META-ANALYSIS

Neural Correlates of Anti-appetite Medications: An fMRI Meta-analysis

Andy Wai Kan Yeung[1],*

[1]*Oral and Maxillofacial Radiology, Applied Oral Sciences and Community Dental Care, Faculty of Dentistry, University of Hong Kong, China*

Abstract: Food craving is a health issue for a considerable proportion of the general population. Medications have been introduced to alleviate the craving or reduce the appetite via a neuropharmacological approach. However, the underlying cerebral processing of the medications was largely unknown. This study aimed to meta-analyze existing neuroimaging findings. We searched PubMed, Web of Science, and Scopus to identify relevant publications. Original studies that reported brain imaging findings using functional magnetic resonance imaging (fMRI) were initially included. The reported coordinates of brain activation available from the studies were extracted and meta-analyzed with the activation likelihood estimation (ALE) approach via the software GingerALE. The overall analysis pooling data from 24 studies showed that the right claustrum and insula were the targeted sites of altered cerebral processing of food cues by the medications. Subgroup analysis pooling data from 11 studies showed that these sites had reduced activity levels under medications compared to placebo. The location of this significant cluster partially overlapped with that attributable to affective value processing of food cues in a prior meta-analysis. No brain regions were found to have increased activity levels by medications. These neural correlates may help explain the physiological effect of food consumption by anti-appetite and anti-obesity medications.

1. INTRODUCTION

Excessive food consumption could lead to unwanted health consequences such as weight gain and diabetes. The prevalence of obesity was reported to be around 4 - 36.5% in Europe [3] and 28.5-32.2% in the United States [27]. Meanwhile, the global prevalence of diabetes was estimated to be 8.8% [5]. One way to reduce appetite or manage obesity is through pharmacological means. A recent meta-analysis showed that common anti-appetite medications, such as orlistat, phentermine plus topiramate, lorcaserin, naltrexone plus bupropion, and liraglutide could all significantly reduce body weight compared to placebo [30].

With the advancement of neuroimaging methods, the use of functional magnetic resonance imaging (fMRI) to investigate the neural correlates of appetite and food perception has become popular. With the accumulated literature, a meta-analysis could pool data across relevant papers to identify brain regions that were consistently reported to be affected by anti-appetite medications. Such a meta-analysis could be performed using the activation likelihood estimation (ALE) approach, which used a probability distribution model [6, 8] to determine the consistency of activated brain regions

reported across multiple experiments. This approach successfully meta-analyzed neuroimaging studies on taste and food stimuli among healthy subjects receiving no pharmacological interventions [39-41]. However, it was largely unknown if the medications exhibited a common pattern in reducing the brain activity level in response to food stimuli that might reflect suppression of appetite or food craving. The aim of this work was to meta-analyze the existing neuroimaging results from pharmacological fMRI studies to reveal which brain regions were commonly targeted by the medications and if these brain regions exhibited a heightened or dampened response to food stimuli.

2. METHODS

2.1. Literature Search and Screening

Adhering to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines, papers were searched in multiple databases, namely PubMed, Web of Science, and Scopus, in May 2021. The following string was used to search for the titles, abstracts, and keywords of papers: (fMRI OR "functional magnetic resonance imaging" OR "functional MRI") *AND* (food* OR appetit* OR eat*) *AND* (pharmacol* OR drug* OR medicat* OR treat*). Reference lists of relevant publications were also searched to identify missed papers.

*Address correspondence to this author at the Oral and Maxillofacial Radiology, Applied Oral Sciences and Community Dental Care, Faculty of Dentistry, University of Hong Kong, China; Tel/Fax: +852-2859-0403;
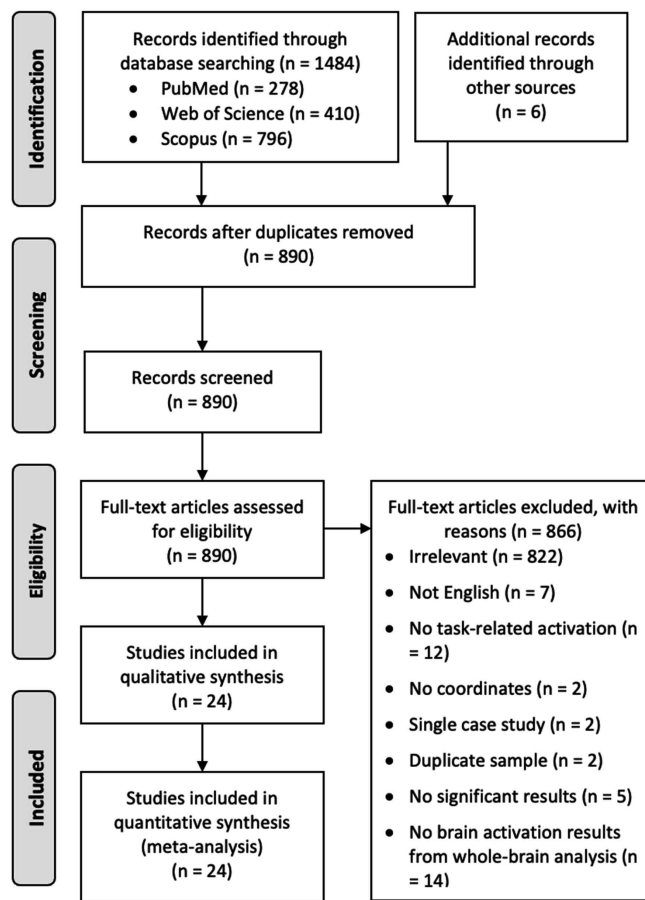E-mail: ndyeung@hku.hk

Fig. (1). Flow diagram showing the process of literature screening.

The search initially yielded 1490 papers. After excluding duplicates, 890 remained. Among them, 866 were excluded after further screening because of being irrelevant, not written in English, no task-related fMRI activation, no coordinates provided, being a single case study, duplicate samples, no significant results, and no results from the whole-brain analysis. Finally, 24 studies remained (Fig. **1**).

2.2. Information Recorded from the Analyzed Papers

Several items were recorded for each of the analyzed papers, such as subject number, female ratio, subject type (healthy or with specific health issues), medication and control used, administration method, dose, fasting time before the scan, type of food cue, and whether medicated or control condition had larger brain activation (Table **1**).

2.3. ALE Meta-analysis

The ALE method is the commonest approach of coordinate-based meta-analysis that pools neuroimaging data from multiple studies to identify brain regions with consistent activation based on probability distribution modeling [7]. The standard coordinates of reported brain areas with activation were pooled. Lancaster transform was deployed to convert coordinates reported in the Talairach system to the MNI system [21]. The software GingerALE 3.0.2 (freely available from http://brainmap.org/ale/) was used to perform the ALE meta-analysis, with the following default parameter settings. Subject-based full-width half-maximum values were applied

[7]. The more conservative mask instead of the dilated mask was used. A cluster of brain voxels was considered significantly activated if it survived a cluster $P < 0.05$ (corrected by familywise error rate, FWE-corrected) with a primary cluster-defining threshold of $P < 0.001$. This threshold followed the latest recommendations to balance between false positive and false negative [9, 25, 42]. Three main analyses were performed: an overall analysis involving all data, and one analysis for [medication > control] and [medication < control] each, respectively. As there were multiple (three) studies reporting [oxytocin > control] results, an exploratory analysis was performed based on this contrast. The thresholded ALE maps were overlaid onto the Colin brain template in MNI space [15] and visualized with Mango 4.0 (freely available from http://ric.uthscsa.edu/mango/mango.html) to show results.

3. RESULTS

3.1. Study Characteristics

There were 24 papers entering the meta-analysis, published between 2010 and 2020. The number of participants per study ranged from 8 to 48. Five studies recruited an equal ratio of males and females, whereas six studies recruited females only, and four studies recruited males only (Table **1**). Twelve studies recruited healthy subjects only, and numerous studies recruiting subjects with overweight/obesity and type 2 diabetes. Many medications were investigated,

Table 1.   **Details of the 24 meta-analyzed papers.**

Study	Subject Number	Female Ratio (%)	Subject Type	Medication	Control	Administration	Dose	Fasting before Scan	Food cue	Medicated or Control Had Larger Brain Activation
Bae *et al.* (2020) [1]	29	62.1	Type 2 diabetes	Lixisenatide	Placebo (saline)	Subcutaneous injection 30 mins before scan	10 μg (single dose)	12 h	Visual	Both
Basu *et al.* (2016) [2]	8	100.0	Healthy	Depo-medroxy-progesterone acetate	Baseline scan	Intramuscular injection 8 week before test scan	150 mg (single dose)	8 h	Visual	Medicated
Farr *et al.* (2014) [10]	12	100.0	Hypolepti-nemic (3); healthy (9)	Metreleptin	(Healthy control)	Taken for 24 weeks before scan	?	12 h	Visual	Both
Farr *et al.* (2016a) [11]	18	50.0	Type 2 diabetes	Liraglutide	Placebo	Taken daily for 17 days before scan	18 mg (total dose)	12 h	Visual	Control
Farr *et al.* (2016b) [12]	36	50.0	Obesity	Lorcaserin	Placebo	Oral intake twice daily for 4 weeks	20 mg (per day)	12 h	Visual	Control
Farr *et al.* (2019) [13]	20	45.0	Obesity	Liraglutide	Placebo	Taken daily for 35 days before scan	60 mg (total dose)	?	Visual	Medicated
Guthoff *et al.* (2010) [14]	9	44.4	Healthy	Insulin	Baseline scan	Intranasal spray 30 mins before test scan	160 IU (total dose)	12 h	Visual	Control
Tobon *et al.* (2020) [36]	20	0.0	Over-weight/obese and ADHD	Lisdexam-fetamine	Placebo	Oral intake 2 h before scan	15 mg (single dose)	No	Odor	Medicated
Horder *et al.* (2010) [16]	22	68.2	Healthy	Rimonabant	Placebo (lactose)	Oral intake for 7 days before scan	20 mg (per day)	No	Visual; taste	Control
Ioannou *et al.* (2017) [18]	14	57.1	Healthy	5-HTP	Placebo (vitamin C)	Oral intake 30-45 mins before scan	100 mg (single dose)	12 h	Visual	Medicated
Killgore *et al.* (2010) [20]	16	50.0	Healthy to obese	Citicoline	Citicoline (lower dose)	Oral intake once daily for 6 weeks	500 or 2000 mg (per day)	?	Visual	Medicated
McCabe *et al.* (2010) [22]	45	53.3	Healthy	Citalopram; reboxetine	Placebo	Oral intake for 7 days before scan	Citalopram 20 mg (per day); reboxetine 8 mg (per day)	No	Visual; taste	Control
Medic *et al.* (2014) [23]	43	51.2	Healthy	Bromocrip-tine; sul-piride	Placebo	Oral intake 2.5 h before scan	Bromocriptine 1.25 mg (single dose); sulpiride 400 mg (single dose)	12 h	Visual	Both

(Table 1) contd….

Study	Subject Number	Female Ratio (%)	Subject Type	Medication	Control	Administration	Dose	Fasting before Scan	Food cue	Medicated or Control Had Larger Brain Activation
Melrose *et al.* (2016) [24]	11	100.0	Healthy	Dextroamphetamine sulfate	Placebo	Oral intake 3 h before scan	0.5 mg/kg (single dose)	3 h	Taste	Medicated
Murray *et al.* (2014) [26]	20	50.0	Healthy	Naltrexone	Placebo	Taken 1 h before scan	50 mg (single dose)	No	Visual; taste	Control
Plessow *et al.* (2018)[28]	10	0.0	Overweight/obese	Oxytocin	Placebo	Intranasal spray 1 h before scan	24 IU (total dose)	10 h	Visual	Both
Rabiner *et al.* (2011) [29]	24	0.0	Healthy	Naltrexone; GSK1521498	/	Taken 4-89 h before scan	Naltrexone 2-50 mg (single dose); GSK1521498 0.4-100 mg (single dose)	8 h	Taste	Both medications
Spetter *et al.* (2018) [31]	15	0.0	Healthy	Oxytocin	Placebo	Intranasal spray 35 mins before scan	24 IU (total dose)	12 h	Visual	Medicated
Stice *et al.* (2018) [32]	40	72.5	Healthy to obese	Gymnemic acid	Placebo	Oral intake 3 mins before scan	3.5 mg (single dose)	0.5 h	Visual; taste	Medicated
Stip *et al.* (2012) [33]	15	26.7	Schizophrenia	Olanzapine	Baseline scan	Taken for 16 weeks before scan	16.18 mg (mean dose per day)	3 h	Visual	Medicated
Striepens *et al.* (2016) [34]	31	100.0	Healthy	Oxytocin	Placebo	Intranasal spray 45 mins before scan	24 IU (total dose)	?	Visual	Medicated
Thomas *et al.* (2018) [35]	24	100.0	Healthy	Meta-chloro-phenylpiperazine	Placebo	Oral intake 2-3 h before scan	30 mg (single dose)	No	Visual	Both
von Bloemendaal *et al.* (2014) [37]	48	50.0	Healthy to Type 2 diabetes	Exendin 9-39; exenatide	Placebo	Intravenous injection throughout the scan	Exendin 9-39 600 pmol/kg/min; exenatide 25 ng/min	12 h	Visual	Control
Wang *et al.* (2014) [38]	46	100.0	Overweight/obese	Naltrexone + buproprion	Placebo	Oral intake for 3 weeks before scan	Naltrexone 32 mg (per day); bupropion 360 mg (per day)	15-17 h	Visual	Medicated

but only oxytocin was investigated in multiple (three) studies. Naltrexone was also involved in three studies, one of which was administered together with buproprion. Overnight or 12 hours of fasting before a scan seemed to be the commonest practice. Besides, 17 studies used visual food cues only. Two studies used taste food cues only, four studies used both visual and taste food cues, and one study used odor.

3.2. Overall Meta-analysis

There was one significant cluster covering the claustrum and insula on the right hemisphere (Fig. **2A**, Table **2**). Seven studies (with no recurring medication shared) contributed to

this cluster, four of them had [medication > control] [24, 32-34] and three had [medication < control] [22, 35, 37].

3.3. Medication > Control

There was no significant result from pooled data from 15 studies for [medication > control]. The same was observed for pooled data from 3 studies for [oxytocin > control].

3.4. Medication < Control

Pooling data from 11 studies showed that there was one significant cluster covering the claustrum and insula on the right hemisphere (Fig. **2B**, Table **2**). Three studies contributed to this cluster, and they investigated citalopram,
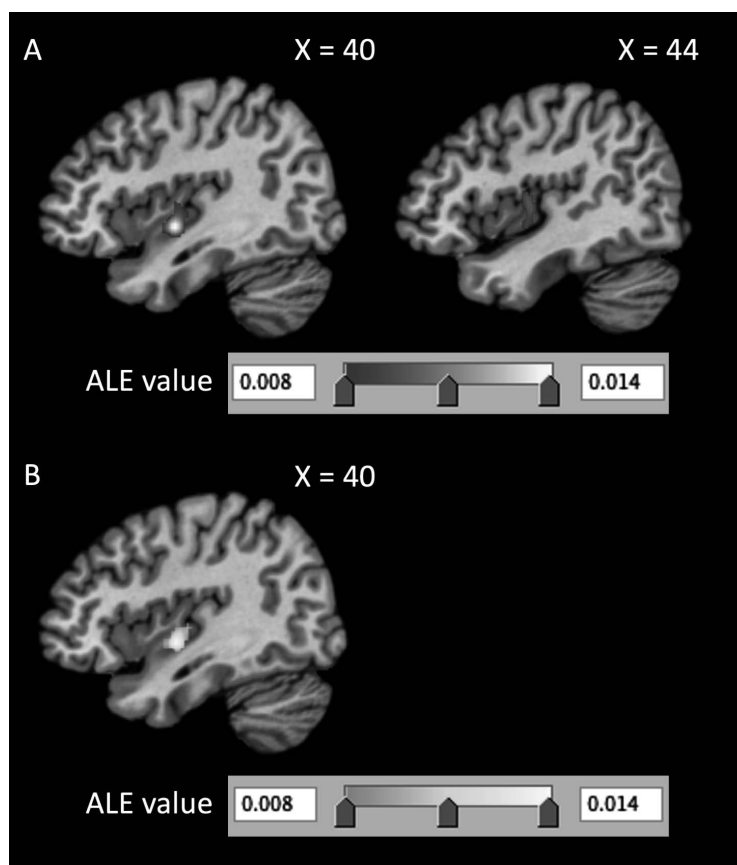
Fig. (2). Meta-analytic results showing significant brain activation from (**A**) overall analysis, and (**B**) medication < control.

Table 2.   Meta-analytic results.

Contrast	Cluster Size (mm³)	Side	Brain Region	Peak Voxel Brain Coordinate			ALE Value (×10⁻²)
-	-	-	-	x	y	z	-
Overall analysis	-	-	-	-	-	-	-
-	1472	R	Claustrum	40	-8	-8	2.23
-	-	R	Insula	44	-8	6	1.41
Medication > control	-	-	-	-	-	-	-
-	Not significant	-	-	-	-	-	-
Medication < control	-	-	-	-	-	-	-
-	888	R	Claustrum/insula	40	-8	-8	1.44
Oxytocin > control	-	-	-	-	-	-	-
-	Not significant	-	-	-	-	-	-

meta-chlorophenylpiperazine, and exenatide, respectively [22, 35, 37].

4. DISCUSSION

This is the first meta-analysis of fMRI studies reporting the effects of medications on food/taste processing in the brain. Overall results showed that the right claustrum and insula were involved by the effect of medications. Results further showed that medications caused reduced brain re-sponses than placebo in the right claustrum and insula, whereas no significant result was found *vice versa*.

Taste processing and eating behavior are complex psychophysiological issues with multiple dimensions. In particular, the five senses of visual, auditory, gustatory, olfactory, tactile, or any combinations of them could be stimulated. Prior meta-analysis showed that visual food cues activated the posterior brain regions responsible for visual processing, including the occipital and cerebellar structures, whereas

gustatory and olfactory food cues activated the anterior brain regions responsible for visceral sensations [17]. Most of the analyzed studies here recruited visual food cues only, implying that the reduced brain activation by medications could perhaps be cautiously interpreted as a suppressed brain activity in response to viewing food, food anticipation, or even imaging food consumption, but not the actual consumption of food. In fact, food appreciation could involve affective value, intensity, and taste quality, which could be segregated in the limbic system [41]. The cluster found in this study was located in the ventral insula, a region relevant to taste processing [40]. It also slightly overlapped with a cluster for affective value but did not overlap with the clusters for intensity and taste quality [41].

Another issue that should be noticed but not addressed in the analyzed studies was the potential influence of sex-related factors on pharmacodynamics and pharmacokinetics. For example, the commonly used naltrexone/bupropion combination might have sex differences in the hypothalamic-pituitary-adrenal axis response, and that oestrogen might potentiate the liver metabolism of bupropion to its active metabolite form [4]. The analyzed studies did not provide direct between-sex comparison results. They also did not accumulate a large number of uni-sex results for conducting a male *vs*. female meta-analysis. Therefore, any sex differences in the neural correlates of medication-mediated food processing remained to be elucidated.

There were several limitations of this meta-analysis. First, several studies recruited few subjects that might hinder the study power by themselves. Also, the studies were not always sex-matched, implying that some results reported from the original studies might not be generalized to the other sex. The heterogeneous sample also implied limitations in the generalization of the results. The authors of studies not reporting coordinates were not contacted to see if they could provide data. Many medications were investigated in one or two studies reporting whole-brain analysis results; therefore, it was not possible to perform medication-specific analysis for them. One study [16] investigated rimonabant, a drug introduced in Europe in 2006 and subsequently withdrawn in 2009 due to the potential of serious psychiatric disorders [19]. Meanwhile, ALE meta-analysis computes the consistency of brain locations involved across studies but not the effect size [6].

CONCLUSION

Within the limitations of this meta-analysis, it was concluded that medications could suppress brain activation in the right claustrum and insula in response to food cues (mostly visual) compared to control/placebo. The involved brain region partly overlapped with an activated cluster attributed to affective value evaluation of food in a prior meta-analysis. These neural correlates may help explain the physiological effect of food consumption by anti-appetite and anti-obesity medications and may be the target sites of future drug development.

CONSENT FOR PUBLICATION

Not applicable.

STANDARD OF REPORTING

PRISMA guidelines and methodologies were followed.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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