



# Exploring resting connectivity and painDETECT in women with endometriosis-associated pain

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## Introduction

Endometriosis, affecting 1 in 10 women of reproductive age, often presents with chronic pelvic pain. Our previous research indicated that 75% of women with endometriosis-associated pain (EAP) may have a neuropathic component, as identified by the painDETECT (PD) questionnaire. To investigate the neural basis of this component, we used functional MRI to examine brain regions where resting-state (RS) functional connectivity correlated with PD scores. Additionally, we compared these RS findings with regions of interest (ROIs) from task-based fMRI during abdominal stimulation. Participants were women with confirmed endometriosis prior to repeat surgery for EAP.

## This study aims to:

- ❖ Use task & resting state fMRI to explore brain activity & connectivity correlating with painDETECT in EAP.

## Methods

Participants underwent RS and task-based fMRI in a 3T MR scanner (Siemens) and completed questionnaires including painDETECT (PD). Imaging analyses were carried out using FSL and Matlab. Preprocessing of RS data included physiological noise modelling and single-subject independent component analysis (ICA) (MELODIC) with manual labelling. Punctate fMRI analysis was carried out as per standard pipelines to identify where activation in response to punctate correlated with painDETECT.

### Multiple RS group level analyses comprised:

- Seed-based whole brain analysis using dual regression with key ROI identified in the task-based scan.
  - FSLNets to determine connectivity of a group of ROIs found to be correlated with painDETECT in the task-based scan.
  - Voxel-based approach utilising group ICA followed by dual regression.
  - Static functional connectivity (sFC) between key regions of the salience network and default mode network.
- All resulting connectivity measures were correlated with demeaned PD scores.

## References

- [1] Coxon L, Wiech K and Vincent K (2021) Is There a Neuropathic-Like Component to Endometriosis-Associated Pain? Results From a Large Cohort Questionnaire Study. *Front. Pain Res.* 2:743812. doi: 10.3389/fpain.2021.743812
- [2] Bosma RL, Kim JA, Cheng JC, et al. Dynamic pain connectome functional connectivity and oscillations reflect multiple sclerosis pain. *Pain*. 2018. doi:10.1097/j.pain.0000000000001332
- [3] Soni A, Wanigasekera V, Mezue M, et al. Central Sensitization in Knee Osteoarthritis: Relating Presurgical Brainstem Neuroimaging and PainDETECT-Based Patient Stratification to Arthroplasty Outcome. *Arthritis Rheumatol*. 2019. doi:10.1002/art.40749
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## Ethics & Funding

Data collected during EndoPain2 project, ethics reference: 15/SC/0372. EndoPain2 was funded by an Investigator Initiated Award from Bayer HealthCare Ltd.

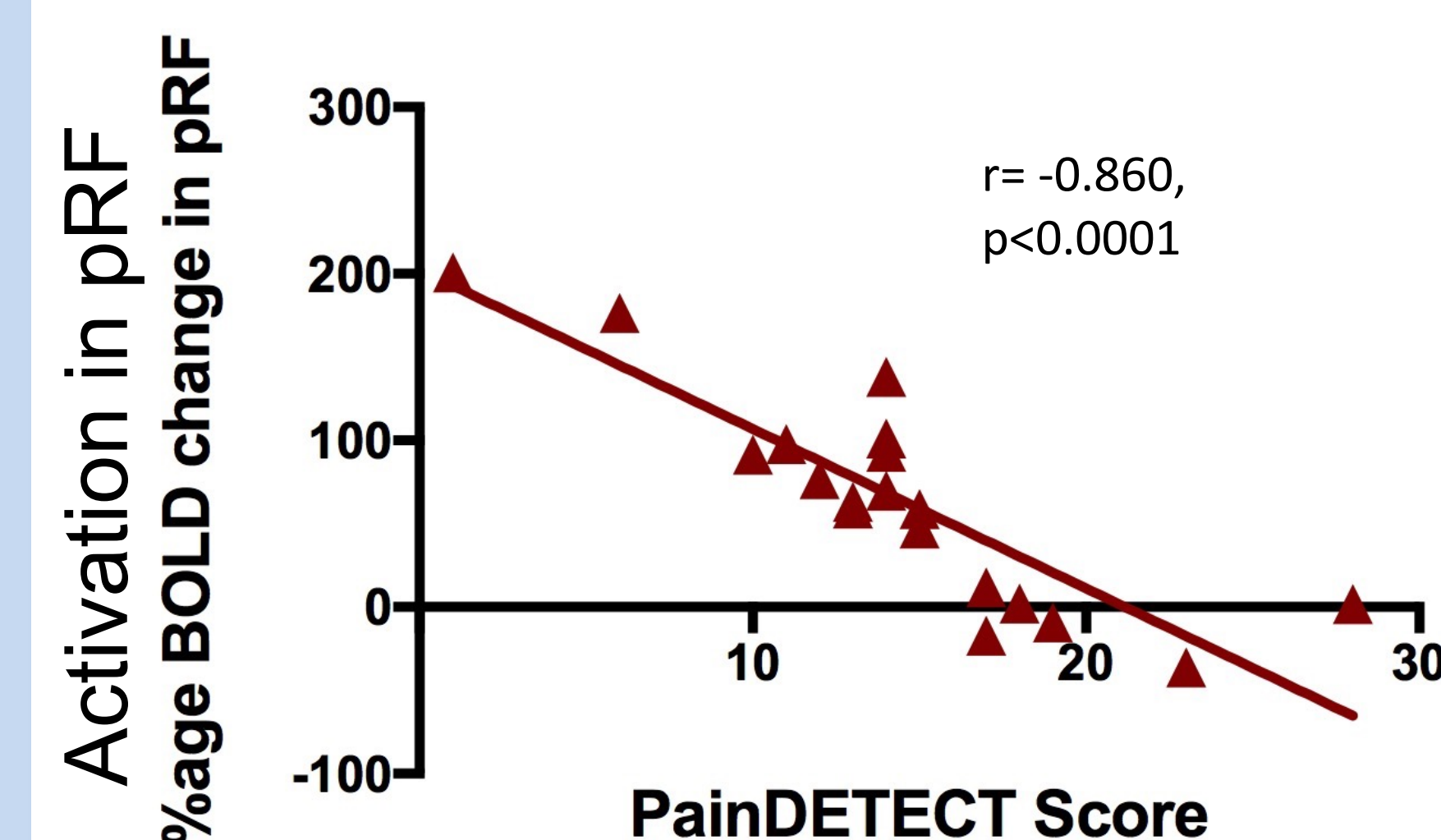
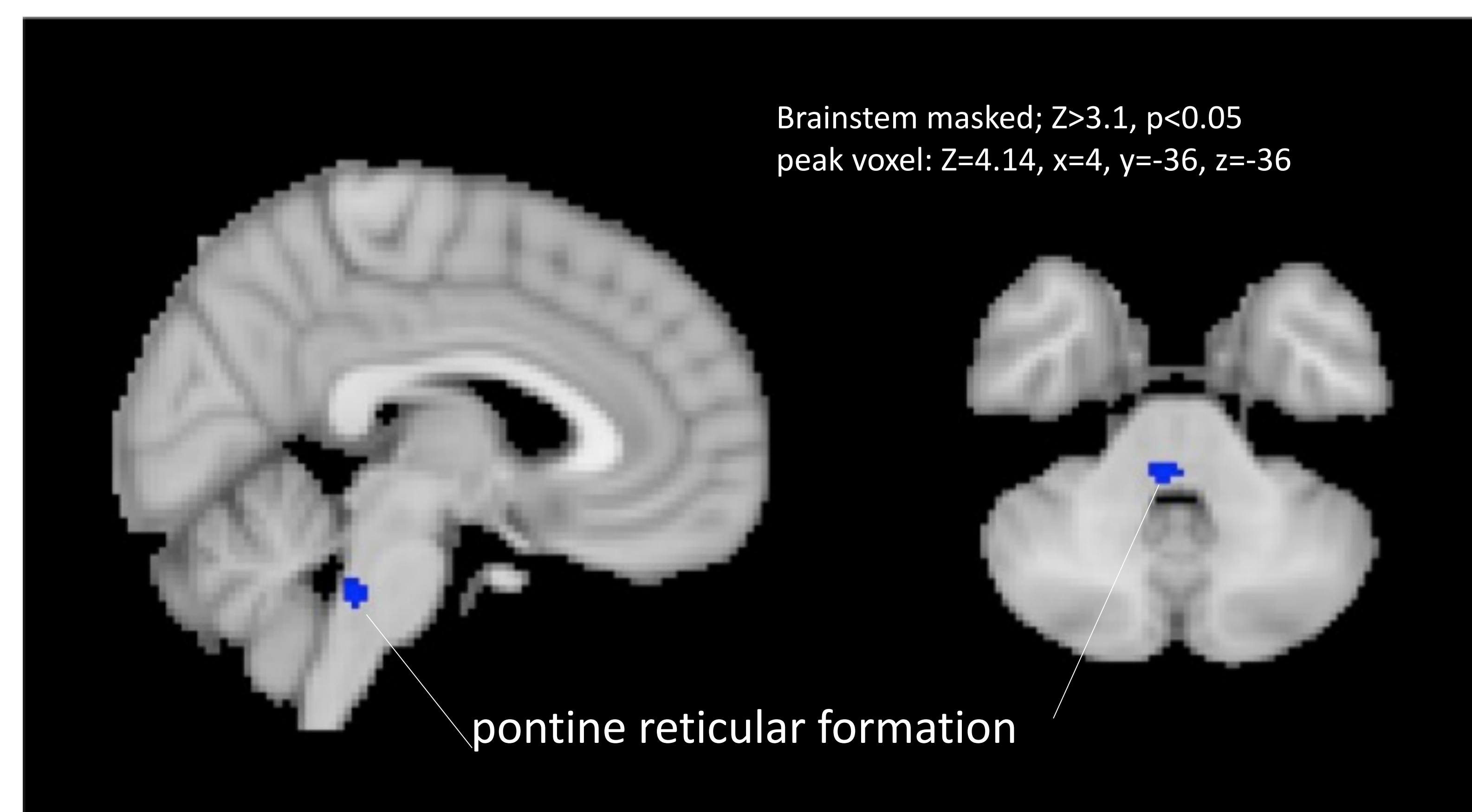
## Results

### Participants

Of the 28 women recruited, N= 26 RS datasets and N= 15 task-based datasets passed quality control checks. painDETECT scores ranged between 1-28 (median: 15). painDETECT scores showed no significant correlation with pain catastrophizing nor state anxiety

### ROIs response to punctate stimuli correlating with painDETECT

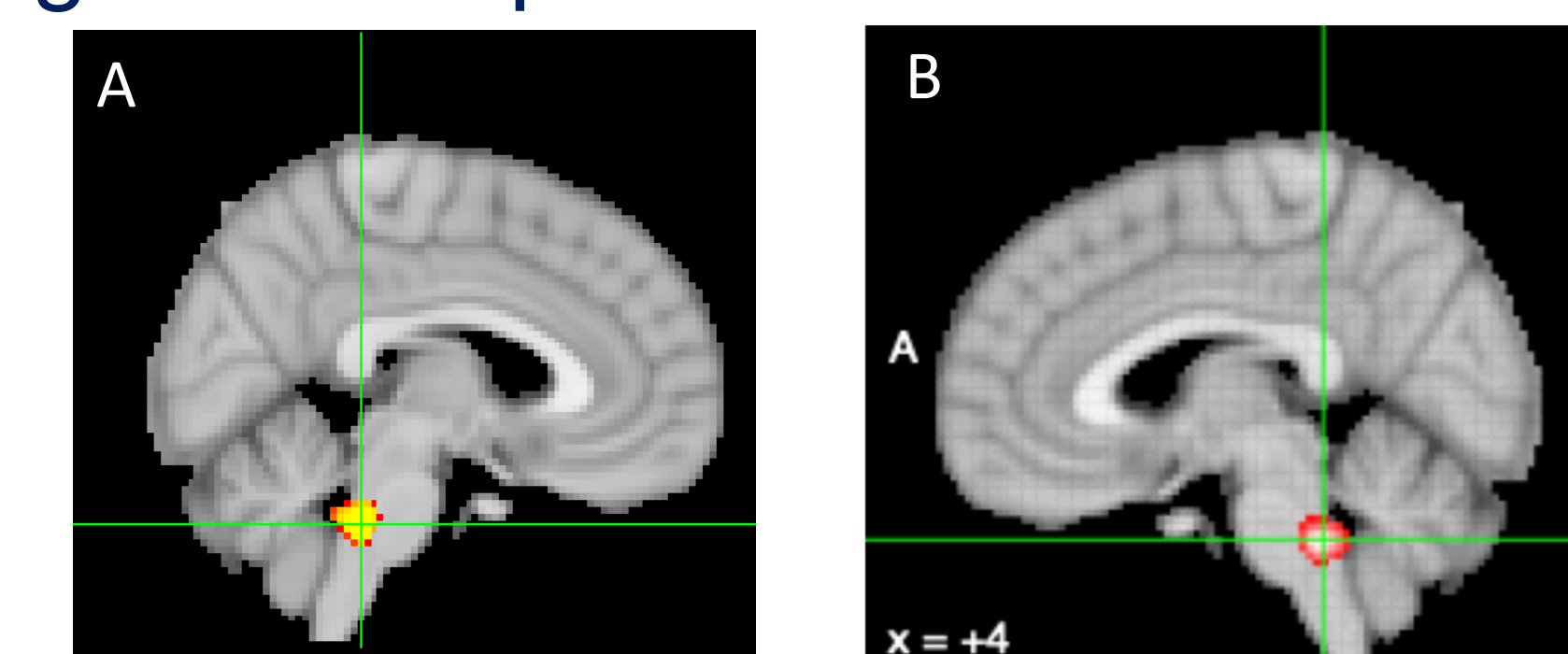
Analyses of punctate-induced activation revealed that painDETECT scores were correlated negatively with activity in the **pontine reticular formation** (pRF; brainstem masked;  $Z>3.1$ ,  $p<0.05$ ).



Significant negative correlations were also found with **left thalamus**, **left insula** & **midcingulate cortex** on whole brain analysis, at lower threshold ( $Z>2.3$ ,  $p<0.05$ ).

### Punctate ROI seed-based whole brain analysis

For each of the identified ROIs (pRF, left thalamus, left insula and midcingulate cortex), whole brain connectivity was calculated, and then correlated with painDETECT score. There was no significant correlation between whole-brain connectivity of the ROIs and painDETECT score at significance  $p<0.05$ .



The pRF showed significant connectivity only to itself (A), which aligns with what is seen using Neurosynth.org, a healthy participant database (B).

### Connectivity between punctate ROIs

None of the ROIs were significantly connected at rest ( $p>0.9986$  with family wise error correction). No significant correlation between painDETECT (controlling for pain scores) and functional connectivity between ROIs.

### Whole brain voxel-based group ICA

A voxel-based ICA analysis gave 25 ICA components. Dual regression with randomise was used to correlate connectivity with painDETECT and analysis found no significant correlations between functional connectivity and painDETECT score.

### Using seeds from other conditions relating to painDETECT

Using seeds for **vIPAG**[4], **RVM**[3], **left NAcc**[3] and **rACC**[3] using both whole brain and between ROI analysis found no connectivity correlating with painDETECT.

Static functional connectivity between the **DMN** and **Salience Network** was calculated as per Bosma et al.[2] using seeds for rTPJ, mPFC, PCC and S1. We found no significant correlation with painDETECT score.

## Conclusions

Whilst the painDETECT score may be useful clinically to stratify patients with endometriosis-associated pain, our data suggests that the variation in these scores is not reflected in resting state connectivity. This is contrary to what has been seen in other conditions with a neuropathic component. **In response to evoked pain painDETECT is negatively correlated with activity in regions implicated in descending modulation of pain**, potentially representing a central network maintaining peripheral neuropathic pain. However, despite our thorough analysis of the resting state data, using a variety of indices, we **found no evidence for changes in RS activity related to painDETECT**. This argues against a role for altered RS functional connectivity in neuropathic-like pain in EAP.

## Relevance for patient care

Women with endometriosis-associated pain describe a wide variety of pain symptoms and these findings suggest there may be important differences in the mechanisms generating and maintaining provoked and unprovoked pain.

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