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Research Article

Systematic Review of fMRI Studies with Visual Food Stimuli in Anorexia Nervosa

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Abstract

Anorexia Nervosa (AN) is a disease with increasing prevalence and relatively high mortality that usually begins in adolescence. Patients with AN avoid food intake and may react specifically toward food images. We present a systematic review of fMRI studies with visual food stimulation in AN, based on a search through PubMed database under the recommendations of the PRISMA guidelines. After applying dates 2004.01.01-2021.01.01, we screened 319 papers and included 27 experimental designs, with only 7 studies focusing on adolescents. Adolescents with AN showed increased activity in the medial prefrontal cortex, the inferior frontal gyrus, the insula, the hippocampus, the fusiform gyrus, the parahippocampal gyrus and the cuneus when watching food images. Adult participants with AN revealed enhanced brain activity due to visual food stimuli in the fusiform gyrus, the inferior frontal gyrus, the lingual gyrus, the medial prefrontal cortex, the right dorsolateral prefrontal cortex, the right angular gyrus. There was deactivation detected in the parahippocampal gyrus, compared to healthy participants. We have found contrary reports according increased/decreased activation of the insula, the amygdala, the hippocampus, the hypothalamus, the anterior cingulate cortex, the thalamus, the orbitofrontal cortex in adults with AN.

Although AN typically develops in adolescence, there is still very little fMRI research in this age group. Careful creation of a homogeneous group of study participants is an important factor determining the reliability and unequivocalness of the experiment. Only a detailed description of participants´ characteristics that may affect the results allows solid comparison of different studies´ findings.

Keywords: Anorexia nervosa; Functional magnetic resonance imaging; Visual food stimuli; Adolescent psychiatry

Abbreviations

fMRI: Functional Magnetic Resonance Imaging; AN: Anorexia Nervosa; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; ED: Eating Disorder; BOLD: Blood Oxygenation Level Dependent; HC: Healthy Controls

Introduction

Anorexia Nervosa (AN) is an Eating Disorder (ED), characterised by restriction of food intake leading to significantly low body weight, intense fear of gaining weight and a distorted body image [1]. Although typically onset of AN is in adolescence [2], studies in this age group are relatively rare. Even though its prevalence rate is growing, it is still underdiagnosed [3]. Onset of AN often overlaps with increased vulnerability due to peers´ and social pressure, but also physical transmission from safe childhood into demanding adulthood. Juvenility is period of elevated need for calorie intake and last possibility to develop healthy body, with proper growth and brain volumes (brain consists in 60% of fat [4]). Limitation of calorie intake in juvenescence often results in significantly lower adult height [5,6]. Starvation and dehydration lead to brain volume loss [7] and influence cognitive processes. This can be crucial in adolescence, because it is usually time of attending final level of education and making decision about future life. As AN has the highest mortality rate of any psychiatric illness [8-10], it seems essential to understand both psychological and neural alterations underlying AN. Especially, that early age of onset, as well as short duration of symptoms and inpatient treatment are related to better prognosis [11].

Development of neuroimaging techniques aroused hope for quicker and more precise diagnose, for possibility to predict course of illness, and to find neuroimaging biomarkers. Although, the first paper performing neuroimaging in psychiatry concentrated on schizophrenia [12], it was soon followed by publication about adolescent anorectic patients [13]. However, among the 100 most highly cited papers about neuroimaging in psychiatry [14], there was no article about ED.

Functional Magnetic Resonance Imaging (fMRI) records activity of specific brain regions *in vivo* using the indirect detection of neuronal activity via hemodynamic changes. When activated, the brain area is supplied by a greater amount of oxygenated blood, so the ratio of oxygenated/deoxygenated haemoglobin is changed in vein vessels. Due to different magnetic properties, they can serve as intrinsic contrast agents and be detected by MR scanners. This method of imaging is relying on the BOLD (Blood Oxygenation Level Dependent) effect [15]. In order to analyse changed brain activation in a given disorder, one can use symptom-provoking paradigms. In AN such a disorder related stimuli can be, beside pictures of body

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Table 1: Systematic review search strategy.

Anorexia **OR** anorectic	**AND**	Image **OR** Imaging **OR** fMR* **OR** "Functional Magnetic Resonance Imaging" **OR** "Neural processing" **OR** Processing	**AND**	Visual **OR** Picture* **OR** Image **OR** Imaging	**AND**	Food **OR** Meal

shapes, food images. They are described as aversive, causing anxiety, even influencing cognitive performance, so they are triggers to cause specific for AN brain reaction, in comparison to Healthy Controls (HC) [16]. It was documented, that adolescents with AN respond faster to high-calorie food images than healthy participants [17].

We present a systematic review of papers related to fMRI studies employing experimental designs in AN using visual stimulation with images of food. Specifically, we focused on adolescents, as not many fMRI studies examined neural responses associated with AN in minors.

Material and Methods

To find matching articles, we have searched via PubMed, applying dates 2004.01.01 to 2021.01.01. The search strategy is presented in a Table 1.

We found 319 matching papers, then screening titles and abstracts we limited results to English language and original papers. Moreover, we excluded case reports, reviews and comorbidity papers. Furthermore, we eliminated studies concerning non-AN patients and animals. Additionally, we have searched through reference lists and eating disorders specialised journals. We were particularly interested in studies on adolescents.

Results

We screened 319 papers and finally included 27 in this review. We excluded 292 papers because of the mentioned exclusion criteria. Figure 1 shows PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram (a tool suggested by Moher D with colleagues for systematic reviews) [18] (Figure 1).

A summary of the results is shown in a Table 2.

Stimuli

The main aspect of this review was to analyse cerebral activation due to the presentation of food pictures because such stimuli can be

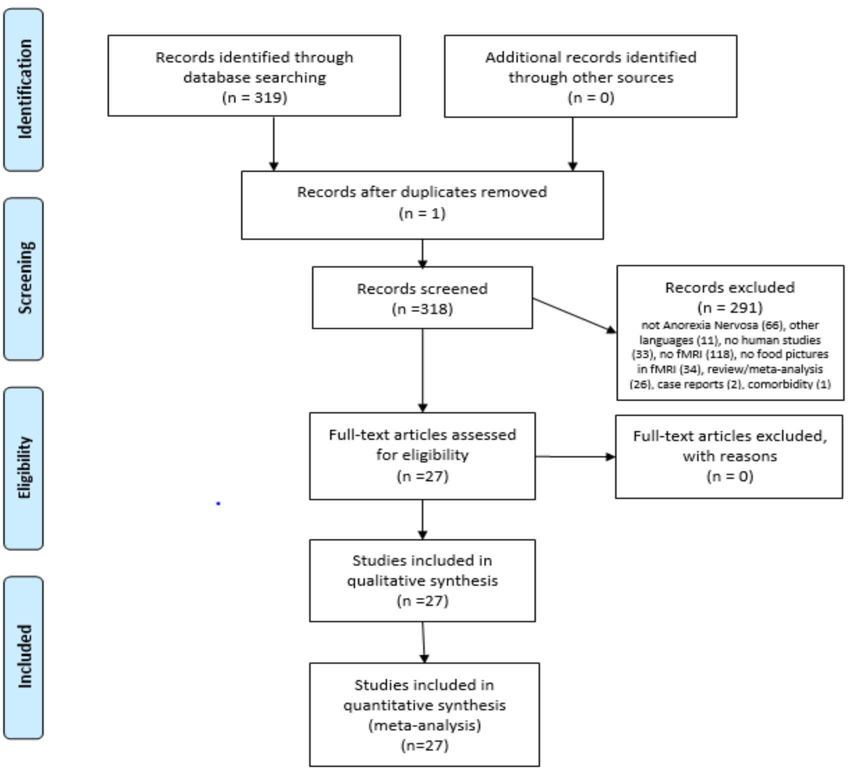

Figure 1: Flowchart PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) presenting the main search strategy and article selection for systematic review.

Table 2: Characteristics of included studies.

Author	Participants	Viewed images	Comments	Key findings	
				Stimulus and comparison	Results of brain area
Horster et al. [19]	31AN/27HC	Images of food and objects	EDI-2, BDI, EDE-Q, MWT-B, STAI, rating of pictures after scanning. Replication study to one conducted by Joos AA et al., 2011	HC: increased activation due to food stimuli:	Right calcarine fissure, right middle occipital gyrus, left superior frontal gyrus, left superior occipital gyrus, left insula, left superior parietal gyrus
				AN: increased activation due to food stimuli:	Left middle occipital gyrus, right calcarine fissure, right lingual gyrus, bilateral fusiform gyrus, left SMA, bilateral superior frontal gyrus, ACC, left middle frontal gyrus (orbital part), left precuneus, bilateral insula, bilateral midcingulate, right supramarginal gyrus, left postcentral gyrus, right angular gyrus
				AN *vs.* HC: increased activation due to food stimuli:	Left MCC, left precentral gyrus, left postcentral gyrus, left middle frontal cortex, right IPL, right angular gyrus, right precuneus, right posterior cingulate gyrus
				HC *vs.* AN: activation due to food stimuli:	No significant results
Young et al. [20]	16AN/21HC	Images of food (H and L) and objects	SCID, EDE-Q, YBC-EDS, DASS, PANAS, rating anxiety during fMRI task. 2 fMRI scans-one before and one after 10 sessions of exposure-based therapy.	AN *vs.* HC, pre-therapy, decreased activation due to food stimuli:	ACC
				AN *vs.* HC, post-therapy, increased activation due to food stimuli:	DLPFC
				AN *vs.* HC, post-therapy, decreased activation due to food stimuli:	superior parietal lobe
				Association between anxiety and changes of brain activation:	insula, middle temporal gyrus/lateral parietal cortex
Ziv et al. [21]	11AN, 7 atypical AN 13-18 yo.	Images of food (sweet & non-sweet) and non-food	EAT-26, STAI	increased activation due to food *vs.* non-food stimuli:	Occipital regions
				decreased activation due to food *vs.* non-food stimuli:	Temporal and parietal gyri
				increased activation due to sweets versus non-food stimuli:	Hippocampus
				increased activation due to sweet *vs.* nonsweet food stimuli:	OFC, ACC
				Positive correlation between STAI and brain activity, when comparing all foods versus non-food stimuli:	OFC, ACC
				Positive correlation between EAT-26 and brain activity, when comparing sweet versus nonsweet stimuli:	ACC, frontal regions
Stopyra et al. [22]	25AN/25HC	H and non-food images	Viewing pictures or solving an arithmetic equation (distraction conditions). Infusion of glucose/ water through the nasogastric tube. SCID, EDE-Q, BDI, hunger rating, cravings rating.	AN: due to food *vs.* non-food distraction: water comparing to glucose	Precuneus
				In a state of hunger: AN *vs.* HC, increased activation due to H *vs.* non-food distraction:	Left middle occipital gyrus, left inferior parietal lobule, left precuneus, left fusiform gyrus
				In a state of satiety: HC *vs.* AN, increased activation due to H *vs.* non-food distraction:	Left PCC, left parahippocampal gyrus, left superior frontal gyrus, left medial OFC, left ACC
				Negative association between cravings rating in AN and brain activation:	Bilateral dorsal striatum
Weinbach et al. [17]	30AN/30HC 12-18 yo.	H & L	SCID, WASI-II, EDE-Q, BDI, STAI, OCI. Food-stop signal task (response inhibition) after food images presentation.	Response time to displayed images, not the specific brain region´s activation due to stimuli.	
				AN *vs.* HC- faster response to H	
Olivo et al. [23]	28atypicalAN/33HC 13-16 yo.	H & L	EDE-Q, MADRS, MINI-KID	Functional connectivity analysis not included in this table.	

Boehm et al. [24]	35AN/35HC 12-19 yo.	30 neutral (i.e. house) and 30 happy social stimuli (i.e. children playing), as well as food pictures (H & L, but not divided)	Pictures presented supraliminally and subliminally SCID, SIAB, EDI-2, WAIS, WISC, hunger rating.	Supraliminal stimuli: AN increased activation due to all stimuli:	Inferior frontal junction (IFJ)
				Supraliminal stimuli: AN increased activation due to food stimuli:	Visual regions (including superior occipital gyrus and the fusiform gyrus/ parahippocampal gyrus)
				Subliminal stimulation	No group differences
Horndasch et al. [25]	Adolescents: 15AN/18HC 12-18 yo Adults: 16AN/16HC 19-40 yo	12 pictures of H & L food and 24 affective stimuli (IAPS)	EDI-2, BDI	**Adolescent AN *vs.* HC**	
				AN increased activation due to H stimuli:	IFG, medial prefrontal gyrus, anterior insula
				AN decreased activation due to H simuli:	right cerebellum
				AN increased activation due to L stimuli:	medial prefrontal gyrus and inferior parietal cortex, cerebellum
				AN decreased activation due to L stimuli:	cerebellum
				Adult AN *vs.* HC	
				AN increased activation due to H & L stimuli:	cerebellum
				AN decreased activation due to L stimuli:	right inferior frontal gyrus and thalamus
				Adult AN *vs.* Adolescent AN	
				Adult AN increased activation due to H stimuli:	superior parietal and cerebellum
				Adult AN decreased activation due to L stimuli:	bilateral superior frontal lobe, bilateral cingulate and left cerebellum
				Adult HC *vs.* Adolescent HC	
				Adult HC increased activation due to H & L stimuli:	left cerebellum
				Adult HC decreased activation due to H stimuli:	cingulate cortex, insula and several cerebellar regions
				Adult HC decreased activation due to L stimuli:	caudate, superior frontal gyrus and similar cerebellar regions
Kerr et al. [26]	20 weight restAN/ 20HC 13-24 yo	Pictures of high/ low palatability food, and objects	Rating of interoceptive sensations intensity, then comparing it with fMRI results. SIAB- EX, SCID, EDI-3, HAM-A.	**Relationship between stomach sensation intensity ratings and brain activation**	
				wrAN: positive relationship due to high palatability stimuli:	amygdala and subgenual ACC
				HC: negative relationship due to high palatability stimuli:	amygdala and subgenual ACC
				wrAN: negative relationship due to low palatability stimuli:	ventral pallidum, ventral tegmental area
				HC: positive relationship due to low palatability stimuli:	ventral pallidum, ventral tegmental area
Scaife et al. [27]	12AN/14 recAN/16HC	40 H & 40 L calorie food pictures	EDE-Q, NART, STAI, BDI, YBC-EDS, LOFPQ	AN *vs.* HC: decreased activation due to food stimuli:	right postcentral gyrus-precuneus (extending to PCC), the left superior parietal lobule-postcentral gyrus
				RecAN *vs.* HC: activation due to food stimuli:	no significant differences
				AN *vs.* HC: increased activation due to H stimuli:	right lateral frontal pole
				AN *vs.* HC: decreased activation due to L stimuli:	right lateral frontal pole (also DLPFC), right supramarginal gyrus
				AN *vs.* recAN: activation due to L stimuli:	no significant differences
				recAN *vs.* HC: activation due to L stimuli:	no significant differences
				Relationship between YBC-EDS score ratings and brain activation	
				AN: negative relationship due to L stimuli:	frontal pole
				Connectivity analyses -Psychophysiological interaction	
				AN *vs.* HC: reduced coherence due to food stimuli between regions:	left amygdala with caudate/putamen (dorsal striatum), dorsal ACC, medial PFC
					the right caudate with left postcentral gyrus – juxtapositional lobule cortex
				AN *vs.* HC: reduced coherence due to H stimuli between regions:	left caudate with the bilateral intracalcarine-lingual gyri

Sultson et al. [28]	14 AN/ 14recAN /15HC	Images of food (H and L) and objects	Instruction to imagine eating/ using what is presented. Rating anxiety and desire to eat. STAI, BDI, BCST	**Significant correlations between perseverative errors and brain activation:**	
				AN: negative correlation during food processing:	dACC, paracentral lobule, precuneus
				AN: negative correlation during non-food processing:	right DLPFC
				recAN: positive correlation during food processing:	left dAAC and VLPFC
				recAN: positive correlation during non-food processing:	left dAAC, anterior insula and medial PFC
				Significant correlations between non-perseverative errors and brain activation:	
				AN: negative correlation during food processing:	right dACC
				HC: positive correlation during non-food processing:	right dAAC and DLPFC
				Correlation between anxiety and brain activation:	
				AN: negative correlation due to non-food stimuli:	precuneus
				HC: positive correlation due to food stimuli:	left DLPFC and dACC
				HC: positive correlation due to non-food stimuli:	left DLPFC
Sanders et al. [29]	15AN/ 14recAN/15HC	Images of food (H and L) and objects	Instruction to imagine eating/ using what is presented. EDE-Q, STAI	AN: increased activation due to food stimuli:	left hippocampus, vermis, right cerebellum, hypothalamus, right middle frontal gyrus, left inferior parietal cortex
				AN: decreased activation due to food stimuli:	superior frontal gyrus, right precuneus, right PCC, right cuneus and left precuneus, left superior temporal cortex
				recAN: increased activation due to food stimuli:	right caudate nucleus, right cerebellum, left hippocampus, vermis, right insula, right middle frontal gyrus
				recAN: decreased activation due to food stimuli:	right PCC
				HC: increased activation due to food stimuli:	hypothalamus, right insula, left middle frontal gyrus
				HC: decreased activation due to food stimuli:	left post central gyrus, right cuneus and left precuneus (but no significant differences between the groups)
Holsen et al. [30]	13AN/ 9wrAN /12HC	Images of food (H and L) and objects	Results of neural activation only in relationship with fasting plasma acylated ghrelin levels. BDI, EDE-Q, appetite ratings.	**Correlation between fasting acylated ghrelin and brain activation:**	
				AN: positive correlation due to L stimuli:	right OFC
				wrAN: negative correlation due to H stimuli:	left hippocampus
				HC: significant positive correlation due to H stimuli:	right amygdala, hippocampus, insula, OFC
				Relationship between desire to eat and brain activation:	
				HC: positive correlation due to H stimuli:	anterior insula
				HC: positive correlation due to L stimuli:	OFC
				wrAN: positive correlation due to L stimuli:	OFC
Kullmann et al. [31]	12AN/12 athletes/ 14HC	Images of food and objects; active and non-active person.	Go/no-go tasks on every pairs of pictures: go food/ no-go object and go object/ no go food; go active /no-go inactive and go inactive /no-go active. EDI-2, EDE-Q, STAI, PHQ-D, BAS/BIS, CES, hunger ratings.	**Response inhibition across subjects to food *vs.* objects stimuli:**	
				Increased activation:	right middle and inferior temporal cortex, bilateral middle frontal cortex, right supplementary motor area, left fusiform gyrus, bilateral insula, right postcentral gyrus, left superior medial frontal gyrus, left supramarginal gyrus, right superior frontal gyrus
				Response inhibition to food *vs.* objects stimuli:	
				Increased activation:	bilateral fusiform gyrus and insula, inferior parietal gyrus and middle frontal gyrus
				Decreased activation:	mOFC, middle temporal gyrus, PCC
				Response inhibition to food *vs.* objects stimuli:	
				AN *vs.* HC: decreased activation:	right putamen
				AN *vs.* athletes: decreased activation:	right putamen
				AN *vs.* athletes and HC: reduced response inhibition for food and objects stimuli.	
				Correlation between brain activation during response inhibition for food/non-food stimuli and tests:	
				significant negative correlation between EDI-2 score:	putamen

				positive correlation between correct go responses:	putamen
				Results of response inhibition to physical activity stimuli, as well as behavioural results are not included in this review.	
Lawson et al. [32]	13AN/10wrAN/13HC	Images of food (H and L) and objects	Comparing fMRI results with peripheral cortisol and ACTH levels; in state of hunger and satiety. BDI, SCID, appetite rating.	Association between cortisol and ACTH levels and brain activation due to H stimuli:	
				AN *vs.* HC: (premeal) increased activation:	amygdala, hippocampus, insula, hypothalamus, OFC
				wrAN *vs.* HC: (premeal) increased activation:	amygdala, insula, hypothalamus
				AN *vs.* HC: (postmeal) decreased activation:	amygdala and insula
				AN *vs.* wrAN: (postmeal) increased activation:	amygdala
				AN *vs.* wrAN: (postmeal) decreased activation:	insula
Oberndorfer et al. [33]	14recAN/12HC	Images of food and objects	Visual anticipatory task *(a square would be followed by food image and a circle by object image)*. Brain reaction during watching food/object pictures, as well as during anticipation of food/object pictures. STAI, BDI, FMPS, TCI, BIS-11, TAS-20. Pleasantness rating of pictures. Scanning after meal.	recAN during object anticipation:	amygdala, IFC, occipital lobes, anterior and superior cingulate gyrus
				recAN during food anticipation:	right middle frontal gyrus, occipital lobes, PCC
				HC during object anticipation:	occipital lobes and left middle frontal gyrus
				HC during food anticipation:	left IFC and occipital lobes
				recAN *vs.* HC: increased activation due to food stimuli:	precuneus
				recAN *vs.* HC: decreased activation due to non-food stimuli:	pregenual ACC
				recAN *vs.* HC: increased activation due to food anticipation:	putamen, superior and medial frontal gyri
				recAN *vs.* HC: decreased activation due to food anticipation:	IPL
				recAN *vs.* HC: increased activation due to food stimuli:	IPL, insula, lateral OFC
				recAN *vs.* HC: decreased activation due to food stimuli:	medial temporal gyrus
				recAN *vs.* HC: increased activation due to food anticipation:	right ventral anterior insula
				recAN *vs.* HC: decreased activation due to object anticipation:	right ventral anterior insula
				Correlation between pleasantness of images rating and brain activation:	
				HC: positive correlation with increased activation:	insula
				AN: no such relationship	
Brooks et al. [34]	18 AN (11 rAN, 7 bp AN)/ 24 HC 16-50 yo	Images of food (H and L) and objects	Instruction to imagine eating/ using what is presented, than rating anxiety. EDE-Q, HADS	rAN: increased activation due to food stimuli:	left cerebellar vermis and visual cortex, right DLPFC, medial PFC
				bpAN: increased activation due to food stimuli:	bilateral cerebellar vermis, right inferior temporal gyrus
				AN *vs.* HC: increased activation due to food stimuli:	right visual cortex
				AN *vs.* HC: decreased activation due to food stimuli:	bilateral cerebellar vermis
				rAN *vs.* HC: increased activation due to food stimuli:	right visual cortex and DLPFC
				rAN *vs.* HC: decreased activation due to food stimuli:	right insula, right cerebellar vermis
				bpAN *vs.* HC: increased activation due to food stimuli:	right visual cortex
				bpAN *vs.* HC: decreased activation due to food stimuli:	left cerebellar vermis, right insula
				rAN *vs.* bpAN: increased activation due to food stimuli:	bilateral visual cortex, left ACC and parahippocampal gyrus

				rAN *vs.* bpAN: decreased activation due to food stimuli:	left visual cortex
Holsen et al. [35]	12AN/10 wrAN/11HC	Images of food (H and L) and objects before and after meal.	fMRI scanning before and after meal. Rating appetite and STAI before and after each scanning. EDE-Q, BDI, pleasantness rating of pictures.	AN *vs.* HC: (premeal) decreased activation due to H stimuli:	anterior insula, amygdala, hypothalamus, hippocampus, OFC
				AN *vs.* HC: (postmeal) decreased activation due to H stimuli:	amygdala, insula
				wrAN *vs.* HC: (premeal) decreased activation due to H stimuli:	hypothalamus, amygdala, anterior insula
				AN *vs.* wrAN: (postmeal) increased activation due to H stimuli:	amygdala
				AN *vs.* wrAN: (postmeal) decreased activation due to H stimuli:	anterior insula
				Correlation between pleasantness of H images rating or appetite rating and premeal brain activation:	
				HC: positive correlation between pleasantness of images and brain activation:	insula
				HC: positive relationship between appetite rating and brain activation:	insula, amygdala
				wrAN: positive relationship between appetite rating and brain activation:	hypothalamus, amygdala
Kim et al. [36]	18AN (6rAN, 12 bpAN)/ 20 BN/ 20 HC	Images of H food and non-food	Hunger rating and food craving (FCCQ-S) before and after scanning, SCID, BDI, BAI, EDI.	AN: increased activation due to H stimuli:	left anterior insula, bilateral IFG, right superior frontal gyrus, left ACC, precuneus and cuneus, bilateral cerebellum
				BN: increased activation due to H stimuli:	left anterior insula, left cuneus, bilateral cerebellum
				HC: increased activation due to H stimuli:	left middle frontal gyrus, cuneus and lingual gyrus, right cerebellum
				AN *vs.* HC: increased activation due to H stimuli:	right IFG, bilateral superior frontal gyrus, left ACC, right cerebellum
				AN *vs.* HC: decreased activation due to H stimuli:	right inferior parietal lobule
				BN *vs.* HC: increased activation due to H stimuli:	right middle frontal gyrus, right cerebellum
				BN *vs.* HC: decreased activation due to H stimuli:	right postcentral gyrus, left inferior parietal lobule
				AN *vs.* BN: increased activation due to H stimuli:	bilateral ACC
				AN *vs.* BN: decreased activation due to H stimuli:	right middle temporal gyrus
				Functional connectivity between the left anterior insula and other brain regions:	
				AN:	right insula, right IFG, mOFC
Lawson et al. [37]	13AN/9wrAN/13HC	Images of food (H and L) and objects	Measurement of oxytocin level as fasted and 3 times after the meal. fMRI before and after the meal. BDI, STAI, EDE-Q	**Association between oxytocin level and brain regions due to food stimuli:**	
				AN *vs.* HC (premeal):	left hypothalamus, amygdala, hippocampus, right OFC, bilateral insula
				wrAN *vs.* HC (premeal):	right insula, bilateral hypothalamus, left amygdala
				AN *vs.* HC (postmeal):	left amygdala and insula
				AN *vs.* wrAN (postmeal):	right amygdala, bilateral insula
Brooks et al. [38]	18AN (11 rAN, 7bpAN) / 8BN /24HC 16-50 yo	Images of food (H and L) and objects	Instruction to imagine eating/ using what is presented, than rating anxiety. EDE-Q, HADS	AN: increased activation due to food stimuli:	left visual cortex, cerebellum, right precuneus and DLPFC
				rAN: increased activation due to food stimuli:	right DLPFC and parietal lobe, cerebellum, left visual cortex
				bpAN: increased activation due to food stimuli:	bilateral cerebellum, right SMA
				BN: increased activation due to food stimuli:	left DLPFC, right insula, right visual cortex, left precentral gyrus
				HC: increased activation due to food stimuli:	right insula, right superior and middle temporal gyri, left caudate, left cerebellum
				AN *vs.* BN: increased activation due to food stimuli:	parietal lobe and PCC
				AN *vs.* BN: decreased activation due to food stimuli:	caudate, insula, SMA
				rAN *vs.* BN: increased activation due to food stimuli:	precentral gyrus

				rAN *vs.* BN: decreased activation due to food stimuli:	PCC, ITG, fusiform gyrus, IPL
				bpAN *vs.* BN: increased activation due to food stimuli:	ITG
				bpAN *vs.* BN: decreased activation due to food stimuli:	PCC, SMA, cerebellum, PHG
				HC *vs.* BN: increased activation due to food stimuli:	insula, visual cortex
Cowdrey et al. [39]	15 recAN /16HC	Pictures of moldy strawberry (aversive) and chocolate (H), matched with taste stimuli	Pleasantness rating of pictures. EDE-Q, BDI, FCPS, SHAPS, STAI, SCID.	recAN *vs.* HC: increased activation due to H taste stimuli:	ventral striatum, PCC, putamen
				recAN *vs.* HC: increased activation due to visual H stimuli:	anterior PFC, occipital cortex, subgenual cingulate/ medial PFC
				recAN *vs.* HC: increased activation due to H visual and taste stimuli:	pallidum
				recAN *vs.* HC: increased activation due to aversive taste stimuli:	insula, putamen
				recAN *vs.* HC: increased activation due to aversive taste and visual stimuli:	caudate, DLPFC, ACC, operculum
Joos et al. [40]	11AN/11HC	Images of food and objects	EDI-2, BDI, MWT-B, rating of pictures after scanning.	HC: activation due to food stimuli:	ACC, bilateral insula, left superior and middle frontal lobe (trends in OFC, MCC, postcentral gyrus)
				AN: activation due to food stimuli:	right amygdala, precuneus, ACC, MCC, right superior and left middle frontal lobes (trends to thalamus and lingual gyrus)
				AN *vs.* HC: increased activation due to food stimuli:	right amygdala
				AN *vs.* HC: decreased activation due to food stimuli:	posterior MCC
				Correlation between disgust ratings and brain activation:	
				AN: negative correlation:	right amygdala
Rothemund et al. [41]	12AN/12HC	Images of food (H and L), food related utensils, neutral objects	SCID, Y-BOCS, TFEQ. VBM and fMRI. Recognition test after scanning, whether pictures were previously seen or not.	AN: increased activation due to H stimuli:	right ITG, left middle occipital gyrus, bilateral lingual, inferior occipital gyrus and precuneus, right cuneus, left culmen, left middle temporal gyrus, right superior frontal gyrus, left middle frontal gyrus
				AN: increased activation due to L stimuli:	right insula
				AN: decreased activation due to L stimuli:	bilateral medial frontal gyrus
				AN: increased activation due to food related utensils stimuli:	right superior temporal gyrus, left middle frontal gyrus, left claustrum, right corpus callosum, left supramarginal gyrus, right cingulate gyrus
				HC: increased activation due to H stimuli:	right precuneus and caudate body
				HC: increased activation due to utensils stimuli:	right DLPFC and middle frontal gyrus
				AN *vs.* HC: increased activation due to H stimuli:	right precuneus and caudate body
				Correlations between psychological tests results and brain regions:	
				Compulsivity due to H stimuli correlated with brain activation:	superior frontal gyrus, inferior frontal gyrus, anterior cingulate cortex, cingulate gyrus , caudate body, cuneus, pre- and postcentral gyrus
Gizewski et al. [42]	12AN/12 HC	Images of H food and neutral pictures (IAPS)	Scanning in state of hunger and satiety. Rating hunger and valence of pictures. SIAB-S, SCID.	AN: activation in state of hunger:	PFC, central cortices and insula
				HC: activation in state of hunger:	ACC, insula
				AN *vs.* HC: activation in state of hunger:	dPCC
				AN: activation in state of satiety:	left insula
				Association between food valence judgment and brain activation in AN:	insula, OFC, cingulate cortex and MTG

Santel et al. [43]	13AN/10HC 13-21 yo	640 images of H food and objects	Scanning in state of hunger and satiety. BDI, TFEQ. Rating hunger and valence of pictures.	**Food vs. objects stimuli:**	
				AN: activation in state of satiety:	right inferior occipital gyrus and cerebellum (declive), left lingual gyrus and cerebellum (declive)
				AN: activation in state of hunger:	left cuneus, right fusiform gyrus
				AN satiated *vs.* hungry:	right middle occipital gyrus
				HC: activation in state of satiety:	right cuneus and middle occipital gyrus, left cuneus and inferior occipital gyrus
				HC: activation in state of hunger:	bilateral lingual gyrus, right fusiform gyrus
				HC satiated *vs.* hungry:	right ACC, left lateral OFC, left middle temporal gyrus
				AN *vs.* HC: decreased activation in satiety:	left IPL
				AN *vs.* HC: decreased activation in hunger:	right lingual gyrus
				Association between psychological tests and brain activation:	
				"Dietary restrain" (TFEQ) correlated negatively with:	left IPL, right lingual gyrus
				"Disinhibition" (TFEQ) correlated positively with:	left IPL, right lingual gyrus
				BMI correlated positively with:	left IPL
Uher et al. [44]	16AN (9rAN, 7bpAN) /10BN /19HC	Images of food and objects, emotional aversive and neutral pictures (IAPS).	OCI, BDI, rating hunger. Asked to think how presented pictures make them hungry/ feeling. After scanning rating for pleasantness, disgust, fear, "desire to eat."	AN: activation due to food stimuli:	left medial OFC, left ACC, PCC, lateral PFC, right cerebellum
				BN: activation due to food stimuli:	left medial OFC, left ACC, PCC, right cerebellum
				HC: activation due to food stimuli:	left parietal cortex, left lateral PFC, bilateral visual cortex and cerebellum
				AN and BN *vs.* HC: increased activation due to food stimuli:	left VMPFC
				AN and BN *vs.* HC: decreased activation due to food stimuli:	left lateral PFC, left DLPFC, left IPL, left cerebellum (declive), left occipital cortex
				AN *vs.* HC: increased activation due to food stimuli:	left VMPFC, right lingual gyrus
				AN *vs.* HC: decreased activation due to food stimuli:	IPL, cerebellum (declive)
				BN *vs.* HC: increased activation due to food stimuli:	left VMPFC, left lingual gyrus, bilateral cerebellum (vermis)
				BN *vs.* HC: decreased activation due to food stimuli:	left DLPFC, left lateral PFC
				AN *vs.* BN: increased activation due to food stimuli:	right apical and lateral PFC, right lingual gyrus
				AN *vs.* BN: decreased activation due to food stimuli:	right cerebellum
				rAN *vs.* HC: increased activation due to food stimuli:	left medial PFC
				bpAN *vs.* HC: increased activation due to food stimuli:	right lateral and anterior OFC
				rAN *vs.* bpAN: decreased activation due to food stimuli:	right anterior PFC and lateral OFC

AN: Participants with Anorexia Nervosa; recAN: Participants recovered from Anorexia Nervosa; wrAN: Weight restored patients with AN; rAN: Restrictive type AN; bpAN: binge/purging type AN; BN: Participants with Bulimia Nervosa; HC: Healthy Participants; yo: years old; H: Presentation of High Calorie Food Pictures; L: Presentation of Low Calorie Food Pictures; IFC: Inferior Frontal Cortex; PFC: Prefrontal Cortex; dACC: dorsal Anterior Cingulate Cortex; DLPFC: Dorsolateral Prefrontal Cortex; VLPFC: Ventrolateral Prefrontal Cortex; VMPFC: Ventromedial Prefrontal Cortex; SMA: Supplementary Motor Area; ITG: Inferior Temporal Gyrus; MTG: Medial Temporal Gyrus; IPL: Inferior Parietal Lobe; PHG: Parahippocampal Gyrus; MCC: Midcingulate Cortex; OFC: Orbitofrontal Cortex; IPL: Inferior Parietal Lobe; dPCC: dorsal Posterior Cingulate Cortex; VBM: Voxel-Based Morphometry; SCID: Structured Clinical Interview for DSM Disorders; MINI-KID: Mini International Neuropsychiatric Interview for Children and Adolescents; BDI: Beck´s Depression Inventory; BAI: Beck´s Anxiety Inventory; STAI: Spielberger Trait Anxiety Inventory; YBC-EDS: Yale-Brown-Cornell Eating Disorder Scale; DASS: Depression Anxiety Stress Scales; PANAS: Positive and Negative Affect Schedule; MADRS: Montgomery-Åsberg Depression Rating Scale; PHQ-D: Patient Health Questionnaire Depression Scale; EDI: Eating Disorder Inventory; EAT-26: Eating Attitude Test-26; Y-BOCS: Yale-Brown Obsessive Compulsive Scale; TFEQ: Three-Factor Eating Questionnaire; EDE-Q: Eating Disorder Examination Questionnaire; BCST: Berg Card Sorting Test; LOFPQ: Leeds-Oxford Food Preference Questionnaire; BAS/BIS: Behavioural Activation/Behavioural Inhibition System; CES: Commitment to Exercise Scale; TAS-20: Toronto Alexithymia Scale-20; FMPS: Frost Multidimensional Perfectionism Scale; TCI: Temperament and Character Inventory; BIS-11: Barratt Impulsiveness

Scale-11; FCCQ-S: State Food Craving Questionnaire; FCPS: Fawcett-Clarke Pleasure Scale; SHAPS: Snaith- Hamilton Pleasure Scale; OCI: Obsessive-Compulsive Inventory; MWT-B: Multiple Choice Verbal Comprehension Test; WAIS: Wechsler Adult Intelligence Scale; WISC: Wechsler Intelligence Scale for Children; WASI-II: Wechsler Abbreviated Scale of Intelligence; SIAB: Structured Interview for Anorexic and Bulimic Disorders; IAPS: International Affective Picture System.

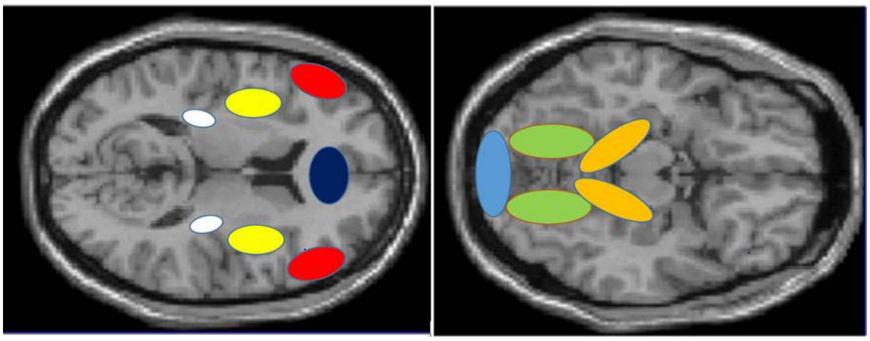

Figure 2: Summary of meta-analytic increased activations due to food stimuli in adolescents with AN. Regional labels are only approximate, shown for illustrative purpose. Navy-the medial prefrontal cortex; red-the inferior frontal gyrus; yellow-the insula; white-the hippocampus; green-the fusiform gyrus; orange-the parahippocampal gyrus; blue-the cuneus.

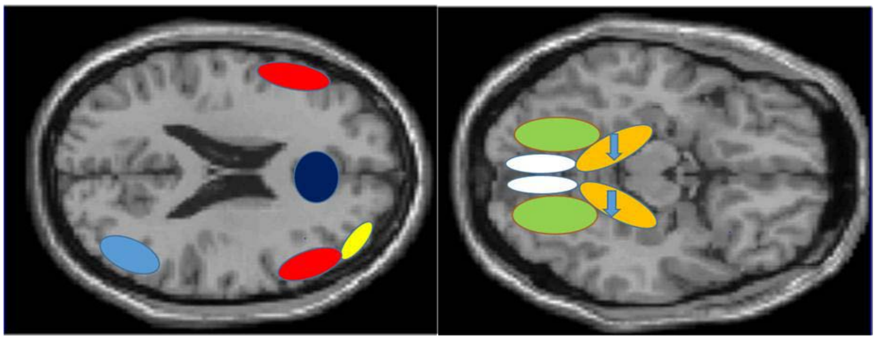

Figure 3: Summary of meta-analytic increased activations due to food stimuli in adults with AN. Regional labels are only approximate, shown for illustrative purpose. Blue-the right angular gyrus; navy-the medial prefrontal cortex; red-the inferior frontal gyrus; yellow-the right dorsolateral prefrontal cortex; white-the lingual gyrus; green-the fusiform gyrus. Orange-decreased activity in the parahippocampal gyrus.

seen as possible symptom provocation. Food pictures categories were either unclassified or divided into high (H) and low-calorie (L). There were also used images of sweet and nonsweet food [21], as well as high and low palatable meals [26]. As this distribution was based on fat and sugar content, it could be compared to high and low-calorie division. When deciding, what kind of object images (as a contrast) should be included, researchers took those with no association to eating. The background of the pictures was as similar as possible (e.g., objects on plates or white circle), so they were matched with food images for arousal and complexity. To enhance comparability between studies, Blechert and colleagues [45] created database of food pictures, with described its features like brightness, contrast within objects, complexity, colours, etc. Images were estimated for number of kilocalories (kcal) and macronutrient composition. Usually, participants were viewing passively presented pictures, but in some studies, to engage them cognitively, they were asked to imagine using/eating items [28,29,34].

Participants´characteristic

While most analyses compared patients with AN to healthy controls (HC), some studies included more categories of subjects, like athletes [31] or participants recovered and weight restored from AN [27-30,32,33,35,37,39]. One study described also acutely ill anorectic patients, but already with normal Body Mass Index (BMI) [26]. Anorectic studies´ participants were usually restricting type, excluding several papers, where some patients were binge-eating/purging [19,22,31,34,35,38,44] or atypical [21,23].

All included papers concerned female subjects, which could be explained by reports, that only 10-25 % of AN (together with BN) patients are male [46,47] and they are commonly underdiagnosed [48].

In numerous studies [20,22,25,27,30-32,34,35,38,40,43,44] patients were on medications (antidepressants, antianxiety, antipsychotic and antiepileptic medications, amphetamine/dextroamphetamine). Drug administration often supports psychotherapy of AN [49], mainly due to comorbid depression and anxiety [50]. However, it can also influence functional MRI scans. After exclusion of patients on medications (and those, who at the day of scanning had already gained the weight, so they did not meet all criteria of ED), the remained drug naïve group had increased activation of anterior cingulate cortex (ACC) and medial orbitofrontal cortex (OFC), also decreased activation of inferior parietal lobe (IPL), lateral prefrontal cortex (PFC) and cerebellum. What is more, patients on Selective Serotonin Reuptake Inhibitors (SSRIs) had increased activation of OFC and decreased activation of lateral PFC [44].

Adolescents

We have planned to review functional MRI studies with food stimuli on adolescents, but very few papers considered juvenile in the participants´ group. Only 7 studies focused on minors [17,21,23-26,43], but two of them referred to functional connectivity [23] and response time to displayed images, not the specific brain region´s activation due to stimuli [17]. Another 2 reports on adults also considered teenagers (from 16 years old) [34,38].

Younger population of anorectic patients were often more occupied with low-calorie food intake than body shape [51], comparing to adult patients. In future, further studies on adolescents with AN are needed and therefore stimuli should be optimized as sensitive for given participants.

Tests

Besides fMRI all studies included also additional psychological and clinical data to their experimental procedures (Table 3). They served mainly as diagnostic tools to define participants, set precise methods or present comorbidity, as anorectic patients often demonstrate dual diagnosis or specific psychological traits [52]. Tests detecting depression or anxiety were explicitly popular. Anxiety is considered both as premorbid trait [53], as well as one of the typical factors of active AN [54,55].

Discussion

Adolescents

Research results concerning adolescents are more consistent than those concerning adults, probably due to the larger homogeneity of the group. Viewing food images led to increased activity in the medial prefrontal cortex, the inferior frontal gyrus, the insula, the hippocampus, the fusiform gyrus, the parahippocampal gyrus and the cuneus in anorectic adolescents. The synthetized results of this meta-analysis are presented on the (Figure 2).

Adults

To summarize, studies concerning anorectic adults revealed enhanced activity due to visual food stimuli in the fusiform gyrus, the inferior frontal gyrus, the lingual gyrus, the medial prefrontal cortex, the right dorsolateral prefrontal cortex, the right angular gyrus. There was deactivation detected in the parahippocampal gyrus, comparing to healthy participants (Figure 3).

There were inconsistent reports according influence of visual food stimuli on activation or deactivation of the insula, the amygdala, the hippocampus, the hypothalamus, the anterior cingulate cortex (ACC), the thalamus, the orbitofrontal cortex (OFC), when comparing healthy participants with those with AN. We hypothesize, that contrary results could be caused by heterogeneity of participants in different studies, i.e. according age, duration of illness. Some of these findings are discussed as follows.

Insula

To analyse the results, we focused on the brain areas correlated to different aspects of AN. A primary taste cortex is found in insula, which integrates information about oral stimuli [56,57]. It underlies also interoceptive awareness [57,58] and other food-related processes [57], which are important components of AN psychopathology. Together with amygdala and ACC, insula compounds fear network [59]. Participants with AN were significantly more anxious than HC when watching food pictures [34], what is consistent with insular role in anxiety. The involvement of insula before exposure-based therapy was associated with reduction in food-related anxiety after treatment [20]. In AN insular reaction to high-calorie food images was increased comparing to HC both in adult population [36] and in adolescents [25]. In healthy population, adolescents' brain activity in the insula (as well as in cingulate and cerebellar regions) was enhanced due to high-calorie food comparing to adult participants [25]. Viewing low-calorie food pictures may also lead to enhancement of insular activity in AN [41]. It was shown, that even anticipating food pictures causes greater activation in the right ventral anterior insula in recovered AN (recAN), comparing to HC [33]. Although in HC they proved correlation between pleasure caused by tasty food and the insular activity, there is no such correlation in recAN [33].

Varied results were found due to satiation state- in hunger insular activity occurred both in AN and HC [42], or enhanced in HC comparing to AN and recAN [35]. There was found correlation between appetite rating and premeal insular activation in HC [35]. Postmeal, insular reaction to high-calorie stimuli normalised in recAN, but remained enlarged in AN [35,42].

Interestingly, increased activity of the insula was also reported in recAN [29,33] as well as in healthy participants [29,38,40]. This could be explained via its role in taste related reward system [57]. In healthy participants pleasantness of images rating was positively correlated with increased activation of the insula [33,35]. Furthermore, Gizewski and colleagues [42] indicated association between food valence judgment and the insular activation in AN.

Fusiform gyrus

A fMRI study on healthy participants reported, that the response of the fusiform gyrus toward the food images depended on the state of satiety- it was stronger in hunger [60]. As previously shown, difficulties in response inhibition characterising AN patients can be caused by altered ventral attention network [61]. Response inhibition to food stimuli comparing to non-food stimuli enhanced activation of the gyrus fusiform [31]. Increased response for food stimuli in the fusiform gyrus was detected in adult AN [19,22,24]. Interestingly, in state of hunger, the activation in the right fusiform gyrus was enhanced due to food stimuli in both groups of young participants: healthy and anorectic (but only $p < .001$) [43].

DLPFC

Anorectic adolescents developed higher bilateral activity of dorsolateral prefrontal cortex (DLPFC) and amygdala due to negative stimuli (in general, not food related) [62]. DLPFC is a crucial component of self-control process not only as a whole, but also in food related behaviours. Significant activation of the left DLPFC was detected in group characterised as successful in self-control - those who choose presented healthy but disliked low-calorie food over unhealthy but liked high-calorie food [63]. Other AN specific behaviours, like inhibition to energy intake or motivation on further goals were also associated with DLPFC activity [64]. Reaction of DLPFC in response to the appetitive stimuli remained unclear [34]. Its increased activation could be responsible for

Table 3: Tests and scales used in included studies.

Diagnostic tests	
SCID	Young et al. [20]; Stopyra et al. [22]; Weinbach et al. [17]; Boehm et al. [24]; Kerr et al. [26]; Scaife et al. [27]; Kullmann et al. [31]; Holsen et al. [30,35]; Kim et al. [36]; Lawson et al. [32,37]; Brooks SJ et al. [34,38]; Cowdrey et al. [39]; Rothemund et al. [41]; Gizewski et al. [42]
SIAB	Boehm et al. [24]; Kerr et al. [26]; Gizewski et al. [42]
DIPS	Horndasch et al. (adults) [25] ; Santel et al. (adults) [43]
DISYPS-KJ	Horndasch et al. (adolescents) [25]; Santel et al. (adolescents) [43]
WAIS/WISC WASI-II	Weinbach et al. [17]; Boehm et al. [24]
MINI-KID	Olivo et al. [23]
Depression scales	
BDI	Horster et al. [19]; Stopyra et al. [22]; Weinbach et al. [17]; Horndasch et al. [25]; Scaife et al. [27]; Sultson et al. [28]; Holsen et al. [30,35]; Lawson et al. [32,37]; Oberndorfer et al. [33]; Kim et al. [36]; Cowdrey et al. [39]; Santel et al. [43]; Uher et al. [44]
MADRS	Olivo et al. [23]
HADS	Brooks et al. [34, 38]
DASS	Young et al. [20]
PANAS	Young et al. [20]
PHQ-D	Kullmann et al. [31]
Anxiety and other traits scales	
STAI	Horster et al. [19]; Ziv et al. [21]; Weinbach et al. [17]; Scaife et al. [27]; Sultson et al. [28]; Sanders et al. [29]; Kullmann et al. [31]; Oberndorfer et al. [33]; Holsen et al. [30]; Lawson et al. [37]; Cowdrey et al. [39]
HAM-A	Kerr et al. [26]
FMPS	Oberndorfer et al. [33]
TCI	Oberndorfer et al. [33]
BIS-11	Oberndorfer et al. [33]
TAS-20	Oberndorfer et al. [33]
BAI	Kim et al. [36]
Y-BOCS	Rothemund et al. [41]
FCPS	Cowdrey et al. [39]
SHAPS	Cowdrey et al. [39]
OCI	Weinbach et al. [17]; Uher et al. [44]
Cognitive and behavioural scales	
BCST	Sultson et al. [28]
BAS/BIS	Kullmann et al. [31]
CES	Kullmann et al. [31]
NART	Scaife et al. [27]
MWT-B	Horster et al. [19]; Joos et al. [40]
CFT 20	Santel et al. [43]
Food related and eating disorder specific tests (including eating behaviour tests)	
EDE-Q	Horster et al. [19]; Young et al. [20]; Stopyra et al. [22]; Weinbach et al. [17]; Olivo et al. [23]; Scaife et al. [27]; Sanders et al. [29]; Kullmann et al. [31]; Brooks et al. [34,38]; Holsen et al. [30, 35]; Lawson et al. [37]; Cowdrey et al. [39]
EDI-2, EDI-3	Horster et al. [19]; Horndasch et al. [25]; Boehm et al. [24]; Kullmann et al. [31]; Kerr et al. [26]; Kim et al. [36]; Joos et al. [40]
EAT-26	Ziv et al. [21]
TFEQ	Rothemund et al. [41]; Santel et al. [43]
YBC-EDS	Young et al. [20]; Scaife et al. [27]
LOFPQ	Scaife et al. [27]
FCCQ-S	Kim et al. [36]
Chocolate	Cowdrey et al. [39]
Hunger rating	Stopyra et al. [22]; Boehm et al. [24]; Holsen et al. [30,35]; Kullmann et al. [31]; Lawson et al. [32]; Kim et al. [36]; Gizewski et al. [42]; Santel et al. [43]; Uher et al. [44]

SCID: Structured Clinical Interview for DSM Disorders; SIAB: Structured Interview for Anorexic and Bulimic Disorders; DIPS: Structured Diagnostic Interview for Mental Disorders; DISYPS-KJ: Diagnostic System for Mental Disorders for Children and Adolescents; WAIS: Wechsler Adult Intelligence Scale; WISC: Wechsler Intelligence Scale for Children; WASI-II: Wechsler Abbreviated Scale of Intelligence;; MINI-KID: Mini International Neuropsychiatric Interview for Children and Adolescents; BDI: Beck Depression Inventory; MADRS: Montgomery-Åsberg Depression Rating Scale; DASS: Depression Anxiety Stress Scales; PANAS: Positive and Negative Affect

Schedule; STAI: State-Trait Anxiety Inventory; HAM-A: Hamilton Anxiety Scale; PHQ-D: Patient Health Questionnaire-Depression Scale; HADS: The Hospital Anxiety and Depression Scale; FMPS: Frost Multidimensional Perfectionism Scale; TCI: Temperament and Character Inventory; BIS-11: Barratt Impulsiveness Scale-11; TAS-20: Toronto Alexithymia Scale-20; BAI: Beck´s Anxiety Inventory; Y-BOCS: Yale-Brown Obsessive Compulsive Scale; FCPS: Fawcett-Clarke Pleasure Scale; SHAPS: Snaith-Hamilton Pleasure Scale; BCST: Berg Card Sorting Test; Behavioral Activation/Behavioral Inhibition System scales; CES: Commitment to Exercise Scale; NART: National Adult Reading Test; MWT-B: Multiple Choice Verbal Comprehension Test; CFT 20: Culture Fair Intelligence Test; OCI: Obsessive-Compulsive Inventory; EDE-Q: Eating Disorders Examination-Questionnaire; EDI: Eating Disorder Inventory; EAT-26: Eating Attitude Test; TFEQ: Three-Factor Eating Questionnaire; YBC-EDS: Yale-Brown-Cornell Eating Disorder Scale; LOFPQ: Leeds-Oxford Food Preference Questionnaire; FCCQ-S: State Food Craving Questionnaire; Chocolate-Rolls-McCabe Questionnaire for Cravers/Non-Cravers of Chocolate.

cognitive and anxious engagement in food stimuli, as suggested by Brooks and colleagues. Especially, that without cognitive component DLPFC was not activated. Furthermore, DLPFC could inhibit insula and cerebellum, that are normally activated when imaging eating food, which is presented on pictures. On the contrary, Sultson and colleagues described a correlation between anxiety and activity of the left DLPFC during food and non-food processing in HC, but not in AN [28]. Activity of the right DLPFC was negatively correlated with perseverative errors during non-food processing by AN, but positively with non-perseverative errors in HC [28]. On the other hand, right DLPFC demonstrated increased activity in healthy subjects due to high-calorie food and food related utensils images [41]; but also decreased activity in AN comparing to HC due to low-calorie stimuli [27]. When taken together patients with AN and Bulimia Nervosa (BN), they showed decreased activation of left DLPFC due to food stimuli [44].

DLPFC in women is more sensitive to visual hedonic food stimuli [64]. As DLPFC activity was negatively correlated with energy intake, it can provide cognitive control on desire to eat [64]. This conclusion is in line with increased activation of right DLPFC (due to food stimuli) in a restrictive type, but not binge eating AN [34,38]. Patients recovered from AN displayed increased activation of right DLPFC due to aversive taste and visual stimuli [39].

VMPFC

DLPFC influences ventromedial prefrontal cortex (VMPFC) in successful self-control [65]. VMPFC (together with ventral striatum and PCC) is crucial for valuating stimuli [66]. The role of VMPFC in valuating food stimuli was proven by Hare and colleagues, when participants were asked to choose which of viewed food images they would like to eat after scanning [65]. Both people who stayed strict to their diet and those who failed, displayed activation of VMPFC during evaluating food for taste. What is more, VMPFC in participants controlling themselves was also involved in estimation of health impact [65]. Perfectionism and strong self-control are significantly higher in anorectic patients [67]. These findings are in line with increased activation of the left VMPFC in active AN when watching images of food [44].

MCC

On the other hand, the midcingulate cortex (MCC) was positively correlated with failed self-control [63], presenting decreased activation of the posterior MCC due to food stimuli when comparing AN *vs.* HC [40]. Surprisingly, activation of MCC due to food stimuli was detected in AN, but also as a trend in HC [40].

Amygdala

Part of the fear network is an amygdala [68], region activated in AN when viewing high-calorie food, with increased activation in AN comparing to HC [40]. During adolescence, in response to high palatability stimuli amygdala´s (and subgenual ACC) activation was related to stomach sensation intensity ratings - positively by weight restored AN, but negatively by HC [26]. It was negatively correlated with disgust ratings by anorectic patients [40]. Disfunction of the hypothalamic-pituitary-adrenal (HPA) axis (HPA) and elevation of cortisol and ACTH level occur in AN due to depression, anxiety disorders and long-term starvation, but also independently [69,70]. Cortisol level was associated with amygdala activity changes - with enhanced signal premeal in acute and weight-restored (wrAN) patients, but decreased post meal in AN [32].

In contrary, amygdala activation was decreased due to high-calorie food stimuli in AN *vs.* HC (pre- and postmeal), wrAN *vs.* HC (premeal), but still increased in AN comparing to wrAN (postmeal) [35]. In HC and wrAN there was found positive relationship between appetite rating and amygdala activity (premeal) [35]. In fear circuitry amygdala is connected with mPFC [68], which activity was increased due to food visual stimuli in recAN [34,39,44] and significantly correlated with perseverative errors during non-food processing [28].

Hippocampus

The amount of papers describing role of hippocampus in feeding decision is growing recently [71,72]. During food image presentation, AN and recAN showed enhanced activation of hippocampus comparing to HC [29]. Adolescents suffering from AN displayed increased activation of hippocampus due to sweet versus nonfood stimuli [21]. On the contrary, Lawson described hypoactivation of hippocampus in AN *vs.* HC, but not in recAN *vs.* HC [37]. Hypothetical reason of changes in hippocampus in AN could be extensive exercising, which is typical behavior for AN. Probably intense physical activity may provide enlargement of the hippocampus, which would be diminished to volume of other anorectic patients after weight restoration [73].

Conclusion

In summary, although there is a growing number of neuroimaging studies concerning pathomechanism of AN, only few of them involved children and adolescents. This noticeable insufficient amount of literature is surprising, considering that AN usually develops in adolescence. There is an urgent need to broaden insight into the neural activity underlying anorexia nervosa in this group of patients. Additionally, it was already pointed by the authors of a replication study, that displayed results were only partially consistent with those from the initial study [19]. A proper number of participants and their homogeneity, along with well-established protocols are features, which are inevitably required to compare any reliably results.

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