



An fMRI meta-analysis of interoception in eating disorders

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ABSTRACT

Eating Disorders (EDs) are associated with disturbed interoception – the sense of the internal condition of the body. Disturbances in interoception across senses have not yet been comprehensively examined in EDs. To do so, we employed an innovative Bayesian author-topic model approach to fMRI meta-analyses that pools together neural deficits across interoceptive senses and task types in participants with and recovered from EDs. Following PRISMA guidelines, our results combine activation patterns from 1,341 initially screened studies and data from 25 manuscripts that met study criteria that compare 463 patients with EDs (current or recovered) to 450 healthy control participants (HC). Altered brain activity was found within vision/sensory processing (precuneus), taste/self-referential processing (claustrum/posterior insula) and reward/set-shifting (global pallidus, medial frontal gyrus, anterior cingulate, precentral gyrus and parietal lobe) components in EDs compared to HC. Our results reveal separate components for bottom-up exteroceptive and interoceptive processing centering around the precuneus and claustrum/insula and also reward processing/set-shifting deficits. Thus, bottom-up sensory and reward processing are key deficits in EDs during ill and recovered states.

1. Introduction

Prior research indicates that aberrant interoception -one's sense of the internal condition of the body - contributes to symptoms in both Anorexia (AN) and Bulimia (BN) Nervosa, two serious life-threatening psychiatric illnesses characterized by disordered eating (Steward et al., 2018). Interoception is associated with internal senses from the body, such as hunger, satiety, slow-stroking touch, pain, breathing, heartbeat detection and the need to defecate and urinate (Craig, 2002). fMRI studies of interoception in eating disorders (EDs) typically only examine one interoceptive sense, making it difficult to know whether interoceptive deficits are present for only particular senses or whether deficits exist across interoceptive sensory processing as a systemic whole in those with eating disorders. Moreover, the modalities used to investigate the neural mechanisms underlying interoceptive senses in EDs vary, making it challenging to identify commonalities in interoceptive deficits across eating disorders. To better understand how interoception contributes to eating disorders, it is important to identify whether common interoceptive neural correlates underlying EDs exist; this has been difficult to study given previous studies within the literature have implemented varying interoceptive tasks. To date, no known studies have comprehensively examined the fMRI data from across multiple

interoceptive studies in eating disorders. This synthesis is important as it may provide more specific insights into the state of interoceptive deficits in both AN and BN.

Comparisons are frequently made across AN and BN since they exhibit symptomatic, neural and behavioural commonalities (Kaye, 2008). It is difficult, however, to objectively measure the overlap between neural patterns in AN and BN with fMRI since the best methods to date have been to conduct coordinate-based meta-analyses methods. Coordinate based fMRI meta-analytic methods are unable to combine data from across clinical disorders and they are only able to examine activation commonalities across similar tasks (Ngo et al., 2019), thus making it difficult to empirically examine the neural commonalities from across eating disorders and also varying recovery states (ill vs fully-recovered).

Therefore, we are proposing to implement novel, data-driven methods that will identify clusters of neural activation across interoceptive sensory types and across eating disorders and recovery statuses. To conduct this study, we are applying the novel Bayesian Author Topic Model (Ngo et al., 2019) to conduct a meta-analysis of interoceptive fMRI studies in eating disorders. This approach allows for us to identify unique clusters of activation that exist across tasks, sensory types and eating disorder diagnostic types and recovery states, namely AN, BN and

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weight restored/recovered subtypes of each diagnosis. Addressing heterogeneity across interoceptive senses as well as recovery states (currently ill versus recovered) will allow us to obtain a more comprehensive understanding of the neural underpinnings of both interoception and eating disorders.

2. Methods and materials

We included original, peer-reviewed whole brain fMRI studies of interoceptive processing in either adult or adolescent human samples that compared either AN or BN (including ill, subthreshold and recovered participants) to healthy control participants. Data was extracted from Pubmed, PsychInfo, and Web of Science databases. The searches adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Page et al., 2021). The pre-determined search terms included: “interoception” and “brain” and “eating disorders”, “interoception” and “brain” and “anorexia”, “interoception” and “brain” and “bulimia”, “insula” and “eating disorders”, “insula” and “anorexia”, “insula” and “bulimia”, “interoception” and “fMRI” and “eating disorders”, “interoception” and “fMRI” and “anorexia”, “interoception” and “fMRI” and “bulimia”. The insula was included as a search term, as it has been identified as a “hub” for interoceptive processing (Craig, 2002). Studies that did not include a non-ED control group, reviews, animal studies, case studies, non-imaging, and paired-sample studies were also excluded.

Data extraction. Initial searches uncovered 1341 articles (See Fig. 1 for the PRISMA flow chart, including quality ratings which are specified in Supplemental Figure 1). The relevant data were extracted from the included studies and briefly summarized. Of the 1341 papers, 717 duplicates were removed. Next, the abstracts of 624 remaining articles were screened for eligibility criteria as specified above, after which an additional 519 were excluded for not meeting inclusion criteria. We screened the full text of the remaining 105 articles and 26 were excluded

for not including whole-brain analyses. The remaining 79 were assessed to verify inclusion criteria. 54 were removed as they contained exclusively resting state data or ROI analyses. Unsupervised Bayesian author-topic model fMRI meta-analysis were conducted on coordinates from 25 whole-brain fMRI articles which contributed to the extracted components reported in results (See Table 1).

Data analysis. The author-topic model approach allows us to identify the underlying brain activation components common across studies investigating interoception in eating disorders, and the brain regions underpinning these components (Ngo et al., 2019). The method shows how the different tasks used in different studies may cluster together in terms of the brain areas activated. We took the experiments selected by our screening process and extracted the relevant experimental contrasts (from a whole brain analysis), with each contrast acting as its own unique task category. The method does not apply weightings based on the sample size of each study. We adapted the model made available by Ngo and colleagues in order to run the author-topic model for our extracted fMRI coordinates. The model uses the collapsed variational Bayes (CVB) algorithm to estimate the model parameters: the probability that an experiment would recruit a component pattern $\Pr(\text{components}|\text{experiment})$ and the probability that a voxel would be involved in a component pattern $\Pr(\text{voxel}|\text{components})$; See Fig. 2). The model was re-run assuming 1, 2, 3, 4, or 5 components, and we used the Bayesian Inclusion Criterion (BIC) value to identify the optimal number of components. To visualize and interpret the components, we used GingerAle to develop z-score maps of activation patterns for each component, and MRICron software (<https://www.nitrc.org/projects/mricron/>) and MANGO (Multi Image Analysis GUI) software (<https://mangoviewer.com/index.html>). To aid comprehension of the patterns, we inspected contrasts with $\Pr(\text{components}|\text{experiment})$ above 0.75 proportional loading for the creation of our figures.

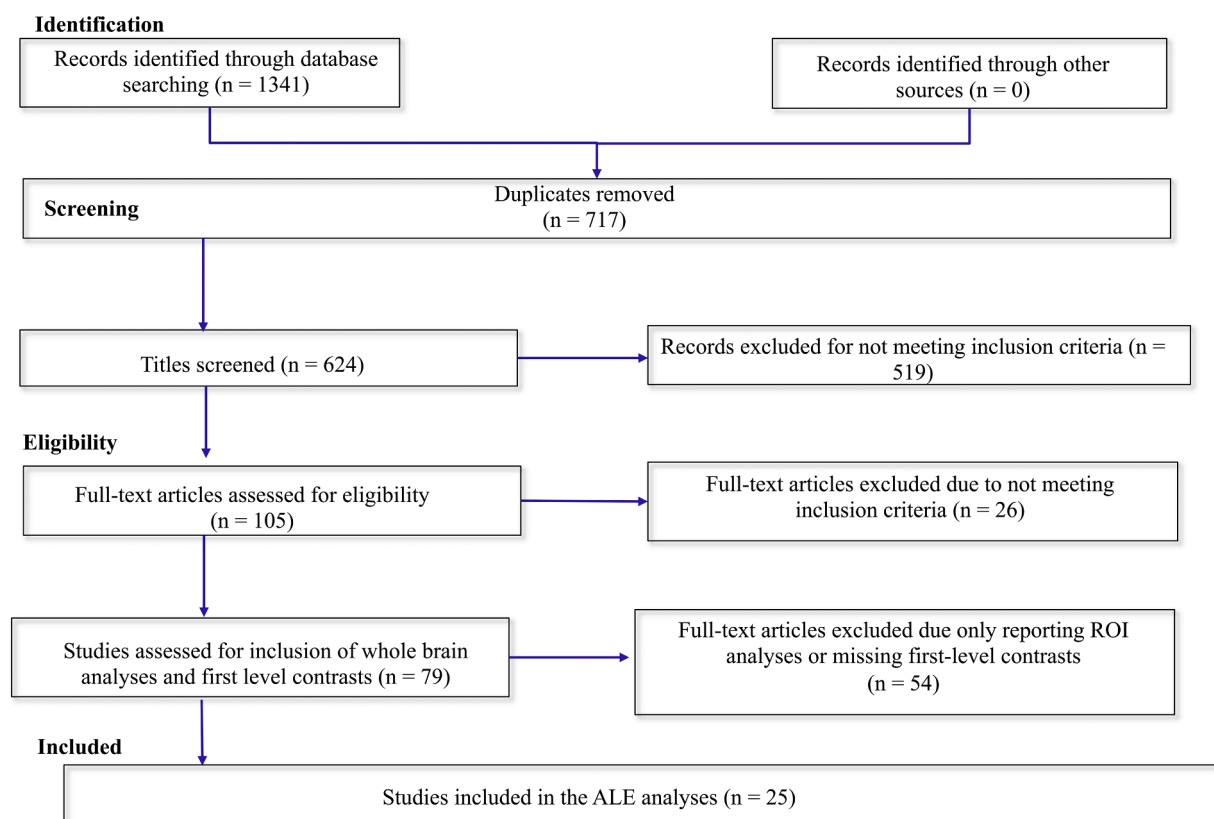


Fig. 1. PRISMA flow chart.

Table 1
Description of articles included in the analyses and their quality ratings.

Author (Year)	Participants	Task	Contrasts	Quality/ 84
Bär et al., (2013)	19 AN restrictive type (3 men and 16 women) and 19 matched controls	Heat pain of 37, 42 and 45C compared to resting 32C	HC > AN: 45 °C > 37 °C AN > HC: 45 °C > 37 °C	54
Bischoff-Grethe et al. (2018)	18 recovered AN women (14 pure restricting, 4 binge purge type but no binge eating history) and 26 healthy control women	Touch with a brush to the forearm compared to the palm	RAN < HC: Soft Touch>Anticipation	54
Berner et al. (2019)	25 recovered from BN and 26 healthy control women	Anticipation of breathing restriction during a continuous performance task	RBN < HC: Anticipation < Post-load	
Brooks et al. (2011)	8 BN, 18 AN and 24 age matched healthy control women	Food verses Non-Food images	HC > BN: Food > Non-Food	55
Brooks et al., 2012	18 AN (11 restrictive type and 8 binge purge type) and 24 aged matched control women	Food verses Non-Food Items	AN > HC: Food > Non-Food HC > AN: Food > Non-Food RAN > HC: Food > Non-Food HC > RAN: Food > Non-Food ANBP > HC: Food > Non-Food HC > ANBP: Food > Non-Food	55
Brooks et al. (2014)	15 adolescent girls with early onset (diagnosed within 6 months) of AN features (mean age of 15) and 20 age & sex matched controls (aged 13–17)	N-back test of working memory	AN Features > HC: High > Low	55
Davidovic et al. (2018)	25 women with AN (aged 17 to 25) and 25 age & sex matched controls	Goat hair brush stroking the forearm vs rest	HC > AN: Brush move > Brush rest HC > AN: Brush move > Baseline	61
Ely et al. (2017)	26 women recovered from BN and 22 control women	Sucrose vs water tastes during fasted and fed states	RBN > HC: Fed > Hungry Fed RBN > HC: Fed > Hungry	48
Frank et al. (2016)	24 women recovered from AN and 24 control women	Expected vs un-expected taste to sucrose, no solution and artificial saliva	RAN > HC: Unexpected no solution > Expected sucrose	47
Friederich et al. (2010)	17 women with AN and 18 age and sex matched controls	Comparison of self to photos of slim bodies as compared to photos of interior home designs	HC > AN: Body Shape Comparison > House Comparison AN > HC: Body Shape Comparison > House Comparison	49
Holsen et al. (2012)	12 women with AN, 10 women recovered from AN and 11 healthy control women	Viewing high vs low calorie food pictures either before or after a meal	HC > AN High Calorie Food > Objects AN > HC High Calorie Food > Objects HC>RAN High Calorie Food > Objects RAN>HC High Calorie Food > Objects HC>AN High Calorie Food > Objects AN>HC High Calorie Food > Objects HC>RAN High Calorie Food > Objects RAN>HC: High Calorie Food > Objects	58
Jiang et al. (2019)	14 women with restrictive type AN, 13 BN and 12 healthy control women	Smelling food vs non-food odours during hungry vs satiety tasks and during liking vs wanting conditions	HC>AN: Food>Non-Food odors AN>HC: High>Low energy density food odors AN>HC: Food>Non-Food odors	48
Kullmann et al. (2014)	12 women with AN (8 restrictive and 4 binge-purge types), 12 healthy endurance athletes and 14 healthy non-athletes as controls	Affective Go No-Go task for physical activity vs non-activity and also food vs non-food	AN > HC: No-go > Go	49
McAdams et al. (2016)	22 women with AN, 19 healthy control women, and 18 women recovered from AN	Social Identity Task Version 2 with self, other and reflective attributions	AN > HC: Self > Friend ANWR > HC: Self > Friend AN > HC: Self-agree > Self-disagree ANWR > HC: Self-agree > Self-disagree AN > HC: Reflected > Self-contrast ANWR > HC: Reflected > Self-contrast	48
Mohr et al. (2011)	16 AN and 16 healthy control women	Distorted photos of one's body size were shown to participants to estimate their size and ideal body size	AN>HC: Satisfaction vs Body Estimation AN>HC: Thinner vs Fatter	51

(continued on next page)

Table 1 (continued)

Author (Year)	Participants	Task	Contrasts	Quality/ 84
Mohr et al., 2011	15 BN and 16 healthy control women	Distorted photos of one's body size were shown to participants to estimate their size and ideal body size	BN>HC: Satisfaction vs Body Estimation BN>HC: Thinner vs Fatter	51
Oberndorfer et al. (2011)	12 women recovered from AN and 12 control women	Inhibition Stop Task	HC > RAN: Hard > Easy Inhibition Trials	53
Setsu et al. (2017)	21 women with BN and 20 healthy control women	Monosodium Glutamate vs water tastes	BN>HC: MSG vs Rest HC>BN: MSG vs Rest	56
Sweitzer et al. (2018)	20 women recovered from AN and 24 healthy control women	Full body images, faces and scrambled images; participants rated attractiveness of images	HC>RAN: Fat Image>Real Image	55
Van Aultreuve et al., 2016 (Van Den Eynde et al., 2016)	16 restricting type AN, 13 binge-purge AN and 15 healthy control women	Task shifting	AN>HC: Switch>Repeat	56
Van Den Eynde et al. (2013)	21 BN and 23 healthy control women	Food (highly palatable)/Body Image (slim models), Baseline (stationary for food comparison and interior photos for body comparison) and low level baseline	BN>HC: Food>Baseline HC>BN: Food>Baseline BN>HC: Body>Baseline HC>BN: Body>Baseline BN>HC: Food>Non Food HC>BN: Food>Baseline BN>HC: Body>Non Body HC>BN: Body>Non Body	46
Via et al. (2015)	20 women with restrictive type AN and 20 matched healthy control women	Acceptance or rejection in a social judgement task	HC>AN: Acceptance > Control AN>HC: Acceptance > Control HC>AN: Rejection > Control AN>HC: Rejection > Control	55
Vocks et al. (2011)	12 women with restricting type AN and 12 healthy control women	Chocolate milk vs water tastes before (hunger) and after a meal (satiety)	AN>HC: Milkshake > Water Hunger HC>AN: Milkshake > Water Hunger AN>HC: Milkshake > Water Satiety HC>AN: Milkshake > Water Satiety	49
Wagner et al. (2003)	13 patients with AN and 10 control participants	Distorted photos of the participant's body compared to colour matched scrambled photos	AN>HC: Distortion > Neutral	41
Zastrow et al. (2009)	15 women with AN (7 with restricting subtype) and 15 age matched healthy control women with no lifetime history of psychiatric illness	Response shifting to pictures of shapes	NC>AN: Correct Target > Standard NC>AN: Correct Shift Target > Standard NC>AN: Correct Target Maintain > Standard NC>AN: Incorrect > Correct	43

3. Results

Two components best fit the data according to the BIC metric (Fig. 3). However, the fit was only slightly better for two than either one or three components, and using three components improved clinical interpretability (Fig. 3). The first component pertains to visual and sensory processing (Table 2). The second involves taste and self-referential processing (Table 3) while the third component includes regions associated with self-referential processing and reward processing (Table 4). Components two and three were merged together when only two components were presented, and component one was the same regardless of whether 1, 2 or 3 components were displayed. Thus, we choose to present within this manuscript the three-component model (See Fig. 4 and Supplemental Figure 2).

3.1. Component 1: Sensory processing/vision

We found BOLD activation differences between adults with AN and healthy control comparisons within regions associated with vision and sensory processing. Activation peaked at the precuneus and expanded into the superior parietal lobe, reaching Broadman's Area (BA) 7 (See Table 2, Figure and Supplemental Figure 2). Participants with AN demonstrated less activation than healthy control participants during tasks that involve seeing food (e.g., visual cues) and feeling pleasant touch. Participants with AN demonstrated more activation when

smelling energy dense food relative to healthy control counterparts.

3.2. Component 2: Taste and self-referential processing

We also found BOLD activation differences between adults with EDs (AN, RAN, BN and RBN) compared to healthy control participants within regions classically associated with interoception. The first activation cluster peaked in the right cerebrum and sub-lobar claustrum, with activation spreading into the insula, lentiform nucleus, inferior frontal gyrus, and inferior frontal gyrus, extra-nuclear, superior temporal gyrus, and the parahippocampal gyrus. The second activation cluster peaked at the left insula, and extended to the superior temporal gyrus, precentral gyrus, claustrum, transverse temporal gyrus, putamen, and postcentral gyrus (See Table 3; Fig. 4 and Supplemental Figure 2). Overall, there were differences between individuals with EDs and healthy controls on tasks involving taste, pain, satiation, set shifting, and inhibition. Individuals with EDs demonstrated greater activation compared to healthy controls on tasks involving set shifting and inhibition, but blunted activation compared to healthy control participants on tasks involving pain, taste, and satiation. Specifically, people with AN demonstrate greater activation of the insula than healthy control participants on tasks involving inhibitory response and set shifting but this pattern was not apparent in individuals recovered from AN and BN.

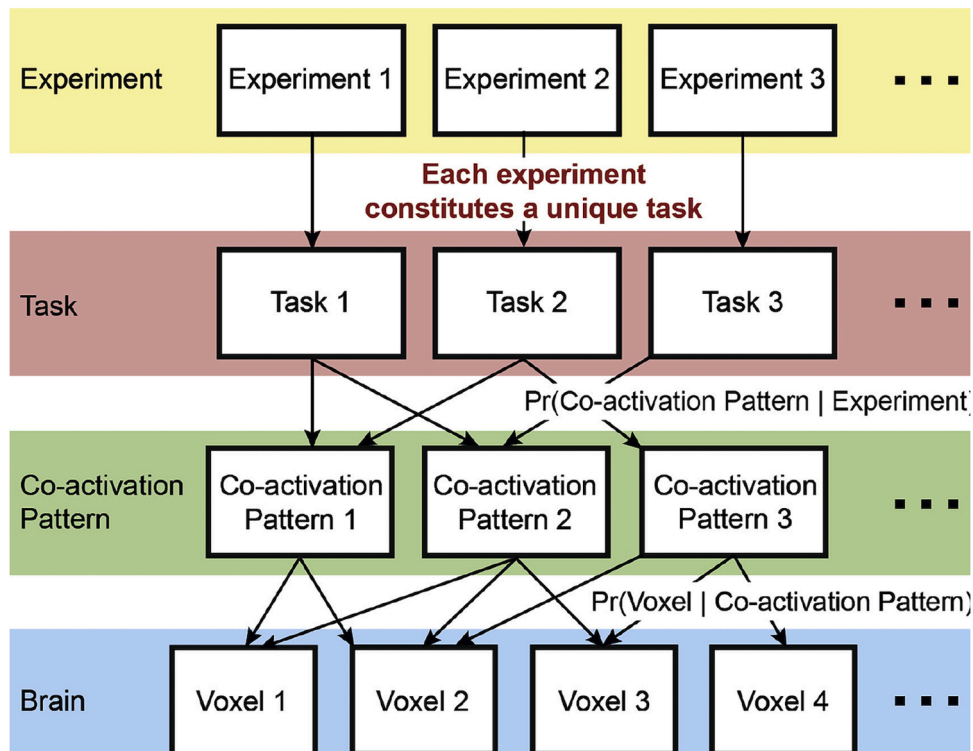


Fig. 2. Table from Ngo et al., 2019 describing the Author Topic Model approach.

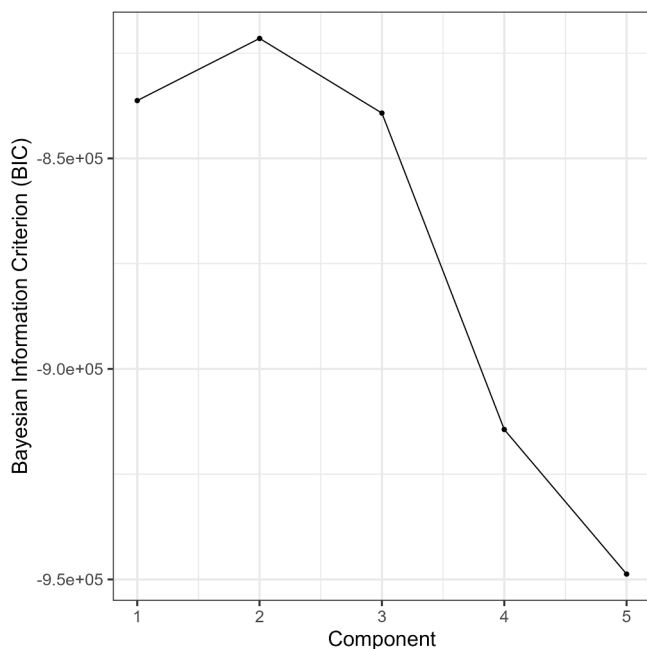


Fig. 3. Bayesian Information Criterion.

3.3. Component 3: Reward network

Lastly, BOLD activation differences were found between individuals with ED (AN and RBN) and healthy controls within reward networks. The first peak of activation coordinates fell within the thalamus and lentiform nucleus, with activation spreading to the parahippocampal gyrus, subcallosal gyrus, and inferior frontal gyrus. The second peak of coordinates fell within the medial frontal gyrus, extending into the paracentral lobule (reaching BA 6). The third peak fell within the

Table 2

Component 1 cluster coordinates.

Region	Cluster Size	Peak Z	Side	BA	Coordinates		
					x	y	z
Precuneus	6960	5.54	R	7	10	-64	48

BA = Brodmann Area. R = right; L = left; B = Bilateral; In regions with more than one cluster of activation, coordinates are listed for the cluster with highest activation. Number of voxels and peak activation are listed only for main clusters; activation is not listed for local maxima regions within clusters.

Table 3

Component 2 cluster and local maxima coordinates.

Region	Cluster Size	Peak Z	Side	BA	Coordinates		
					x	y	z
Clastrum	13,208	4.49	R	-	34	6	-8
Inferior Frontal Gyrus	-	4.09	R	47	34	18	-4
Insula	9496	4.79	L	13	-44	-10	8

BA = Brodmann Area. R = right; L = left; B = Bilateral; In regions with more than one cluster of activation, coordinates are listed for the cluster with highest activation. Number of voxels and peak activation are listed only for main clusters; activation is not listed for local maxima regions within clusters.

anterior cingulate, reaching BA 24 and BA 32. The last coordinate cluster peaked at the precentral gyrus, extending into the middle frontal gyrus, the superior frontal gyrus, and extending into BA 6 (See Table 4, Fig. 4 and Supplemental Figure 2). The reward network was activated more for healthy control participants during set shifting and reward related tasks as compared to participants with AN. With AN participants, blunted activation was found for tasks involving set shifting, reward, and learning in comparison to healthy control participants. The opposite pattern, however, was detected when comparing BN to healthy control

Table 4
Component 3 cluster and local maxima coordinates.

Region	Cluster Size	Peak Z	Side	BA	Coordinates		
					x	y	z
Medial Globus Pallidus	12,272	5.02	R	-	12	-8	-6
Thalamus	-	4.57	B	-	4	-14	4
Subcallosal Gray	-	3.55	R	-	20	6	-14
Medial Frontal Gyrus	2672	4.06	L	6	-2	-18	58
Anterior Cingulate	1368	3.86	L	24	-4	36	0
Precentral Gyrus	1256	4.09	R	6	30	-12	62
Parietal Lobe	640	4.08	L	3	-30	-30	68

BA = Brodmann Area. R = right; L = left; B = Bilateral; In regions with more than one cluster of activation, coordinates are listed for the cluster with highest activation. Number of voxels and peak activation are listed only for main clusters; activation is not listed for local maxima regions within clusters.

participants.

4. Discussion

The author model-based approach revealed two and three component models that were similarly weighted in terms of model fit. However, the three-component model demonstrated better clinical interpretability. The three components include vision/sensory processing, taste/self-referential processing and reward/set-shifting.

For the first component, the visual and sensory processing component primarily included the precuneus and superior parietal lobe, which are involved in visual and bottom-up sensory processing. When viewing foods, AN participants demonstrated decreased activation in visual processing regions of the brain compared to healthy controls, suggesting that visual processing may be impacted in those with AN. Our results are consistent with those detected within an ALE based fMRI meta-analysis of visual processing in AN (Bronleigh et al., 2022). Thus, visual processing difficulties may be an integral mechanism underlying AN

symptoms, such as disturbed body image perception. There is a relatively large body of literature using neuropsychological testing to demonstrate impaired visuospatial central coherence as a possible endophenotype for AN (Lindner et al., 2013). These data have been previously interpreted within a cognitive framework, suggesting that those with AN focus more on the details of a visual picture at the expense of its global features, thus compromising overall perception (Madsen et al., 2013; Li et al., 2015). However, it is possible that central coherence impairments demonstrated in AN are due to more bottom-up visual processing disturbances rather than global top-down processing. For example, the detail oriented cognitive style observed on the Rey-Osterrieth Complex Figure task might be interpreted as disturbances in visual processing, as compared to the interpretation commonly seen in the ED literature, which assumes that these disturbances are due to a more due to deficits in top-down global cognitive organization strategies in EDs. (Demartini et al., 2021; Lang et al., 2016; Madsen et al., 2013) This interpretation is consistent with the visual perception literature in Autism Spectrum Disorder. Autism spectrum disorders – like EDs - demonstrate sensory processing difficulties that contribute to symptoms (Maekawa et al., 2011; Richard and Lajiness-O’Neill, 2015) and their bottom-up visual deficits are now well documented (Little, 2018) and are thought to contribute to the central coherence problems noted within this disorder. Visual processing deficits are also well noted in body dysmorphia, a disorder associated with significant body image disturbances that are highly similar to and are often comorbid with AN and BN. (Brooks et al., 2020; Groves et al., 2020)

Our results include but expand beyond visual processing to other aspects of sensory processing. In addition to observing differences within this component for visual processing, disturbances were also seen for other senses, such as affective touch and smell. Decreased activation was found in AN compared to healthy controls during affective touch. However, increased activation was found in AN compared to healthy controls when smelling foods. Thus, these findings reflect different patterns of activation in response to sensory processing. Sensory processes such as affective touch and smell are frequently argued to be

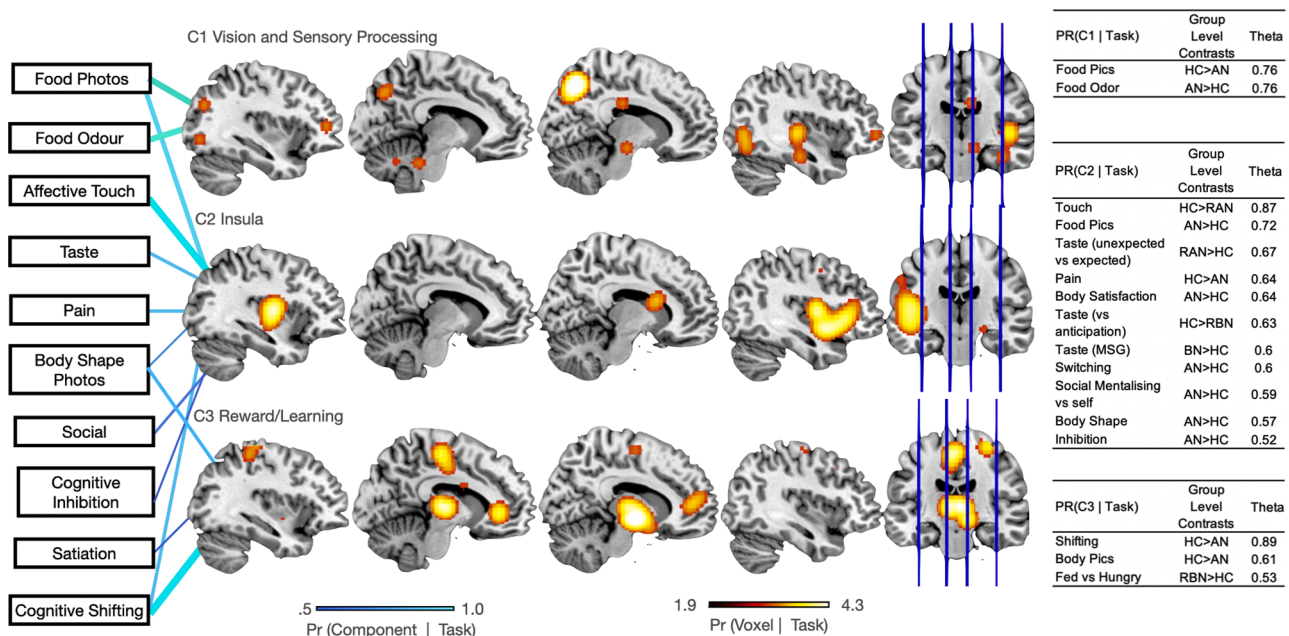


Fig. 4. Brain patterns revealed within three components and their correspondence to task type. Components of interoception in eating disorders. Estimates for the 3-component model. Lines connect each task type to components based upon the strength of the loading (a theta weight value between 0 and 1.0) of a particular task category onto each component. Each component is represented by a separate z cluster map thresholded at 1.9 minimum to 4.3 maximum cluster correction. The loadings of different task categories, highest theta weights for each category, and the group-level diagnostic contrasts are displayed on the right. C, component; Pr, probability.

“exteroceptive” rather than purely interoception since they rely on stimulation from outside as compared to stimulation coming from inside the body. Our results may further support this claim since the abnormal activation patterns detected components with other aspects of exteroceptive sensory processing, such as vision, rather than other interoceptive senses such as taste, which mapped onto component 2. Thus, our findings suggest the importance of interpreting both ED symptoms and interoceptive senses through a lens of sensory processing difficulties.

For component two, the insula and neighboring regions (lentiform nucleus, inferior frontal gyrus, superior temporal gyrus, parahippocampal gyrus, superior temporal gyrus, pre and post central gyrus, claustrum, transverse temporal gyrus, and putamen) demonstrate abnormal activation in EDs in comparison to healthy controls during body/shape comparison, body satisfaction, set-shifting, inhibition, self-perception, taste, and anticipation tasks. The directionality of the patterns that arose across those with EDs evidenced increased activation in participants with AN as compared to healthy controls for body shape comparison tasks, inhibition, and set shifting. Decreased activation was found in RAN and RBN participants for touch and taste when compared to healthy control participants. This is consistent with literature (Kim et al., 2012; Wagner et al., 2008) which suggests that hyperactivation of the insula occurs during interoceptive tasks in individuals with EDs as compared to healthy controls. Our results indicate that insula activation does not necessarily include tasks that are typically considered interoceptive since a variety of tasks and cognitive processes activate the anterior insula. Our results also demonstrate abnormal insula activation across a wide range of tasks, further indicating the robustness of the deficits observed within the insula for those with EDs. For the tasks that activate this component we find abnormal activation for taste processing (which is considered an interoceptive sense), anticipation, executive functioning (inhibition, & set shifting) (Gaudio et al., 2016; Gaudio et al., 2018) and also tasks that pertain to self-referential thought (body shape comparisons or body satisfaction and also self-perception tasks) (Canna et al., 2017). The association of the interoceptive sense of taste to executive functioning and self-referential thought suggests the link that the processing of senses from the body have on other psychological processes that are more commonly associated with cognitive processing, such as inhibition, anticipation, and bodily/self-perception. Therefore, for future studies -and also clinically- it is important to consider that these aspects naturally cluster together, meaning that bodily processing in the form of interoception is likely to influence one’s sense of anticipation and ability to inhibit behavior in addition to also influencing one’s sense of self and bodily understanding and acceptance. Thus, therapeutically targeting interoceptive deficits in EDs may have cascading effects that further influence both executive functions associated with behavioural impulsivity and anticipation in addition to one’s sense of self and body image satisfaction.

The third component demonstrated abnormal brain activation in regions involved in reward processing and set-shifting (inflexibility to changes) when comparing EDs to control participants. Specifically, hypoactivation in reward related areas of the brain (e.g., anterior cingulate cortex, ventral striatum) was found when comparing AN to healthy controls for tasks involving taste, social interactions, and monetary non-food reward. The opposite pattern, however, is reported in individuals with BN when compared to healthy control participants (Boehm et al., 2014; Frank et al., 2013; Monteleone et al., 2018; Monteleone et al., 2017; Via et al., 2015). Reward processing deficits and their links to symptom expression and development in EDs are well documented (Cowdrey et al., 2011; Monteleone et al., 2017; Via et al., 2015; Cowdrey et al., 2011; Chao et al., 2020; Via et al., 2015). Additionally, set-shifting abnormalities loaded onto the reward processing network when comparing EDs to healthy control participants. Previous evidence indicates that set shifting difficulties are associated with aberrant reward processing in healthy participants, thus further demonstrating a link between reward processing and set-shifting and also providing a rationale as to why component 3 showed common

activation patterns for both set-shifting and reward processing deficits in EDs (Avila et al., 2003).

Impaired set shifting is commonly observed in AN and may continue to persist after recovery and has thus been proposed as a potential trait that contributes to the development of anorexia. Set-shifting deficits are also associated with acute stress, which is state driven (Butts et al., 2013; Shields et al., 2016), thus making it unknown whether set shifting deficits in EDs are due to heightened amounts of stress present in the clinical group or are biological traits that predispose one to developing AN (King et al., 2019). Set shifting difficulties also span components 2 and 3, which may be why two components (instead of three) best fit the data. For interpretative purposes, however, it is helpful to see how activation patterns differ during self-referential processing/taste/executive functioning (activation centering within the insula) and reward processing/set-shifting tasks (activation centering within reward processing regions). Importantly, most set-shifting tasks included within our study rely on processing visual stimuli and, therefore, it is important to consider that the visual deficits evident in component one may further influence set-shifting deficits observed in other components. In other words, bottom-up sensory processing deficits appear to contribute to set-shifting (and other executive processing and reward) difficulties in EDs. In Autism Spectrum Disorders and other neurodevelopmental disorders, atypical visual patterns, including aberrant visual attentional processing, have been noted (Bakroon and Lakshminarayanan, 2016; Bellocchi et al., 2017) and also appear to impact other higher-level executive functioning deficits seen in autism (Richard and Lajiness-O’Neill, 2015; Yerys et al., 2009). Therefore, despite finding three components, brain activation does not occur in isolation and activation patterns are likely to influence deficits in another components.

Despite previous studies of eating suggesting that prefrontal deficits are a core biological component that appear to contribute to eating disorder symptoms (Berner et al., 2023; Uher et al., 2005), our findings did not indicate significant deficits anchored within prefrontal regions; deficits associated with executive functioning were rather linked to limbic and self-referential processing deficits. This may be because our study focused on examining brain activation patterns associated with interoceptive deficits in eating disorders instead of cognitive processes that are known for recruiting prefrontal activity. Nonetheless, our results highlight that prefrontal deficits do not appear to drive the deficits that are associated with interoceptive processing in eating disorders. Rather, interoceptive deficits in eating disorders involve bottom-up sensory processing difficulties, deficits in self-referential processing, and reward processing rather than cognitive processing deficits.

When examining distinct patterns for AN and BN separately, we found that deficits in AN loaded onto all clusters while deficits in BN primarily loaded onto the domain of reward processing. In cluster 4 of the reward component, abnormal activation patterns in BN were the opposite of those noted in AN. Furthermore, when looking at differences across ill and recovered states, we found within the cluster associated with self-referential processing that participants with AN demonstrated less activation than controls, however, the opposite pattern of activation was seen in those who had recovered from an AN and BN. This may suggest that with recovery, differences in self-referential processing and associated blunted activation during the ill state may remit or change. While our results do not include a large enough pool of data on recovered or remitted participants, it is important to consider what features of eating disorders associated with the ill state, such as impaired self-referential processing, may improve with weight restoration and symptom remission.

Current adult eating disorder treatments primarily focus on addressing deficits in cognitive processing, which are processed primarily within the prefrontal cortex. Our results suggest, however, that it may be beneficial to further consider the development of treatments for eating disorders that focus on improving sensory processing deficits, self-referential processing, set-shifting/inhibitory processing and also how one experiences reward. It is also unknown whether sensory

processing, self-referential and reward processing within the brains of people with eating disorders demonstrate long term changes over time and also in response to treatment. Thus, future studies should explore interventions and examine whether they contribute to long-term changes within the brains of people with EDs. For example, future studies might find it beneficial to examine treatments that address visual processing deficits and their influence on body image in eating disorders and to also directly target the disturbances in reward processing in EDs that may be unassociated with cognitive processing. If long-term changes are unable to be made within brain networks associated with these processes, then it would make sense to examine whether compensatory strategies can be taught to patients to help them better manage processing deficits associated with EDs. Furthermore, treatments should also address stress levels in those with EDs to see whether stress reduction might impact the set-shifting deficits seen in EDs.

4.1. Strengths and limitations

This study is not without limitations that should be considered. First, only 25 studies were included in this review; this demonstrates the dearth of brain imaging studies in eating disorders. Furthermore, the sample sizes of the studies reviewed were very low: thus, we only compared 442 participants in the ED group (which consisted of 263 women with AN (restrictive and binge purge type), 65 women with BN, 74 women recovered from AN, 25 women recovered from BN and 15 adolescent girls with early onset AN features) and 452 healthy controls (control athletes were not included in analyses) across all 25 articles as a part of this meta-analysis. This suggests that fMRI papers that have examined interoception in EDs have an average of 18 ED participants and 18 controls, which are very low sample sizes when it comes to conducting generalizable research. Thus, our study is important since it combines results from all studies that have examined interoception in EDs, thus making this the largest known study to examine the brain using fMRI in EDs. It also provides evidence of commonalities and between diagnostic tendencies that have not been able to be observed by examining diagnostic type separately, despite the limited number of participants falling in within the differing diagnostic categories for each study.

When examining studies to be included in this meta-analysis, several studies were excluded because they did not report whole brain analyses or report both first and second-level contrasts. This is problematic since many conclusions are made in the literature about specific ROIs and their deficits in EDs, however, studies have not specified whether ROI findings are truly hypothesis-driven or whether significance was not found for whole brain activation patterns and, thus, authors only presented ROI results. Furthermore, many studies also only reported results from either first or group level contrasts instead of reporting results from both first and group level analyses. This is problematic, as it decreases the reproducibility and comparability of findings across studies and potentially hides null findings that may not be present when comparing task contrasts (first level) and also between different clinical groups (group level). In order to improve transparency and reproducibility within the ED field, it is recommended that fMRI reporting standards such as the COBIDAS reporting recommendations for task-based MRI studies (Nichols et al., 2017) are followed in addition to reporting non-significant results when examining both first and second level analyses. Thus, this study suggests that it is critical for future ED research to conduct fMRI studies in ED more consistently and uniformly in order to not only produce more generalisable research, but also to generate aggregated and well-powered datasets that can be further analyzed by machine learning approaches such as ours in the future. Because of their acute clinical symptoms, EDs are a difficult population to study, thus our meta-analytic approach provides a robust way to pool together a large number of participants in a way that significantly increases the comparability and generalizability of findings within difficult to study clinical populations. Additionally, because we used the insula as one of

our search terms for extracting studies that pertained to interoception, some of our results are “circular” and, thus, included studies involving the insula that did not necessarily include interoception. Although including the insula as a search term allowed for us to identify studies that might not have self-identified as interoceptive, it did introduce tasks and cognitive functions into the results of our paper which stray from the classical sense of interoception, since not all function of the insula can be considered interoceptive.

5. Conclusions

Overall, our results suggest that ED symptoms may be partially explained by visual processing difficulties, contributing to symptoms such as body image disturbance and rigid thinking styles. Moreover, the implications of reward and set shifting findings in these aggregated results confirm existing findings of aberrant reward related circuitry in EDs, through an interoceptive lens. The implementation of our innovative Bayesian Author Topic Model method allowed us to conduct fMRI meta-analyses across EDs, as it is not limited by a span of behavioral tasks recruiting various brain regions probing the same construct. Indeed, this methodology allowed for the assessment of three distinct clusters of brain activation across a variety of tasks, which helped elucidate novel data-driven clusters of systems within EDs. Furthermore, this approach added to our field by examining eating disorders across diagnostic categories, and also by noting processing clusters where deficits were found across EDs. Thus, this approach may add to the NIMH’s Research Domain Criteria (RDoC) matrix, as our identified patterns of activation that are associated with interoception may be further applicable to other diagnoses. For instance, our interoceptive results map onto RDoC subsystems, including cognitive systems, reward valuation, and sensory motor systems, which have been found implicated in neurodevelopmental disorders broadly. This lends insight into how interoception may span beyond exclusively internal body signaling and influence cognitive and reward processes in different disorders. To that end, our results also additionally suggest that it may be helpful for future studies to further investigate whether treatments targeting set-shifting, self-referential processing and reward impact the brain clusters identified within this study and, thus, may be helpful for the future evaluation of effective treatments for EDs.

CRedit authorship contribution statement

Nandini Datta: Writing – original draft, Data curation. **Anna Hughes:** Writing – review & editing, Software, Methodology, Formal analysis. **Mattia Modafferi:** Writing – original draft, Data curation. **Megan Klabunde:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Project administration, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data and code availability statement

The code used to conduct this study can be referred to by Ngo et al., 2019 who have the code readily shared for use in analyses. Data was obtained by gathering coordinates from all reported papers included in the study; coordinates can be obtained by request.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.neuroimage.2024.120933](https://doi.org/10.1016/j.neuroimage.2024.120933).

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