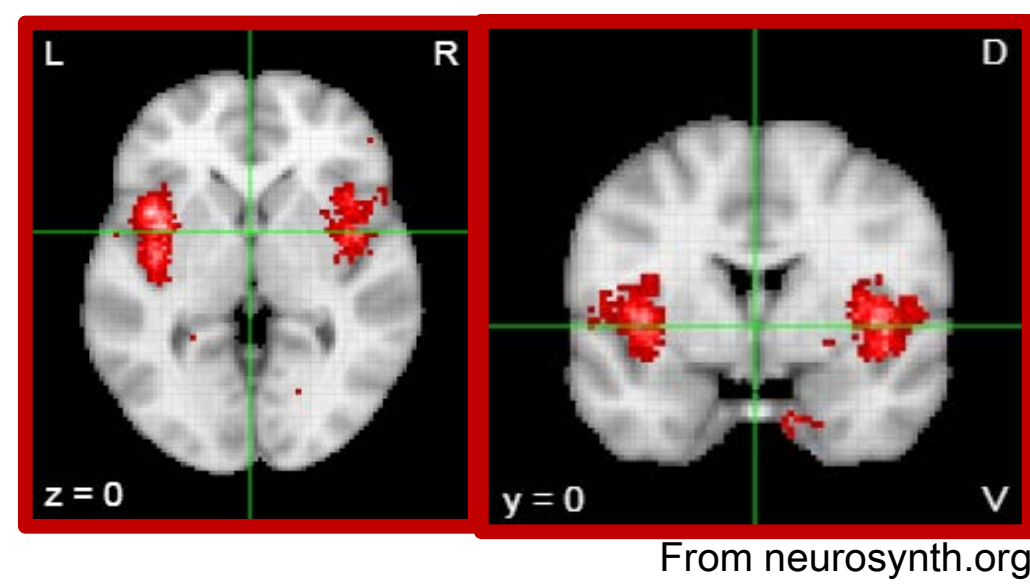


## Introduction

- Anorexia nervosa (AN) is a severe psychiatric disorder characterized by recurrent refusal of caloric intake, resulting in emaciation.
- Identifying whether neural networks that process food-related stimuli are affected in AN is important for understanding the biological basis of this illness, particularly severe food restriction.
- The insular cortex is a key area that has been implicated; this brain region is associated with interoceptive awareness and gustation.

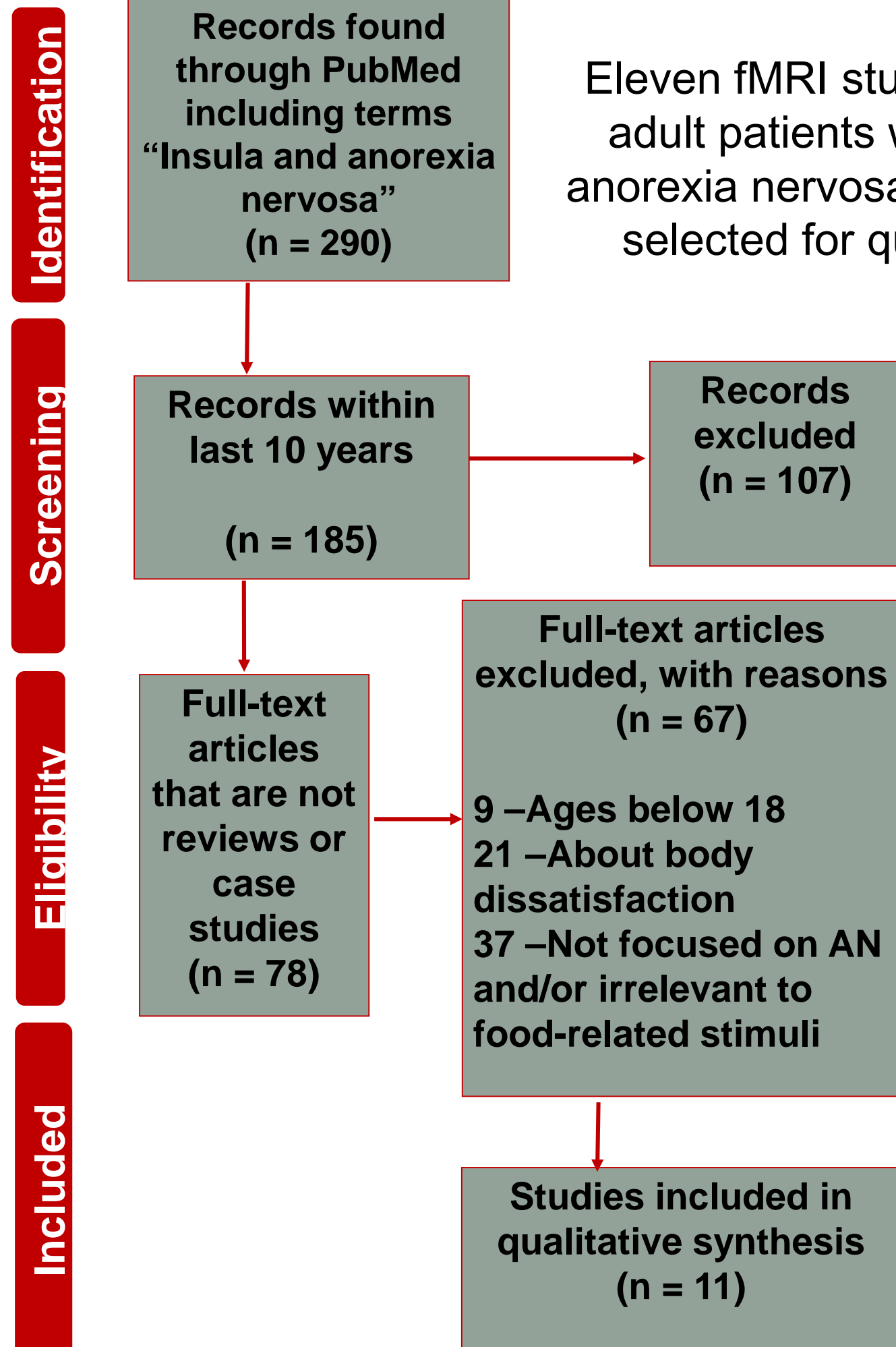


Typical insular-cortex activation imaged by an automated meta-analysis of 185 fMRI studies

## Objective

- To systematically review the literature for links between exposure to food-related stimuli and insular-cortex activation in patients with AN.

## Methods



Eleven fMRI studies that addressed adult patients with current or past anorexia nervosa and the insula were selected for qualitative analysis.

**Participants:** Sample sizes varied across studies (see Table 1), resulting in a total of 225 patients with past or current AN and 207 age-matched healthy control participants.

## Results

- Eight out of eleven studies saw differentiated insular activation between patients with AN and healthy controls during tasks. Seven of the studies implicated the right anterior insula, however hypo- or hyperactivation was unclear.
- Differing features included in the task paradigms across selected studies were seen (e.g., hunger & satiety state, anticipation of food-related stimulus).
- Eligibility criteria for the recruited participants were inconsistent.

**Table 1: Subject Demographics & Direction of Effect**

| Authors                             | Participants | Age (yrs)<br>Mean (SD) | BMI<br>Mean (SD) | ED duration<br>Mean (SD) in months | Insula Region         | Type of Activation          |
|-------------------------------------|--------------|------------------------|------------------|------------------------------------|-----------------------|-----------------------------|
| <b>Studies Using Taste-stimuli</b>  |              |                        |                  |                                    |                       |                             |
| <b>Ill-state patients with AN</b>   |              |                        |                  |                                    |                       |                             |
| Frank et. al (2012)                 | iAN = 21     | 22.52 (5.79)           | 16.10 (1.08)     | 77.76 (63.48)                      | Right Insula          | ^ During URS                |
|                                     | HC = 23      | 24.78 (5.64)           | 21.50 (1.42)     | --                                 | --                    | --                          |
| Frank et. al (2016a)                | iAN = 21     | 22.90 (6.10)           | 16.00 (1.10)     | --                                 | --                    | Taste Discrimination        |
|                                     | HC = 27      | 26.20 (7.00)           | 21.50 (1.40)     | --                                 | --                    | --                          |
| Frank et. al (2016b)                | iAN = 26     | 23.23 (5.26)           | 16.20 (1.09)     | 79.44 (67.80)                      | --                    | White Connectivity          |
|                                     | HC = 26      | 24.39 (3.49)           | 21.60 (1.21)     | --                                 | --                    | --                          |
| Monteleone et. al (2017)*           | iAN = 20     | 25.50 (7.80)           | --               | 91.20 (80.40)                      | Right Anterior Insula | ^ During Sweet Stimulus     |
|                                     | HC = 20      | 27.10 (4.70)           | --               | --                                 | --                    | --                          |
| Vocks et. al (2011)                 | iAN = 12     | 27.42 (10.57)          | 14.10 (1.78)     | 84.5 (42.80)                       | --                    | No Significance             |
|                                     | HC = 12      | 25.33 (3.58)           | 21.40 (1.62)     | --                                 | Left Insula           | ^ During (S)                |
| <b>Recovered patients with AN</b>   |              |                        |                  |                                    |                       |                             |
| Frank et. al (2016a)                | rAN = 19     | 27.00 (5.30)           | 20.20 (1.10)     | --                                 | --                    | --                          |
|                                     | HC = 27      | 26.20 (7.00)           | 21.50 (1.40)     | --                                 | --                    | --                          |
| Frank et. al (2016c)                | rAN = 24     | 30.30 (8.10)           | 20.80 (2.37)     | 70.8 (62.52)                       | Left Posterior Insula | ^USO                        |
|                                     | HC = 24      | 27.40 (6.30)           | 21.60 (1.26)     | --                                 | --                    | --                          |
| Wagner et. al (2007)                | rAN = 16     | 26.40 (6.20)           | 20.70 (2.20)     | --                                 | Bilateral Insula      | v All taste stimuli         |
|                                     | HC = 16      | 26.80 (6.30)           | 22.90 (2.20)     | --                                 | Bilateral Insula      | ^ with pleasant ratings     |
| <b>Studies Using Visual Stimuli</b> |              |                        |                  |                                    |                       |                             |
| <b>Ill-state patients with AN</b>   |              |                        |                  |                                    |                       |                             |
| Brooks et. al (2012)*               | iAN = 11     | 26.00 (7.20)           | 15.20 (1.20)     | 108 (88.80)                        | Right Anterior Insula | v viewing food images       |
|                                     | HC = 24      | 26.00 (9.50)           | 21.70 (2.40)     | --                                 | --                    | --                          |
| Gizewski et. al (2010)              | iAN = 12     | 27.40 (--)             | 14.10 (1.80)     | 84.5 (42.80)                       | Anterior Insula       | ^ viewing food images (H)   |
|                                     | HC = 12      | 25.30 (--)             | 21.40 (1.50)     | --                                 | --                    | --                          |
| Holsen et. al (2012)*               | iAN = 12     | 21.80 (2.70)           | 18.00 (0.80)     | 60 (32.40)                         | Anterior Insula       | v viewing food images (H&S) |
|                                     | HC = 11      | 21.60 (1.30)           | 22.40 (1.30)     | --                                 | --                    | --                          |
| <b>Recovered patients with AN</b>   |              |                        |                  |                                    |                       |                             |
| Holsen et. al (2012)*               | rAN = 10     | 23.40 (2.30)           | 22.10 (2.20)     | 48 (27.60)                         | Anterior Insula       | v viewing food images(H&S)  |
|                                     | HC = 11      | 21.60 (1.30)           | 22.40 (1.30)     | --                                 | --                    | --                          |
| Oberndorfer et. al (2013)           | rAN = 14     | 28.90 (6.60)           | 22.00 (1.60)     | 88.80 (88.80)                      | Right Anterior Insula | ^ viewing food images       |
|                                     | HC = 12      | 26.00 (6.80)           | 21.90 (1.00)     | --                                 | Bilateral Insula      | ^ with pleasant ratings     |

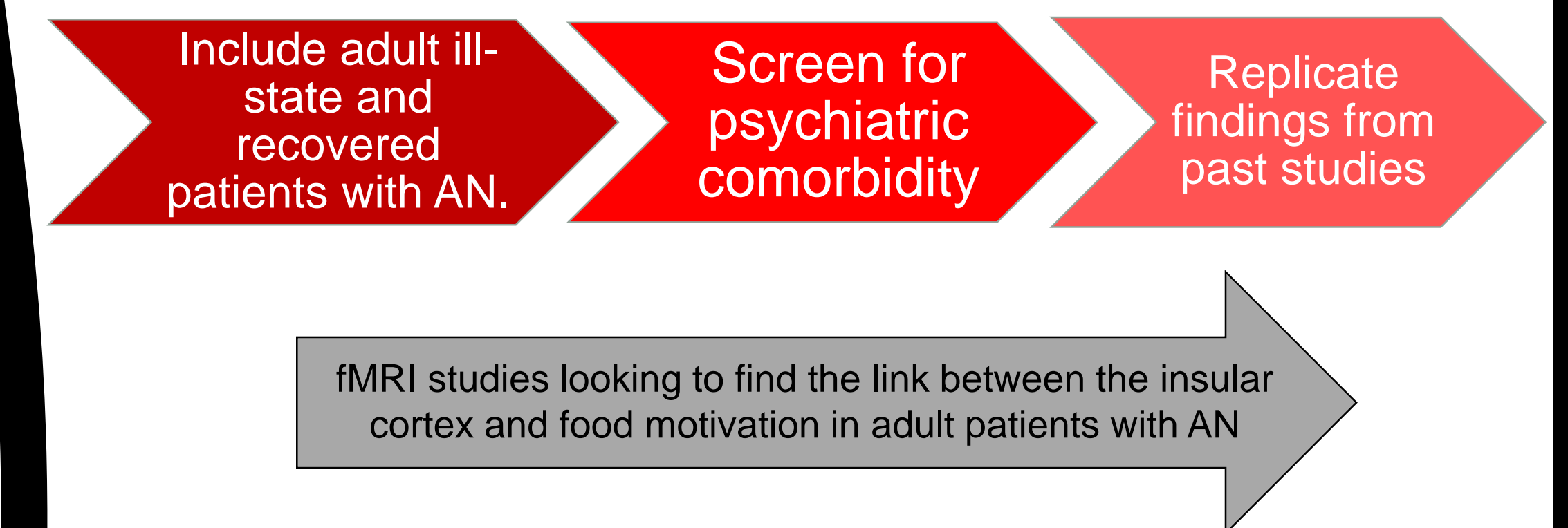
KEY: ^ = Increased activation; v = Decreased activation; URS = Unexpected Receipt of Sweet Stimulus; USO = Unexpected Sweet stimulus Omission; H = Hunger state; S = Satiated state; \*Study did not exclude binge/purge type AN

## Conclusions

- The literature is inconsistent on whether there is or is not hypoactivation or hyperactivation of the insula in patients with AN during taste or viewing of food.
- Whether insular-cortex activation correlates with appetitive experience or aversion during exposure to food-related stimuli is also unclear due to mixed findings.

## Future Studies

- More studies are required to determine whether the insula plays a role in altered food motivation in adult patients with AN.
- Observing insula activation and related pathways during anticipation versus experience of food-related stimuli may be an area for further study.
- Examining within-person changes in insular-cortex activation to food-related stimuli, from the ill-state of AN versus the recovered state, may be a useful next step to more clearly elucidate 'state' versus 'trait' effects and possible between-person differences in hypo- versus hyper- activation.



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From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med* 6(7): e1000097. doi:10.1371/journal.pmed1000097  
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