood Images
Charbonnier et al., 2018	122 (63F)	33,52 (23,08)	20,74 (1,48)	10	Block	High Caloric and Low Caloric Foods	Office Supplies	Both
Chen et al., 2017	36 (36F)	19,64 (1,31)	23,87 (3,09)	2	Event	Palatable Foods	Nonfood Scenery	Food Images > Nonfood Images
Dorton et al., 2018	40 (16 F)	21,84 (1,89)	27,99 (6,58)	10	Block	High Caloric and Low Caloric Foods	Office Supplies	Both
English et al., 2017	47 (27F)	23,56 (2,99)	22,1 (2,24)	1	Block	High Caloric and Low Caloric Foods	Furniture	Both
García-García et al., 2020	58 (58F)	26,33 (3,69)	25,63 (5,84)	2,16 (2,45)	Block	Palatable Foods	Objects	Food Images > Nonfood Images
Hermann et al., 2019	29 (26F)	47,59 (12,64)	36,88 (5,5)	4	Block	High Caloric and Low Caloric Foods	Neutral Objects	Both
Horster et al., 2020	27 (24F)	8,86 (1,2)	16,66 (2,56)	2	Block	Food On Plates	Nonfood Objects on Plates	Food Images > Nonfood Images
Karra et al., 2013	24 (0F)	22,54 (3,02)	21,96 (1,56)	12	Block	High Caloric and Low Caloric Foods	Household And Office Items	Both[a]
Luo et al., 2019	111 (68F)	8,6 (0,98)	19,11 (4,21)	10	Block	Palatable Foods	Household Objects and Supplies	Food Images > Nonfood Images
Nolde et al., 2019	23 (0F)	24,3 (2,62)	23,45 (1,34)	28	Event	Food Images Rated by Participant	Nonfood Items	Both[a]
Smeets et al., 2013	30 (30F)	22,1 (2,02)	23,56 (1,97)	3	Block	Palatable Foods	Office Supplies	Food Images > Nonfood Images
van Meer et al., 2016	59 (39F)	28,71 (16,77)	21,87 (5,03)	9,58 (3,94)	Block	High Caloric and Low Caloric Foods	None	High Caloric Food Images > Low Caloric Food Images
van Meer et al., 2021 (in prep.)	350 (190F)	29,71 (14,24)	23,57 (5,77)	3,82 (2,18)	Block	High Caloric and Low Caloric Foods	None	High Caloric Food Images > Low Caloric Food Images
Total	1044 (636F)	23,65 (15,98)	24,96 (7,11)	7,61 (7,08)				

[a] *Note*: For the contrast Food Images > Nonfood Images, we took the contrast High Caloric Food Images > Nonfood Images

Data Synthesis

A major challenge for mega-analyses is data synthesis. As mentioned earlier, mega-analyses are used to pool across resting state fMRI images in clinical groups (compare ENIGMA consortium; Adhikari et al., 2019; Thompson et al., 2014), but are rarely used for task-based fMRI. Overall, the field of mega-analysis is new and to the authors' knowledge guidelines about methods do not exist.

Preliminary considerations about suitable methods. Given the data to be collected, the most suitable model seemed to be a mixed effects model. To our mind such model would allow for taking within and between subject, as well as within study and between study variability into account. This initial idea led us to consider 3dMEMA (Chen et al., 2012) a mixed analysis meta-analysis R package for fMRI data analysis in AFNI (Cox, 1996). After correspondence with developer, it became clear that the package could only take within and between subject variability into account, but not variability underlying study differences. The opposite was the case for 3dLME (Chen et al., 2013a), this package would take between and within study variability into account but omit variability underlying subject differences. Besides the limitations of both packages, we were not familiar with the software and were concerned about lacking guidelines for data harmonisation.

A recent publication of Zunhammer et al. (2021) investigating neural systems underlying placebo analgesia from provides a GitHub (available at: https://github.com/mzunhammer/PlaceboImagingMetaAnalysis) in which the authors document their approach to subject-level data pooling. Opposed to resting state fMRI mega-analysis which commonly uses subject-level beta images (Adhikari et al., 2019), Zunhammer et al. (2021) used and created contrast images (e.g., placebo versus control) for their whole-brain analysis. Besides the similarity in types of images used, the procedure provided us with a guiding script in more familiar programming language and software (i.e., Matlab 18b and

SPM12). Consequently, we adopted and adapted Zunhammer's procedure, one of many possible procedures for this type of analysis.

Preliminary considerations about data inclusion. Before data synthesis, we had to make several decisions about the final inclusion criteria of the data received. First, for studies with repeated measures, we included only one scan per participant. That is, for intervention studies (e.g., batik surgery or diet) we included the pre-scan, for studies where participants' hunger state was altered, we included participants in their fasted state, for studies in which participants received water or glucose before the scan, we included the water condition. One reason for this choice was that the inclusion of multiple images per participant would violate the assumption of independence of observations. The other reason was that SPM12 has difficulties handling more complex models (Chen et al., 2013) (here: a model that would accommodate a hierarchical grouping factor, several between subject factors and in cases of some data within subject factors). Second, for the contrast F>NF we preferably took the contrast of averaged food images (high caloric and low caloric) compared to non-food images. However, in the case of two studies, this contrast was not available, and we included the contrast high caloric food images > non-food images, rather than low caloric food images > non-food images (see Table 1). Third, our dataset contained two studies (Charbonnier et al., 2018; van Meer, 2021 *in prep*.), in which data was collected at different sites. We did not account for scanner site to avoid overfitting of the model (see model specification study dummies). While we might miss out on accounting for a potential confound (i.e., scanner site), these studies used the same food viewing paradigm, protocol and pre-processing procedures. We aimed at providing a parsimonious model preserving enough degrees of freedom to avoid overfitting (Babyak, 2004; Hawkins, 2004).

Pre-processing and Harmonizing Data. Each study pre-processed their images differently. To harmonise the data, we followed and adapted the pre-processing procedures

from Zunhammer et al. (2021). Besides the difference in subject matter, a major difference was that we used only contrast images, while Zunhammer et al. (2021) used a combination of beta images and contrast images. As mentioned earlier, contrast images are a subject's averaged brain response to one condition subtracted by another, whereas beta images are a subject's averaged brain response to one condition. Opposed to Zunhammer et al (2021), we did not have to define new contrasts using the beta images for different conditions in our script (available at: https://osf.io/g54d7/). We combined the images as follows: first, we imported the data and the relevant metadata. Second, we realigned, resampled and masked the images. Specifically, we realigned the images to MNI space, resampled them at 2x2x2 voxels and masked them using SPM12's template brain mask available in the FieldMap toolbox (Appendix A). Third we vectorised all images to determine outliers and mask missing voxels. An overview of the 90% coverage for all studies combined as well as each individual study can be found in Appendix B1 and B2, respectively. Appendix C demonstrates the proportion of missing brain voxels of each study. Most studies have about 17% of missing voxels. Subjects with a total coverage of two standard deviations below the average coverage were excluded from the analysis. The total number of subjects excluded was 43. This corresponds to a total number of subjects of 594 for the contrast F>NF and 668 for the contrast HC>LC.

Food Viewing Mega-Analysis

We ran two multiple regression analyses of the entire brain in SPM12. For this, we analysed subject-level contrast images for F>NF (n=594) and HC>LC (n=668) across studies. Consequently, our outcome variables were the difference in brain response to F>NF and HC>LC.

The following covariates of interest were included into the analysis: gender, age, BMI and hunger state. The latter three were mean centred across studies. We included dummy nuisance variables for all studies to control for differences between studies. Hence, for the

analysis of F>NF, we include 13 studies, amounting to 12 dummy variables. For the analysis HC>LC, we include 8 studies, amounting to 7 dummy variables.

Initially we planned to correct for multiple comparisons using p=.05 family wise error (FWE). We lowered this threshold for most reported activations, because the FWE correction did not yield any significant activations. Missing voxels were masked out from the analyses (SPM12 default).

Coordinates were reported in MNI space and matched to brain regions using the Automated Anatomic Labelling map (Tzourio-Mazoyer et al., 2002) in MRIcron (Rorden & Brett, 2000) and NeuroSynth (Yarkoni, et al., 2011).

Results

Image quality

The included studies aimed at covering the entire brain. Image alignment was satisfactory for all studies, yet brain coverage differed between studies (Appendix B2). The missing voxels may be explained by between-study differences in field of view and signal dropout artefacts (Zunhammer et al., 2021). For the both main analyses missing voxels were excluded on a subject level, that is a voxel was removed from an analysis, if it was missing in at least one subject of that analysis (SPM12 default). Subsequently, the large number of subjects, resulted in a large number of missing voxels that were excluded from the analyses (see Appendix D). This may have led to an increase in Type II error (Vaden et al., 2012).

Main Analysis

Food Versus Nonfood Viewing. The results of the multiple regression for the contrast F>NF are summarized in Table 2. We explored different models with the inclusion of different combinations of the covariates gender, age, BMI and hunger state. The models covered 70125 voxels. We found significant peak activations in the anterior cingulate cortex [-12 -6 28] for food compared to non-food images (z=3.36, p<.001) in almost all models

tested (Table 2). The model with the dummy variables and the covariates gender and BMI yielded a significant peak activation at the superior temporal gyrus/ insula ([14 4 26], z =3.35, p<.001) for the contrast F>NF. The model with the dummy variables and BMI only yielded additional activations in the right caudate ([14 4 26], z =3.35, p<.001), the right rolandic operculum ([42-20 26], z =3.29, p<.001; [40 -22 28], z=3.18, p<.001) and the left insula ([-40 6 8], z=3.16, p<.001; [-36 -16 22], z=3.12, p<.001).

Of the covariates tested, only gender and BMI modulated brain response to F>NF in some brain regions. In females, brain response to F>NF was stronger in the opercular part of the left inferior frontal gyrus ([-40 6 26], z=4.09, p<.001), the left superior frontal gyrus and the precentral gyrus ([-6 -24 42], z=3.48, p<.001); the precentral gyrus ([54 4 32], z=3.31, p<.001), the right middle temporal gyrus ([52 -34 0], z=3.20, p<.001) and the right parahippocampal gyrus ([30 -36 -8], z=3.13, p<.001) compared to males (see Table 3). Males on the other hand demonstrated on average higher activations for F>NF in the left middle temporal gyrus ([-34 -48 6] z=3.77, p<.001; [-42 -58 6] z=3.24, p<.001) the anterior cingulate and paracingulate gyri ([12 50 12], z=3.23, p<.001) as well as the right caudate ([4 20 12] z=3.17, p<.001) compared to females (Table 3).

With respect to BMI, subjects with larger BMIs were more likely to demonstrate higher activations for F>NF in middle temporal gyrus([-36 -42 6], kE=109, p<.001) the right and left middle frontal gyri ([34 40 4], kE=176, p<.001); ([-28 42 28], kE=28, p<.001), the left orbital part of the inferior frontal gyrus ([-34 22 -14], kE=294, p<.001), the left hippocampus ([-22 -42 2], kE=100, p<.001) as well as the right and left thalamus ([26 -24 6], kE=111, p<.001); ([-12 -16 14], kE=42, p<.001) (Table 4).

Table 2.
Brain activation for food versus to non-food viewing

Contrast Model	Z	MNI coordinates x	y	z	Associated Brain Region
Food > Non-food					
Dummies	-	-	-	-	-
Dummies + gender	-	-	-	-	-
Dummies + age	-	-	-	-	-
Dummies + BMI	4.03*	-10	-8	26	Anterior Cingulate Cortex L
	3.43*	14	2	26	Caudate R
	3.29*	42	-20	26	Rolandic Operculum R
	3.18*	40	-22	28	Rolandic Operculum R
	3.16*	-40	6	8	Insula L
	3.12*	-36	-16	22	Insula L
Dummies + gender + age	-	-	-	-	-
Dummies + gender + BMI	4.00*	-12	-6	28	Anterior Cingulate Cortex L
	3.35*	14	4	26	Superior Temporal Gyrus/Insula
Dummies + age + BMI	3.68*	-10	-6	28	Anterior Cingulate Cortex L
Dummies + gender + age + BMI	3.68*	-12	-6	28	Anterior Cingulate Cortex L
Dummies + gender + age + BMI + HS	3.10*	-12	-6	28	Anterior Cingulate Cortex L

Note: * indicates $p<.001$ (uncorrected).

Table 3.
Gender differences for food versus non-food viewing.

	Z	MNI coordinates x	y	z	Associated Brain Region
Female>Male	4.09*	-40	6	26	Inferior Frontal Gyrus, Opercular Part L
	3.52*	48	30	16	Inferior Frontal Gyrus, Triangular Part R
	3.48*	-6	-24	42	Superior Frontal Gyrus, Medial L
	3.31*	54	4	32	Precentral Gyrus R

	3.20*	52	-34	0	Middle Temporal Gyrus R
	3.13*	30	-36	-8	Parahipoocampal Gyrus R
Male>Female	3.77*	-34	-48	6	Middle Temporal Gyrus L
	3.24*	-42	-58	6	Middle Temporal Gyrus L
	3.23*	12	50	12	Anterior Cingulate and Paracingulate Gyri R
	3.17*	4	20	12	Caudate R
	3.15*	-38	-48	26	Middle Temporal Gyrus L

Note. The associated brain regions are reported for the full model (including all covariates), models with fewer covariates demonstrated similar brain regions. * indicates $p<.001$ (uncorrected).

Table 4.
Association of BMI with food versus non-food images.

	kE	MNI coordinates			Associated Brain Region
		x	y	z	
BMI	109*	-36	-42	6	Middle Temporal Gyrus L
	28*	-28	42	28	Middle Frontal Gyrus L
	294*	-34	22	-14	Inferior Frontal Gyrus, Opercular Part L
	176*	34	40	4	Middle Frontal Gyrus R
	42*	-12	-16	14	Thalamus L
	100*	-22	-42	2	Hippocampus L
	111*	26	-24	6	Thalamus R

Note. The associated brain regions are reported for the full model (including all covariates), models with fewer covariates demonstrated similar brain regions. * indicates $p<.005$ (FWE).

High Caloric Versus Low Caloric Food Viewing. The analysis of HC>LC analyses comprised 69877 voxels. While in the analyses of the contrast F>NF, leaving out covariates led to the significant activation of additional, this was not the case for the contrast HC>LC. Overall, our models did not yield differences in activations upon viewing high caloric compared to low caloric food images.

We found significant differences in peak activations between males and females. Upon high caloric food images, we found higher brain activations in the left caudate ([-4 22 12], z=3.38, p <.001), the left middle cingulate gyrus ([-50 -46 4], z=3.53, p <.001) and the right caudate ([8 14 14], z=3.19, p <.001) in females compared to males. On the other hand, males demonstrated increased activations in the right inferior frontal gyrus ([28 18 18], z=3.71, p <.001), the left middle temporal gyrus ([-50 -46 4], z=3.53, p <.001), the left Rolandic operculum ([-46 -18 26], z=3.47, p <.001) as well as the triangulate part of the left inferior frontal gyrus ([-44 38 0], z=3.38, p <.001) compared to females (Table 5).

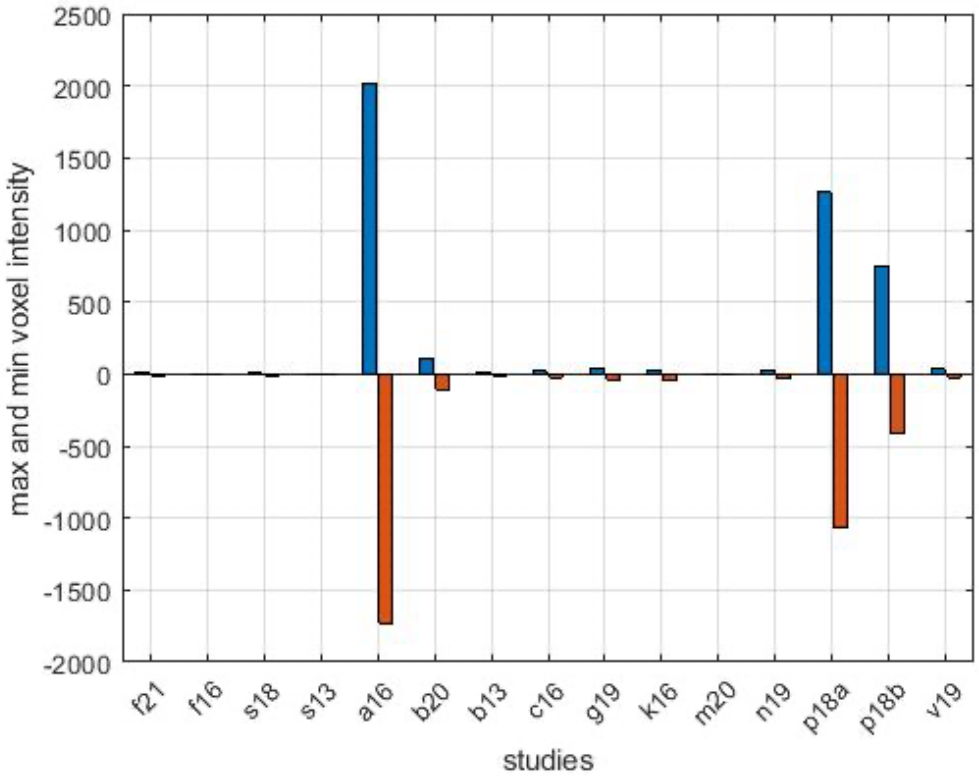
Table 5.
Brain activation for high caloric versus low caloric food viewing for the full model including all covariates.

Contrast	Z	MNI coordinates			Associated Brain Region
		x	y	z	
HC>LC	-	-	-	-	-
Female>Male	3.38*	-4	22	12	Corpus callosum/caudate L
	3.23*	-8	-18	26	Middle Cingulate Gyrus L (bilateral)
	3.19*	8	14	14	Caudate R
Male>Female	3.71**	28	18	18	Inferior Frontal Gyrus R
	3.53**	-50	-46	4	Middle Temporal Gyrus, L
	3.47**	-46	-18	26	Rolandic Operculum L
	3.38**	-44	38	0	Inferior Frontal Gyrus, Triangular Part L
Age	-	-	-	-	-
BMI	3.98***	28	12	26	Caudate R
	3.89***	46	-12	0	Superior Temporal Gyrus R
	3.85***	16	14	20	Caudate R
Hunger State	-	-	-	-	-

Note. The associated brain regions are reported for the full model (including all covariates), models with fewer covariates demonstrated similar brain regions. * indicates $p<.001$ (uncorrected); ** indicates $p<.0005$ (uncorrected); ***$p<.0001$ (uncorrected)

Exploratory Analysis

While intensity nonuniformity can create bias in single studies (Arnold et al., 2001), it may result in large distortions when pooling across studies. Consequently aligning intensity distributions across studies is an essential component of multisite fMRI data harmonisation (Wrobel et al., 2020). To test wether intensity nonuniformity was a problem in our data, we compared voxel intensities of the averaged masked contrast image of each study with each other. We found large differences between studies. In particular, the intensity ranges of the datasets of Allen et al. (2016), Luo et al. (2017) and Dorton et al. (2018) deviated from other studies (Figure 3).



Note: Abbreviations on the x axis refer to the studies included: f21 – van Meer et al. 2021; f16 – van Meer et al., 2016; s18 - Charbonnier et al., 2018; s13- Smeets et al., 2012; a16-Allen et al., 2016; b20 - Bach et al., 2021; b13- Karra et al., 2013; c16- Chen et al., 2017; g19 - k16- English et al., 2017; m20 - García-García et al., 2020 ; n19 - Nolde et al., 2019; p18a- Dorton et al., 2018; p18b - Luo et al., 2019; v19 - Hermann et al., 2019

Figure 3. Averaged masked maximum and minimum voxel intensities per study. Figure created in Matlab 18b.

Consequently, we decided to check the effect of nonuniformity in our analyses and reran the multiple regression without the mentioned studies. This meant that for the analysis of F>NF we excluded three studies and for the analysis of HC>LC we excluded one study resulting in 422 and 637 subjects, respectively. For these exploratory analyses we used the full model including all covariates. The exploratoy F>NF and HC>LC analyses comprised 76622 and 73340 voxels, respectively. The results for both analyses are specified in Table 6 and 7. Interestingly, leaving out these studies did not improve the overall masks (Appendix E3 and E4).

The volume coverage of the F>NF analyses comprised 76622 voxels. For the analyses of F>NF we found peak activations in the left and right insula ([-36 -6 6], z=4.46, p <.001); ([-38 6 -12], z=3.93, p <.001) (Figure 4a) as well as the cuneus ([14 -92 8], z=3.28, p <.001) for the contrast food versus nonfood images. Compared to men, women demonstrated a higher activation in the left inferior temporal gyrus([-48 -52 -12], z=3.52, p <.001) (Figure 5). In this analysis age and BMI did not covary with brain resonse to food versus non food viewing. However, hunger state affected subjects' response to food images, such that hungrier subjects demonstrated higher peak activations in left calcerine ([-4 -76 18], z=5.11, p<.05(FWE)), the left cerebellum ([-14 -50 -12], z=4.80, p<.05(FWE)), as well as the right inferior temoral gyrus ([52 -56 -12] z=4.65, p<.05(FWE)) and the right hippocampus([20 -30 -4], z=4.10, p<.05(FWE)).

For the analyses of HC>LC we found peak activations in the left hippocampus([-20 -20 -16], z=4.50, p <.001) (Figure 4b), the left amygdala ([-20 -4 -14], z=3.83, p <.001), the left middle temporal gyrus ([-48 2 -20], z=3.64, p <.001), the left hypthalamus ([-2 -4 -8], z=3.32, p <.001) and the right fusiform gyrus ([28 -64 -6], z=3.12, p <.001). The covariates did not yield any significant effects.

Table 6.
Intensity corrected brain activation for food versus to non-food viewing for the full model including all covariates

Contrast	Z	MNI coordinates			Associated Brain Region
		x	y	z	
Food > Nonfood	4.46*	-36	-6	6	Insula L
	3.93*	-38	6	-12	Insula L
	3.28*	14	-92	8	Cuneus R
	3.16*	40	10	-14	Insula R
Female>Male	3.55*	-48	-52	-12	Inferior Temporal Gyrus L
Male>Female	-	-	-	-	-
Age	-	-	-	-	-
BMI	-	-	-	-	-
Hunger state	5.11**	-4	-76	18	Calcarine L
	4.80**	-14	-50	-12	Cerebellum L
	4.65**	52	-56	-12	Inferior Temporal Gyrus R
	4.10**	20	-30	-4	Hippocampus R

Note. The associated brain regions are reported for the full model (including all covariates).
* indicates $p<.001$ (uncorrected); **indicates $p<.05$ (FWE).

Table 7.
Intensity corrected brain activation for high caloric versus low caloric food viewing for the full model including all covariates.

Contrast	Z	MNI coordinates			Associated Brain Region
		x	y	z	
High Caloric<Low Caloric	4.50*	-20	-20	-16	Hippocampus L
	3.83*	-20	-4	-14	Amygdala L
	3.64*	-48	2	-20	Middle Temporal Gyrus L
	3.32*	-2	-4	-8	Hypothalamus L
	3.16*	-48	-60	0	Middle Temporal Gyrus L
	3.12*	28	-64	-6	Fusiform Gyrus R
	3.12*	-46	-62	2	Middle Temporal Gyrus L

Note. The associated brain regions are reported for the full model (including all covariates).
* indicates $p<.001$ (uncorrected)

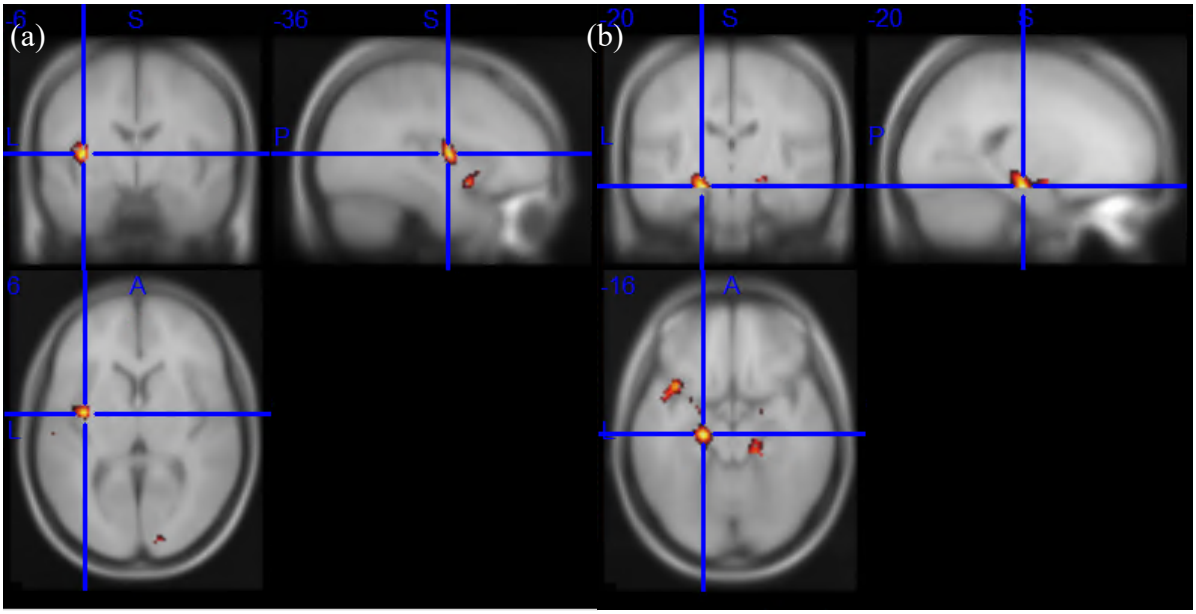


Figure 4. Intensity corrected brain activation to (a) food versus non-food viewing, activation in the right insula and (b) high caloric versus low caloric food viewing, activation in the left hippocampus. Image create in MRIcron (Rorden & Brett, 2000) using SPM12 canonical 305 averaged T1 template

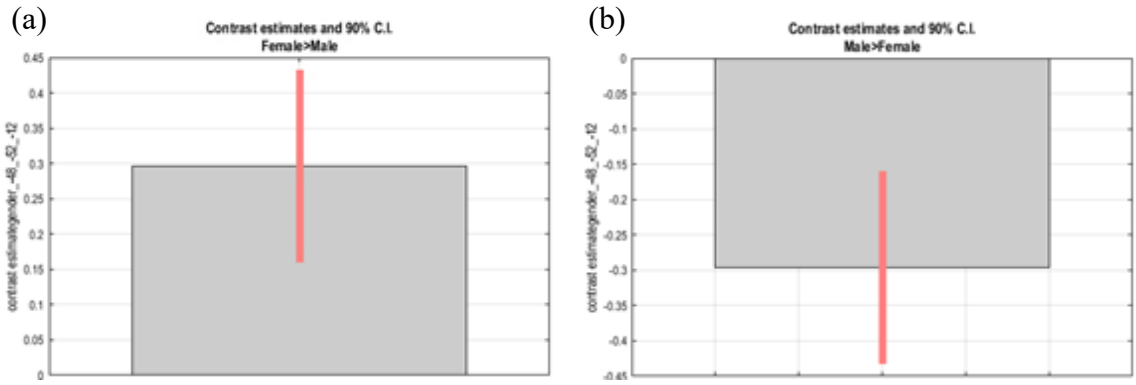


Figure 5. Intensity corrected average cluster activation in (a) Females > Male and (b) Male>Female in the left inferior temporal gyrus for food versus non-food viewing. Image created in MarsBar (Brett et al., 2002).

Discussion

A preliminary approach towards a fMRI mega-analysis of food viewing was provided. The analyses included 15 studies and 1030 subjects. Data synthesis proved challenging and despite the high number of subjects, brain activations were arbitrary. One reason may be the large number of missing voxels resulting in brain coverage. Consequently, the results of the paper at hand may have suffered from undetected effects and should be interpreted with caution. Another reason was the high differences in intensities that may have biased results for the main analyses of F>NF and HC>LC. After correcting for intensities, brain coverage was not improved, and activations found in both corrected analyses may still be subject to chance. For F>NF, peak activations in the insula and the right cuneus were found. Compared to males, females demonstrated higher brain activations in the left inferior frontal gyrus for F>NF. Hungrier participants showed higher brain activations in the left calcarine and cerebellum as well as the right inferior temporal gyrus and the right hippocampus. For HC>LC peak activations in the left middle temporal gyrus, the left hippocampus and amygdala as well as the hypothalamus were found. Gender, age, BMI and hunger state did not affect brain response to HC>LC.

Mega-Analysis Food Viewing

The mega-analysis presented did not brain response to F>NF and HC>LC. Only after lowering the threshold some peak activations were found. Given the large number of subjects, these activations may be false positives. In addition, brain coverage (Appendix D1 and D2) in both analyses was poor. In particular, large fMRI datasets are susceptible to inconsistently missing voxels across subjects which negatively affects the analyses if not handled appropriately (Vaden et al., 2012). While fMRI mega-analyses offer the potential of detecting small effects, poor brain coverage obstructs firm conclusions about the effect sizes of the findings. One reason for the high number of missing voxels in this analysis may be large

differences between studies due to the scanner, including field of view scanner artefacts. Another reason for poor coverage, in particular in prefrontal and temporal brain regions include factors such as nearby air circulation and bone (Cutler et al., 2018). Yet, another reason may be problems underlying the data harmonisation procedure. Harmonisation procedures were adapted from Zunhammer et al. (2021). This yielded good alignment between studies but did not correct for the large number of missing voxels in the main analyses. Poor brain coverage was also reported by Zunhammer et al. (2021). However, their main analysis was a generic inverse variance method which is robust against missing voxels of single subjects, unlike the analyses presented here (Deeks & Higgins, 2007). Different ways to handle poor brain coverage are discussed below.

Another unexpected finding was the difference in intensities between studies. Removing the studies with the most extreme differences in intensities changed the overall brain activations for both analyses (F>NF and HC>LC). Consequently, the results of both main analyses are likely biased. Therefore, only results of the intensity corrected analysis are discussed further. However, after removing the studies differing in intensity brain coverage remained poor and the significant threshold low. Poor brain coverage is susceptible to an elevated risk of type II error, whereas a low significant threshold increases the risk of type I error. This should be kept in mind when interpreting the findings below.

Food Versus Nonfood Viewing

For F>NF, activated brain regions activated comprised right and left insula as well as the right cuneus. The insula plays a prominent role in a variety of human functions including sensory and affective processing as well as higher-level cognition (Uddin et al., 2017). Within nutritional neuroscience, the insula has been identified as a crucial component in the appetitive brain network (Neseliler et al., 2017). A meta-analysis found, that the insula was the only brain region consistently activated upon cross-modal food cues (i.e., taste, smell,

sight) (Huerta et al., 2014). Moreover, the insula has been associated with encoding the reward value of foods, nutritional expectations and information underlying food choice (Neseliler et al., 2017). Even though the significance threshold was low in the intensity corrected F>NF analysis, increased brain response in the insula upon food versus non-food cues is in line with the literature (Dagher, 2012; Neseliler et al., 2017; Smeets et al., 2012).

The function of cuneus has been associated to primary and secondary visual processing. Moreover, extrastriatal areas of this region have been demonstrated to be involved in higher cognitive functioning such as reward anticipation, attention, working memory processes (Cohen, 2018). Even though a fMRI food viewing meta-analysis (Huerta et al., 2014) and a systematic review (Pursey et al., 2014) report increased activation in the cuneus for food versus non-food viewing, the authors do not interpret its role. In one study, Tuulari et al. (2015) found increased activation in the cuneus for F>NF when participants were instructed to inhibit urges to eat food compared to imagining eating the food. The authors suggest that the cuneus may play a role in goal-directed appetite control. Even though, this mega-analysis aimed at revealing small effects, the role of the cuneus in F>NF remains questionable in the light of the poor coverage and otherwise lacking brain response upon food versus non-food cues.

For F>NF, females demonstrated increased activation in the left inferior temporal gyrus. Moreover, Figure 5 demonstrates that within this brain females' activation is increased, whereas that of males is inhibited. Functionality of this brain region has been linked to language comprehension and production and higher order visual processing (Guido, 2011). A systematic review of gender differences in food viewing did not yield increased activations in the left inferior temporal gyrus for females upon food versus non-food cues (Chao et al., 2017). This review demonstrated that females compared to males demonstrate higher activations in frontal and striatal brain regions as well as the fusiform gyrus upon F>NF. A

primate study suggested that the inferior temporal lobe plays a role in projecting higher level visual cues to the orbitofrontal cortex, which in turn is involved in the evaluation of food cues (Murray & Izquierdo, 2007). In that study no indications of gender differences were implied. Overall, the lack of literature associating the left inferior temporal gyrus to gender differences in food cue reactivity, combined with the poor brain coverage and the low significant threshold the role of the left inferior temporal gyrus remains uncertain.

For F>NF, there was a modulating effects of hunger state in the left calcarine and cerebellum as well as the right inferior temporal gyrus and hippocampus. Neither of these regions have been consistently to be associated to hunger state in F>NF. Specifically, the calcarine is involved in primary visual processing (Meadows, 2018) and has been linked to increased activation to high caloric versus low caloric food viewing (van Meer et al., 2016). The cerebellum is best known for its involvement in motor coordination (Zaydan, 2011), but it is also connected to prefrontal and posterior parietal regions suggesting its involvement in cognition and affect (Strick et al., 2009). While the hippocampus has traditionally been linked to learning and memory, it also plays a role in motivation and eating behaviour (Neseliler et al., 2017). Rat and lesion studies have shown that the hippocampus is involved in the utilisation of hunger state signals (Davidson & Jarrard, 1993) and may play a prominent role in regulating energy intake (Davidson et al., 2007). However, meta-studies and systematic reviews (e.g. Brooks et al., 2013; Huerta et al., 2014; Pursey et al., 2014) did not report associations of these regions to hunger state in F>NF. Overall, no compelling evidence for an effect of hunger state on either of the four brain regions activated upon food versus non-food cues was found in this analysis. It seems more likely that the activations were false positives resulting from a low significant threshold.

In sum, the activation in the insula for F>NF is in line with the literature. The modulating effects of gender and hunger state are less conclusive. Low significant thresholds and poor coverage may have increased Type I and II error respectively.

High Caloric Versus Low Caloric Food Viewing

For HC>LC, peak activations in the left middle temporal gyrus as well as the left hippocampus and amygdala were found. The middle temporal gyrus has been associated to a range of different functions including language and semantic processing, perception and multimodal sensory integration (Onitsuka et al., 2004). One food viewing study (Junghans et al., 2015) reported higher activation in the middle temporal gyrus for high caloric versus low caloric food images. The authors suggest this may reflect increased attention towards the high caloric food cues. Both the amygdala and the hippocampus are part of the appetitive brain network (Dagher, 2012; Neseliler et al., 2017; Smeets et al., 2012). The amygdala is involved in emotional processing reward valuation and ingestive behaviours and affects cognitive, attentional and memory processes (McQuiston, 2018). Therefore, the amygdala is well connected to the hippocampus. IN food viewing studies, it has been suggested that higher activations in the amygdala for HC>LC may reflect an increased emotional processing load which in turn affects reward and memory processes (Beaver et al., 2006). Similarly, an increased activation in the hippocampus may reflect emotional processing (Wallner-Liebmann et al., 2010) as well as recalling previous experiences with perceived food (Papies, 2013). In sum, the activations in the left middle temporal gyrus as well as the left hippocampus and amygdala found in this analysis are in line with the literature.

Strength, Limitations and Future Outlook

The study at hand has several strengths: First, it is the first attempt to pool across subject-level functional scans in nutritional neuroscience. One of many possible procedures was provided and alternatives may prove more suitable. From this attempt, many lessons

learnt can be derived including the importance of standardised procedures, time, preparation and organisation, challenges of data harmonisation and missing voxels and the adoption of a suitable analysis (See Appendix E for an overview). Second, a major part of data harmonization was realized including aligning, reslicing and masking the images (Appendix B2). This demonstrates external validity of Zunhammer et al. (2021) harmonization procedure. Third, in a relative short timeframe, many authors declared their willingness of collaboration and provided their datasets. This suggests an interest in data pooling in the field.

Limitations of the study include time constraints, the categorisation into high and low caloric food images and the statistical analyses. First, this project was a Master Thesis project and constraint to half a year. Within this time frame study search and selection, as well as data extraction synthesis and analysis had to be performed. Moreover, the conceptual considerations regarding appropriate harmonisation and analysis proved time-consuming. An additional laborious factor was the adaptation of Zunhammer and colleagues (2021) harmonisation procedure. Also, the correspondence with authors and obtaining the data took its time. As a result, the analysis presented here is the initial approach towards a fMRI mega-analysis on food viewing and the project will be continued.

Second, the categorization into high and low caloric food images was imperfect: each study used slightly different contrasts. For example, van Meer et al. (2021, 2016) used healthy and unhealthy foods; English et al. (2017) and Charbonnier et al. (2018) differentiated between high and low energy dense foods; then again Nolde et al. (2019) used prior ratings by the participant to categorize images into liked (usually higher energy density) and unliked (usually lower energy density) food images. The ambiguous terminology and coarse categorization may have confounded the effects underlying processing of high caloric food images (Poldrack et al., 2011). Consequently, the results at hand emphasize the importance of

consistent terminology and careful consideration of categorization when pooling across studies.

Third, the statistical analyses presented here was imperfect. Here a multiple regression analyses with dummy variables for the studies included was conducted. The large number of dummies reduced the models' degrees of freedom and consequently affected the significance threshold. Instead of taking a conservative p=.05 family-wise error correction as planned the significance threshold was adjusted to p=.0001 (uncorrected). While it is important to account for the variability between studies, there are more appropriate ways to account for between study variability: For example, one could adopt a statistical analysis more appropriate for the nested data inherent to mega-analyses. A hierarchical mixed effects model combines fixed and random effects. Fixed effects comprise the variables of interest, here gender, age, BMI, and hunger state. Random effects comprise the effects arising from variability between grouping variables, here the different studies pooled across (level 2) and the variability arising from each subject (level 1) (Singmann & Kellen, 2019). To the authors knowledge, such models can only be realized in SPM12's first level analyses which combines the time series of a subject and not for SPM12's second level analysis which combines all subjects (Friston et al., 2005). Thus, different software may provide more flexible approaches to handle nested data. For example, AFNI's 3DLME implements a mixed effects analyses on the group level (Chen et al., 2013b).

In sum, strengths of the analyses at hand include the provision of a novel approach to pool across food viewing studies, external validity of Zunhammer et al. (2021) harmonisation procedure as well as relevance of data pooling. Limitations include time-constraints, the categorisation into high caloric and low caloric stimuli as well as problems underlying multiple regression analyses.

Future Outlook

We provided one of many possible approaches towards fMRI subject-level data pooling. It is recommended to consider two points: how missing voxels should be handled and how intensities should be corrected.

First, there are different ways to handle missing voxels: one way is to mask out all voxels for which one subject lacks data resulting (SPM12 default). This may be appropriate for small datasets, but in a large dataset the method results in an overall poor brain coverage which in turn increases the potential of Type II errors (Mulugeta et al., 2017; Vaden et al., 2012). Another way to handle missing voxels is to replace them with zeros. While this method improves the mask it does not affect the results of the analyses. The consequences of this approach may be problematic: Consider a missing voxel, surrounded by highly activated voxels: the likelihood of this voxel being not activated is low. Consequently, replacing it by zero would similarly to the first option increase the risk for Type II errors. A third way to handle missing data is to use multiple imputations. For example, Vaden et al. (2012) demonstrate, how multiple imputations reduce false negatives compared to voxel omission. In comparison to mean replacement, that is the missing voxel is replaced by the mean surrounding it, multiple imputations retain variance comparable to voxels with no missing data and reduce false positives (Vaden et al., 2012). Importantly, in a mega analysis, imputations should be done on a study level, because voxels are likely to be missing at random within a particular study, but not across studies. As the coverage in Appendix B2 suggests, studies differ in their overall brain coverage (data not missing at random). A recent preprint provides an alternative imputation method using deep learning architectures (Calhas & Henriques, 2020).Multiple imputations provide a promising approach to handle missing voxels, whether it is appropriate for mega-analysis is subject to future research.

Second, removing the studies with the most extreme differences in intensities changed the overall brain activations for both analyses (F>NF and HC>LC). Rather than excluding

studies an additional step in harmonising the data, that is adjusting the intensities of the signal, may be appropriate. Overall, a different harmonisation procedure may be adopted: ComBat was originally proposed to adjust batch effects in genomic data (Johnson et al., 2007). Since then, it has been adapted and applied to diffusion tensor imaging (Fortin et al., 2017), cortical thickness measurements (Fortin et al., 2018) as well as fMRI functional connectivity analyses in multisite studies (Yu et al., 2018). In all scenarios, ComBat removed unwanted variability arising from different scanners and sites, while preserving variability arising from covariates of interest. The documentation of ComBat suggests that the procedure does not include (multiple) imputation procedures to correct for missing data. Nevertheless, ComBat provides a promising tool to harmonise data including the correction of variability arising from differences in intensities.

In sum, future studies should consider implementing multiple imputations in their analysis and adopt ComBat for harmonisation procedures.

Conclusion

FMRI mega-analysis may improve between study variability in food viewing and elucidate the neural response towards these cues. This paper demonstrates the challenges when pooling fMRI data on the subject level. We found little activations at a very low threshold and struggled with an overall poor brain coverage. The consideration of multiple imputations, data harmonisation using ComBat and more appropriate statistical analysis is strongly encouraged.

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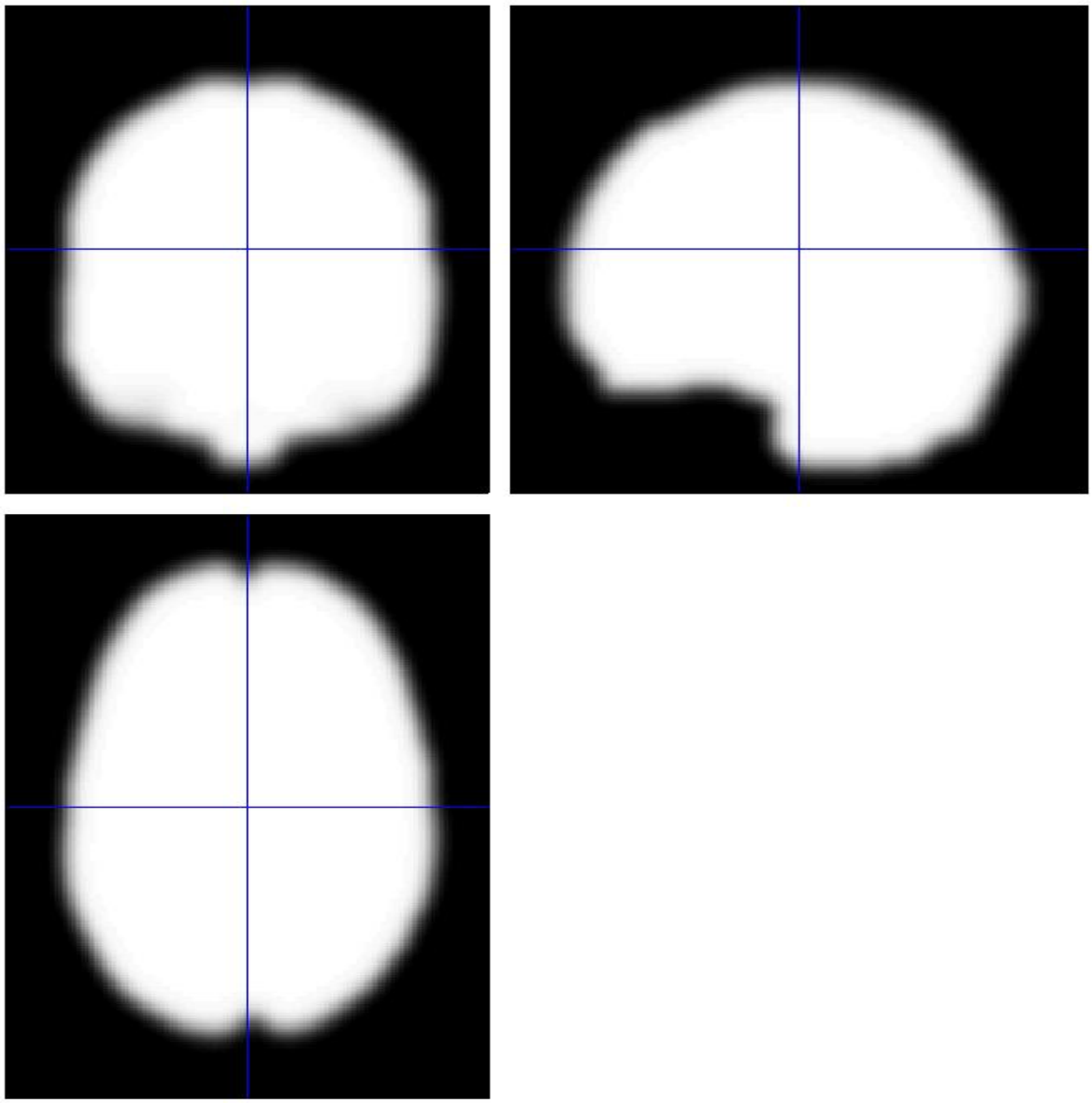
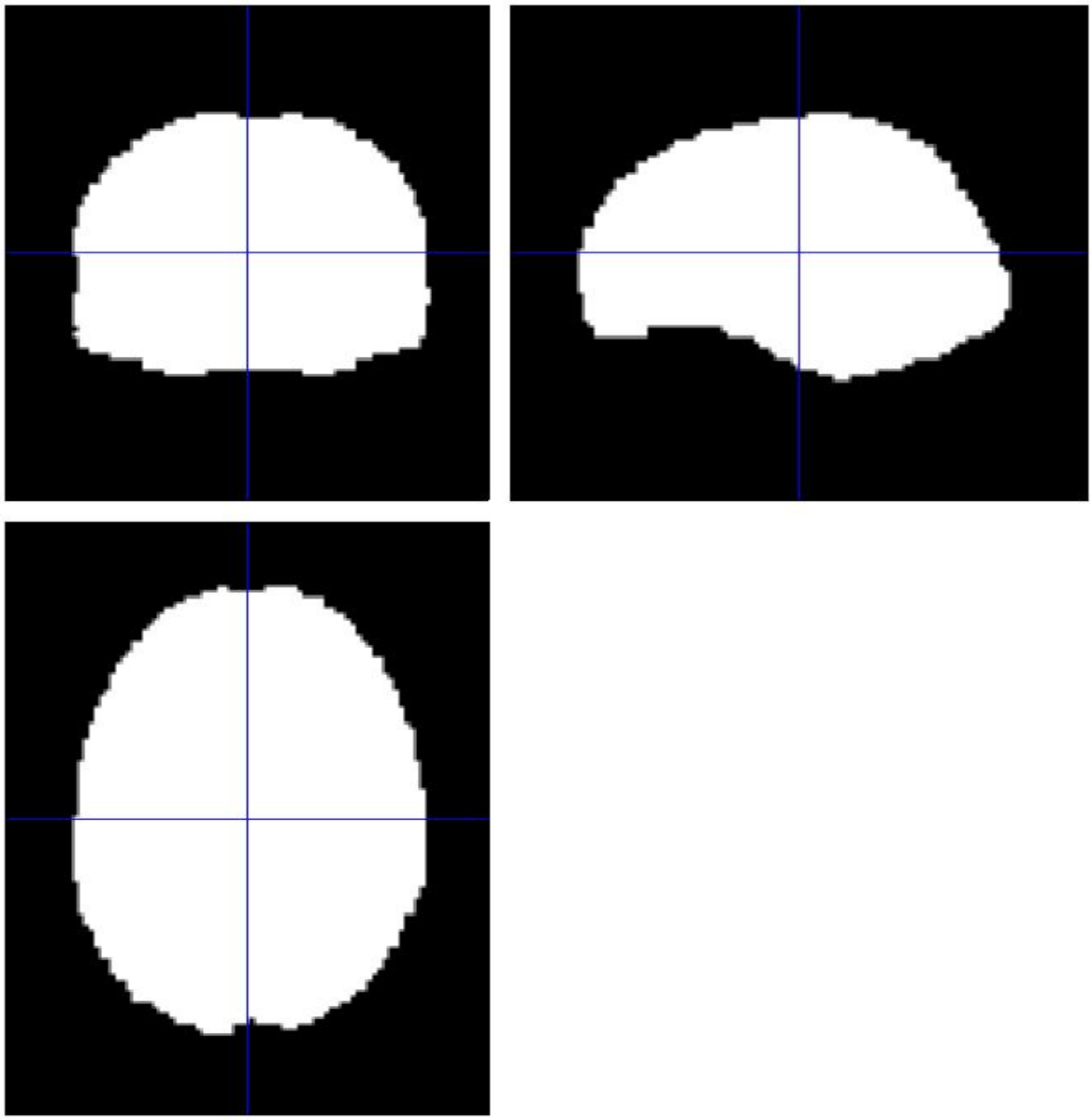
Appendix A



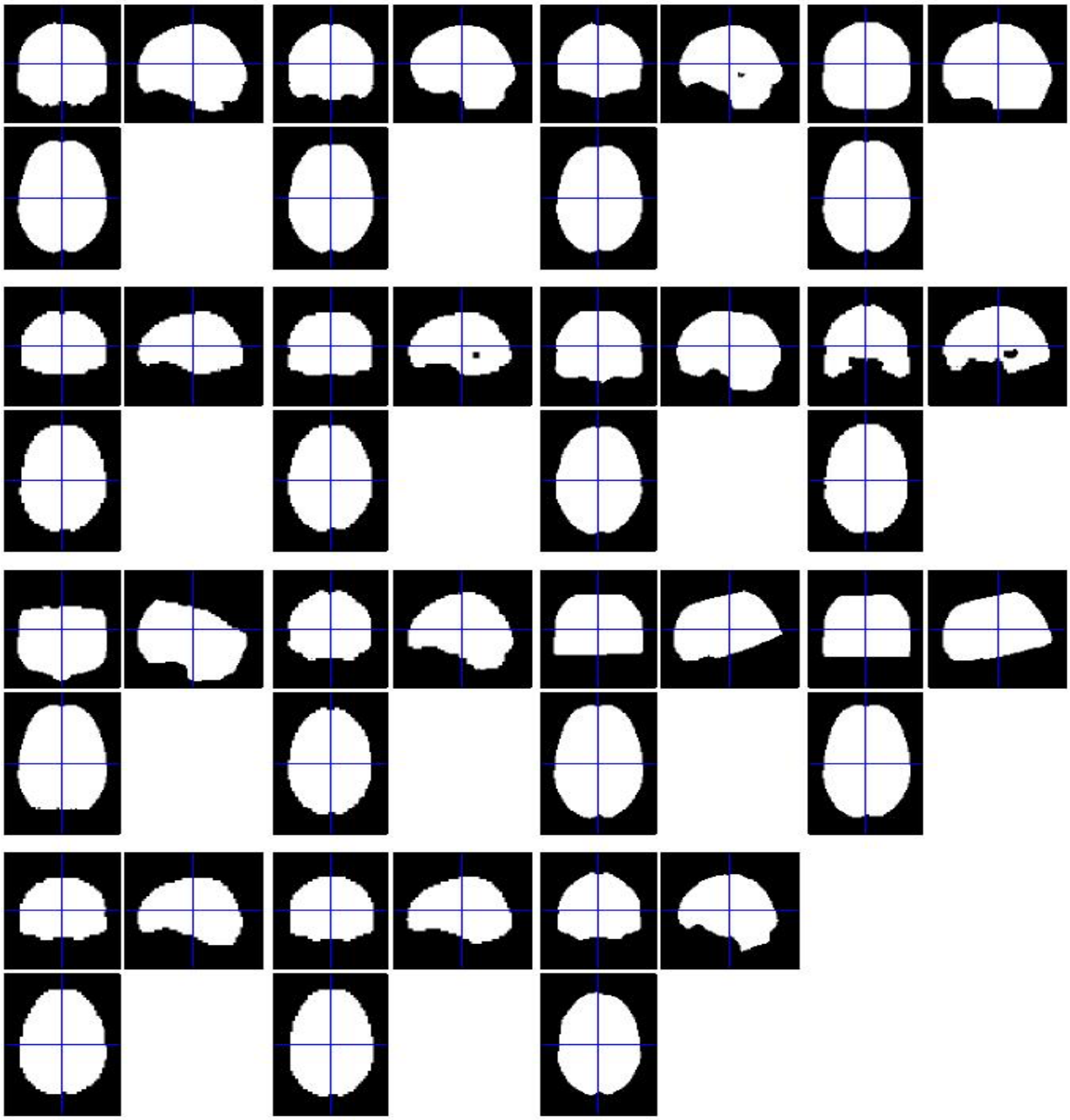
Appendix A. Brain mask SPM12 Toolbox Fieldmap

Appendix B

Ninety percent coverage of data

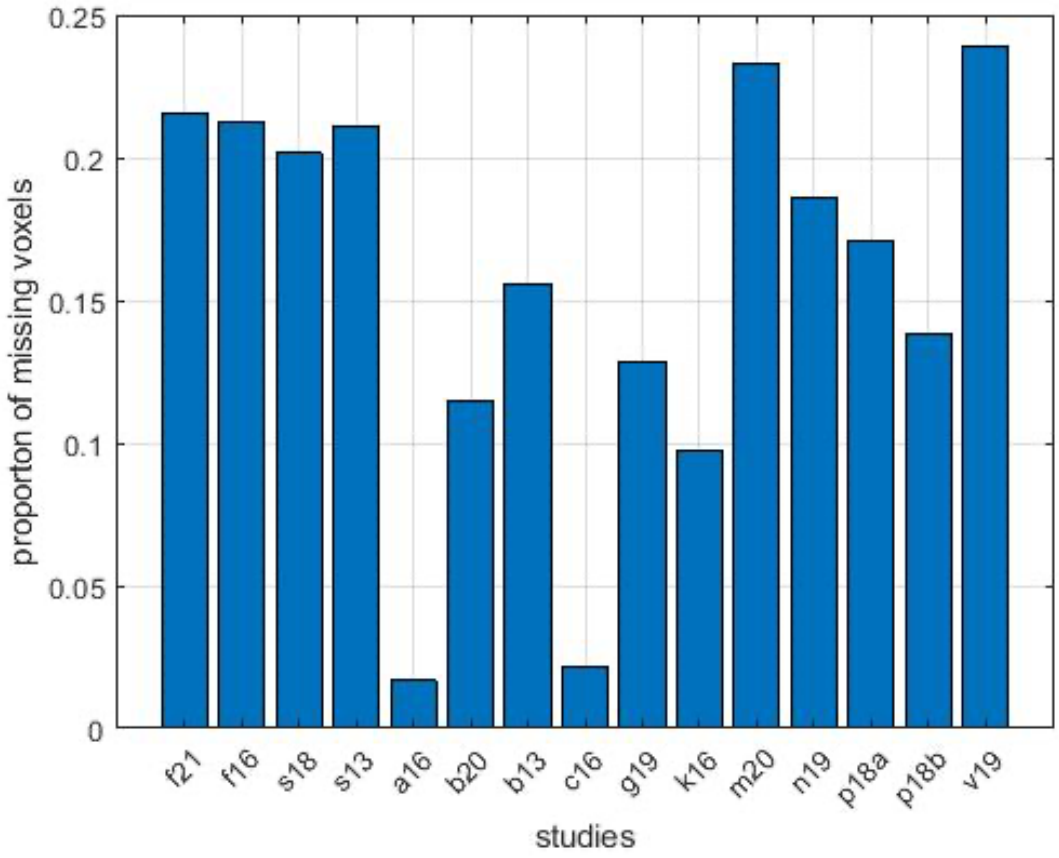


Appendix B1. Overview of overall 90% coverage for all studies. Created in SPM12



Appendix B2. Overview of overall 90% coverage for each individual study. Created in SPM12

Appendix C

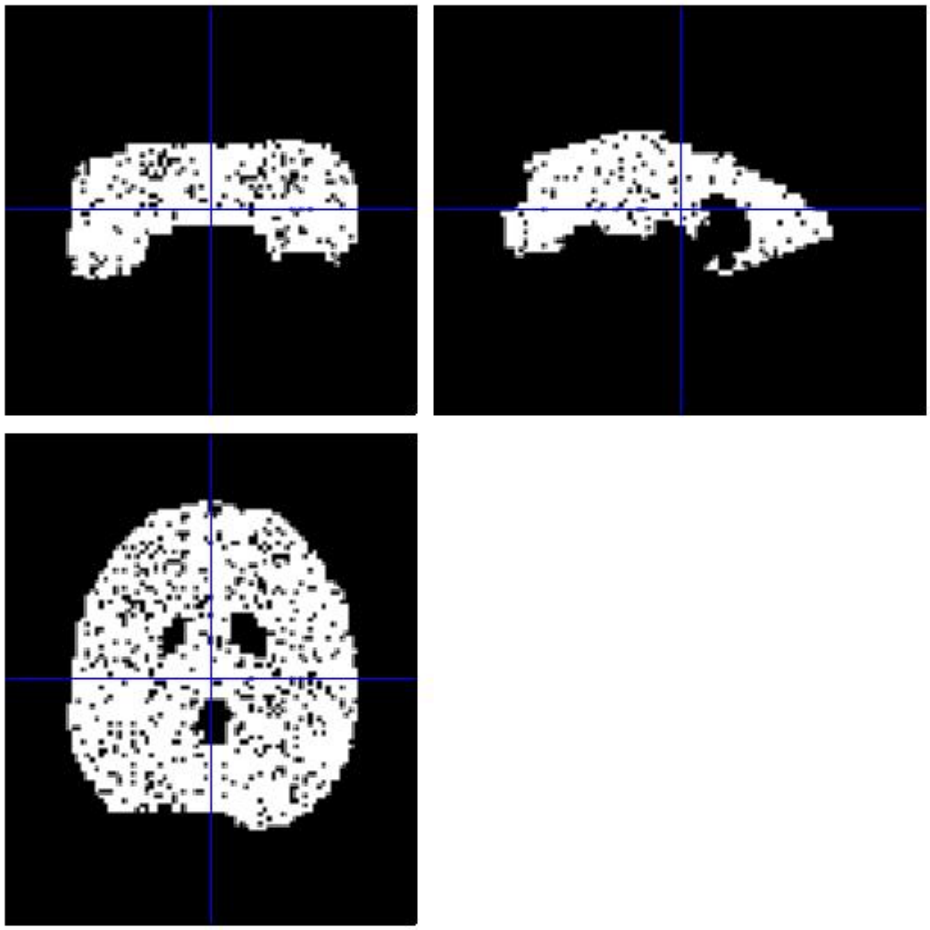


Note: Abbreviations on the x axis refer to the studies included:: f21 – van Meet et al., 2021; f16 – van Meer et al., 2016; s18 – Charbonnier et al. 2018; s13- Smeets et al., 2012; a16-Allen, et al. 2016; b20 - Bach et al., 2021; b13- Karra et al., 2013; c16- Chen et al., 2017; g19 - k16- English et al., 2017; m20 - García-García et al., 2020 ; n19 - Nolde et al., 2019; p18a- Dorton et al., 2018; p18b - Luo et al., 2019; v19 - Hermann et al., 2019

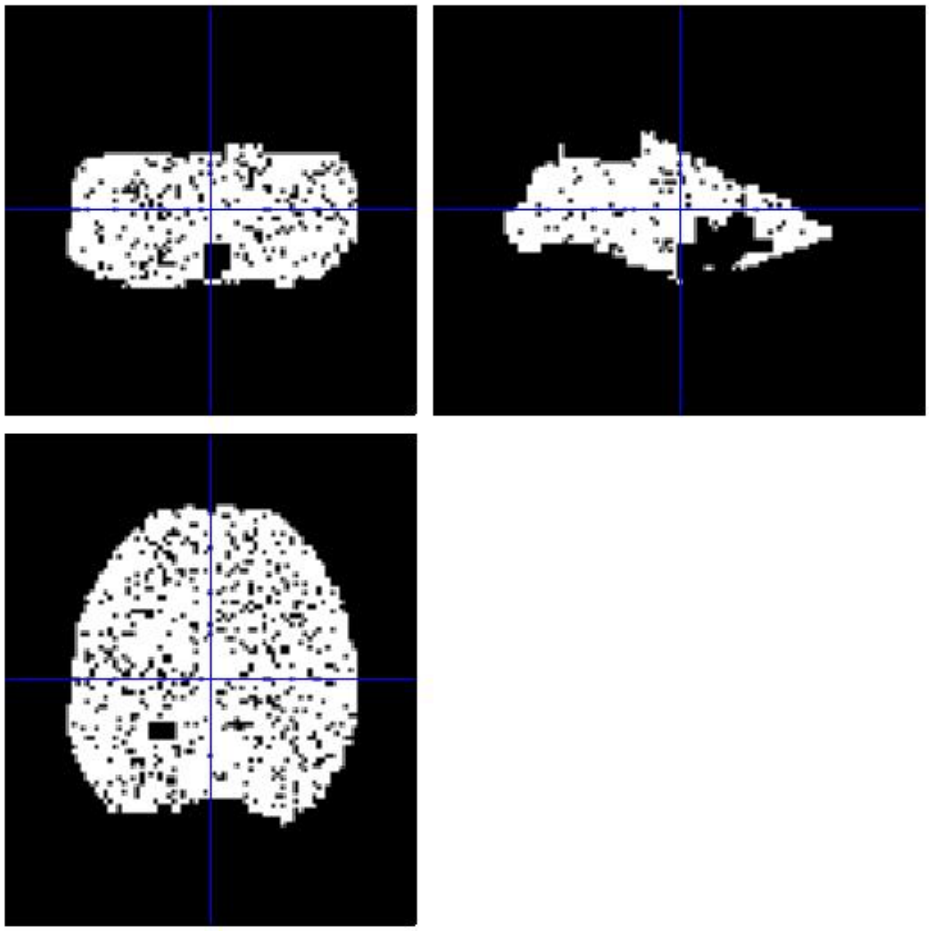
Appendix C. Proportion of missing voxels per study.

Appendix D

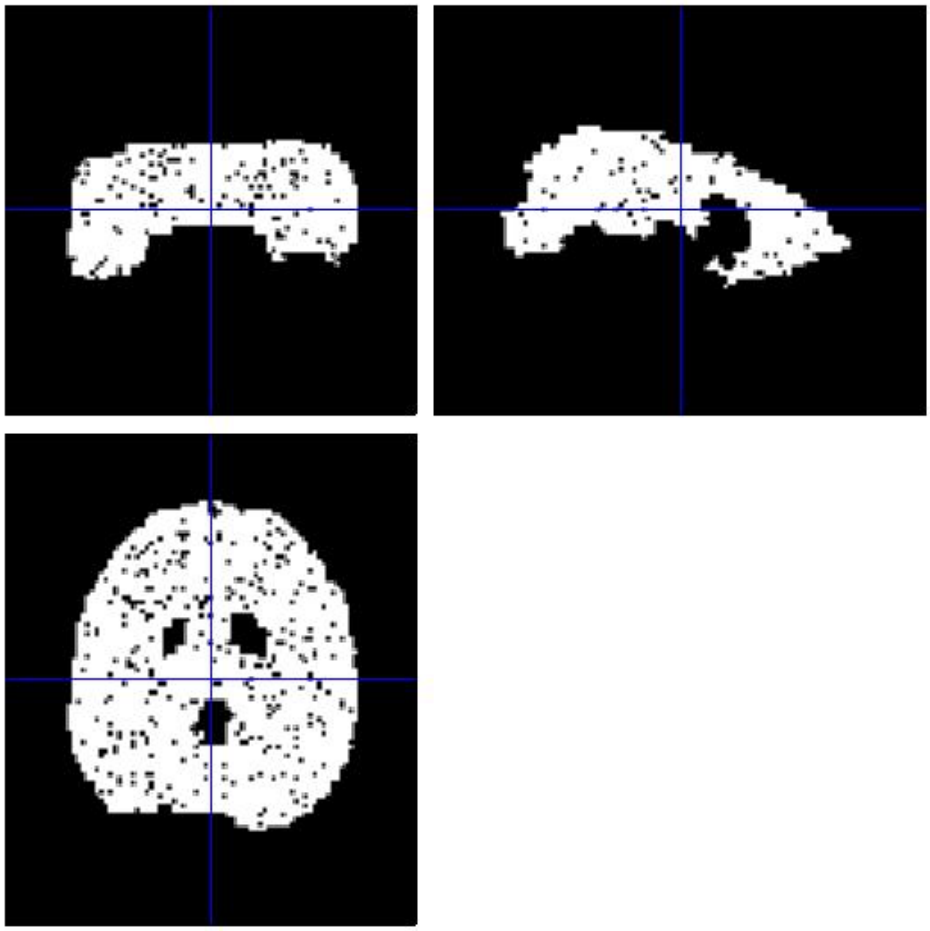
Brain Masks of Main Analyses



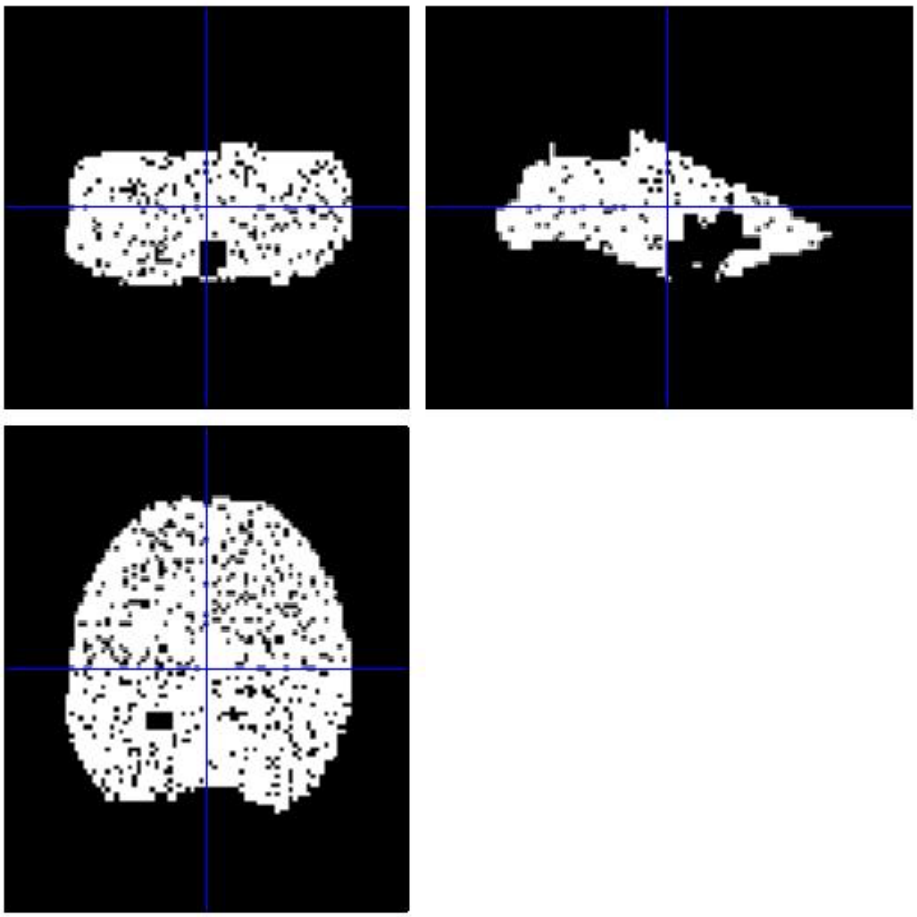
Appendix D1. Brain mask displaying the surviving voxels (white) of the analysis food images > non-food viewing



Appendix D2. Brain mask displaying the surviving voxels (white) of the analysis high caloric food images > low caloric food viewing



Appendix D3. Brain mask displaying the surviving voxels (white) of the analysis food images > non-food viewing



Appendix D4. Brain mask displaying the surviving voxels (white) of the analysis high caloric food images > low caloric food viewing

Appendix E

Appendix F: Summary of lessons learnt

	Description
Standardisation	The lack of standardised procedures in fMRI research and the many potential processing pipelines (Carp, 2012) complicate pooling strategies. Transparent reporting and or the standardisation of fMRI protocols is highly recommended to facilitate future pooling endeavours. For example, fMRIprep (Esteban et al., 2019) offers an easily accessible transparent and robust pipeline for fMRI pre-processing.
Time	Enough time for the conducting of a mega-analyses should be planned in. This includes time for the selection of appropriate studies, time for authors to provide their data and time for data harmonization and main analyses.
Preparation	Preparation includes careful consideration of inclusion and exclusion criteria, as well as a narrow definition of the images required. Here an emphasis on quality, rather than quantity should be made. This may decrease miscommunications with collaborators and increase responsiveness
Organisation	Organisation refers to the data sharing and storage. Here data was shared using NeuroVault - an open-source platform accommodating possibilities for private and public data sharing as well as standardized metadata. Data on NeuroVault can be best processed in Python among other options data does not have to be downloaded to be analysed. Considering the large datasets of mega-analyses, running analyses in Python may be a suitable software to reduce storage shortage of servers.
Harmonisation	Harmonisation refers to the combination of data from different studies or sites with the aim of making its combination more meaningful. Here harmonization procedures were realized from Zunhammer et al. (2021), which is one of many ways to harmonise data. Other tools include ComBat (Fortin et al., 2017, 2018; Wrobel et al., 2020) or Neuroharmony (Garcia-Dias et al., 2020).
Missing Voxels	Missing voxels are common in large datasets and pose a threat to false negatives (i.e. inflated Type II Error) (Vaden et al., 2012). Consequently, accounting for them is essential and should be determined before the actual analyses, for example in a preregistration. One possibility may be multiple imputations (Calhas & Henriques, 2020; Vaden et al., 2012)
Type of Analyses	The type of analyses remains an important point of consideration. Here a multiple regression is presented, mega-analyses comprise nested data, that is subjects are nested in studies. A mixed effects analyses including study as a random factor may be more appropriate than the inclusion of many (number of studies -1) dummy variables in a multiple regression. Alternatively, harmonisation tools like ComBat can correct for site effects of multi-site studies (Yu, 2018).