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European Journal of Paediatric Neurology 41 (2022) 80–90

Contents lists available at ScienceDirect

European Journal of Paediatric Neurology

journal homepage: www.journals.elsevier.com/european-journal-of-paediatric-neurology

Altered anterior insula functional connectivity in adolescent and young women with endometriosis-associated pain: Pilot resting-state fMRI study

Edina Szabo [a,b,i,1], Inge Timmers [c,d,1], David Borsook [e,f,g], Laura E. Simons [d,2], Christine B. Sieberg [a,b,h,2,*]

[a] Pain and Affective Neuroscience Center, Department of Anesthesiology, Critical Care, and Pain Medicine, Boston Children's Hospital, Boston, MA, USA
[b] Biobehavioral Pain Innovations Lab, Department of Psychiatry and Behavioral Sciences, Boston Children's Hospital, Boston, MA, USA
[c] Department of Rehabilitation Medicine, Maastricht University, Maastricht, the Netherlands
[d] Department of Anesthesiology, Perioperative, and Pain Medicine, Stanford University School of Medicine, Palo Alto, CA, USA
[e] Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA
[f] Department of Radiology, Massachusetts General Hospital, Boston, MA, USA
[g] Department of Anesthesiology, Harvard Medical School, Boston, MA, USA
[h] Department of Psychiatry, Harvard Medical School, Boston, MA, USA
[i] Department of Anesthesia, Critical Care, and Pain Medicine, Beth Israel Deaconess Medical Center, Boston, MA, USA

ARTICLE INFO

Keywords:
Adolescent endometriosis
Resting-state fMRI
Anterior insula
Dorsolateral prefrontal cortex
Cerebellum
Anxiety
Fear of pain

ABSTRACT

Background: Endometriosis is the leading cause of chronic pelvic pain. Alterations in brain functional connectivity have been reported in adult women with endometriosis-associated pain (EAP), however, it is still unknown if similar patterns of changes exist in adolescents. **Methods**: In this pilot study, resting-state fMRI scans were obtained from 11 adolescent and young women with EAP and 14 healthy female controls. Using a seed-to-voxel approach, we investigated functional connectivity between the anterior insula, medial prefrontal cortex, and the rest of the brain. Furthermore, we explored whether potential functional connectivity differences were correlated with clinical characteristics including disease duration, pain intensity, and different psychosocial factors (pain catastrophizing, fear of pain, functional disability, anxiety, and depression). **Results**: Our findings revealed that patients with EAP demonstrated significantly decreased connectivity between the right anterior insula and two clusters: one in the right cerebellum, and one in the left middle frontal gyrus compared to controls. Additionally, functional connectivity between the right anterior insula and the right cerebellum was positively associated with pain intensity levels. In patients with EAP, brain changes were also correlated with state anxiety and fear of pain. **Conclusions:** Our results are relevant not only for understanding the brain characteristics underlying EAP at a younger age, but also in enhancing future pain treatment efforts by supporting the involvement of the central nervous system in endometriosis.

1. Introduction

Endometriosis is defined by the presence of ectopic endometrial tissue ('lesions') outside the uterus, and it is usually associated with pain and/or infertility [1]. The pathophysiology of endometriosis-associated pain (EAP) has remained unclear. Although the majority of studies has considered the lesions as the most probable source [2], central sensitization may be particularly significant in endometriosis since: (1) many patients continue to report pain (or the pain recurs) even after endometrial lesions were treated or removed; (2) patients exhibit hyperalgesia outside of the areas of the pelvis as well; and (3) there is only weak association between endometriosis severity (disease stage) and pain intensity [3,4,5]. Additionally, many of the symptoms of endometriosis begin in adolescence or early adulthood, a period when the central nervous system (CNS) is still developing and sensitive to persistent or recurrent pain [6].

However, little research has investigated central processing of pain via brain alterations in patients with EAP, and existing studies have

* Corresponding author. Biobehavioral Pain Innovations Lab, Boston Children's Hospital, 21 Autumn Street, Office AT110.2, Boston, MA, 02115, USA.
E-mail address: Christine.sieberg@childrens.harvard.edu (C.B. Sieberg).
[1] Biobehavioral Pain Innovations Lab.
[2] Contributed equally to this manuscript.

https://doi.org/10.1016/j.ejpn.2022.10.004
Received 3 May 2022; Received in revised form 12 September 2022; Accepted 24 October 2022
Available online 29 October 2022

Table 1
Demographics and clinical characteristics of the participant groups.

Subject group	Patients with EAP $n = 11$	Healthy controls $n = 14$	Test statistic	p value
Age (years)	17.1 ± 1.9 (13–21)	16.6 ± 2.7 (13–21)	$t(23) = 0.45$	0.65
PCS-C	17.9 ± 8.6 (0–34)	11.7 ± 7.1 (0–24)	$t(23) = 1.97$	0.06
FOPQ-C	40.1 ± 4.8 (15–67)	15.2 ± 8.7 (2–32)	$t(23) = 5.26$	**< 0.001**
FDI	13.2 ± 9.3 (1–33)	1.6 ± 2.7 (0–8)	$U = 9.00$	**< 0.001**
STAI-S-C	50.5 ± 2.7 (45–55)	48.4 ± 3.1 (41–52)	$t(23) = 1.78$	0.09
STAI-T-C	12.3 ± 8.4 (0–29)	12.4 ± 8.3 (1–32)	$t(23) = 0.03$	0.98
CDI-2	52.5 ± 7.6 (41–63)	47.9 ± 8.1 (40–63)	$t(23) = 1.21$	0.25
Pain severity (average pain in the last week, 0 to 10)	5.6 ± 1.6 (3–8)	–	–	–
Pain duration (month)	36.6 ± 32.6 (4–117)	–	–	–
Painful days per month	18.55 ± 11.77 (5–30)	–	–	–
Using hormonal contraceptives	11 (100%)	3 (27%)	$\chi 2 = 15.43$	**< 0.001**
Length of menstrual cycle (days) [a]	–	32.7 ± 7.6 (23–49)	–	–
Day of menstrual cycle (at the time of the scan) [a]	–	12.5 ± 10.8 (2–36)	–	–

Note. Data are expressed as mean ± *SD* (range) or number of patients (%). Continuous data were analyzed using the independent-sample *t*-test for parametric variables or the Mann-Whitney *U* test for nonparametric variables. Categorical data were analyzed using Chi-square ($\chi 2$) test.
EAP, endometriosis-associated pain; PCS-C, Pain Catastrophizing Scale—Child version; FOPQ-C, Fear of Pain Questionnaire for Children; FDI, Functional Disability Inventory; STAI-S-C, State-Trait Anxiety Inventory for Children–State scale; STAI-T-C, State-Trait Anxiety Inventory for Children–Trait scale; CDI-2, Children's Depression Inventory-2.
The *p* values for test statistics that reached significance are bolded.
[a] Length and day of the menstrual cycle are presented for heathy subjects not using any hormonal contraceptives ($n = 11$).

focused on adult women. In the study by Ref. [7]; decreased grey matter volume (GMV) was observed in regions implicated in pain processing, including the insula, thalamus, cingulate gyrus, and middle frontal gyrus, among patients with EAP compared to pain-free controls. Interestingly, these GMV reductions were found in women with both endometriosis and chronic pelvic pain but not in asymptomatic patients. Another study from the same research group found increased anterior insula functional connectivity to the medial prefrontal cortex, and greater levels of excitatory neurotransmitters within the right anterior insula which may be a key region in the pathophysiology of EAP [8]. Notably, functional connectivity between these two regions was related to pain intensity, and more severe anxiety and depressive symptoms in endometriosis.

While resting-state fMRI is commonly used to investigate CNS function, no previous studies have explored functional connectivity in adolescents and young women with EAP. Imaging studies in children with chronic pain are still limited, but further support the role of the anterior insula and medial prefrontal cortex in different pain conditions [9,10,11]. Given that pediatric chronic pain in general has been linked with increased risk of anxiety and depression, greater physical and pain-related disability [12], it is reasonable to believe that, similar to adult women, these psychosocial indices are connected to neural alterations in adolescents with EAP. In addition, studies have shown that pain catastrophizing or pain-related worry [13] and pain-related fear [14] could be a significant marker for pain experience in youth (for a review, see Ref. [15].

To address some of the issues noted above, the current study sought to investigate resting-state functional connectivity in adolescent and young women with EAP. We hypothesized that: (1) functional connectivity of the anterior insula and the medial prefrontal cortex would differentiate patients with EAP and controls; and (2) that these alterations would be correlated with disease duration, pain intensity and psychosocial functioning in patients. As such, the data could provide a basis for understanding pain-psychosocial function as an index of severity and resistance to treatment.

Table 2
Brain regions showing decreased functional connectivity with the right anterior insula in patients with endometriosis-associated pain (EAP) compared to healthy controls.

Cluster	Cluster size	Peak MNI coordinates			Cluster *p*	Cluster *p-uncorr*
		x	y	z	(FDR)	
Right cerebellum	153	50	−72	−42	0.012	0.0005
Left middle frontal gyrus/frontal pole	145	−30	30	38	0.012	0.0007

Note. Clusters are significant at $pFDR < 0.05$ following an initial cluster defining threshold of $p < 0.001$. Coordinates are in Montreal Neurological Institute (MNI) space.

2. Materials and methods

2.1. Participants and study procedure

Twenty-eight right-handed young women were included in this study. Twelve patients diagnosed with endometriosis were recruited during a multidisciplinary evaluation for chronic pain at the Pain Treatment Service, at Boston Children's Hospital and 16 heathy participants were recruited through advertisements. From the 12 patients, 11 had surgically confirmed endometriosis, and one patient was clinically diagnosed by the same gynecologist surgeon based on symptoms and family history (the patient elected not to have surgery). This study was part of a larger project examining fear acquisition and extinction in adolescents and young adults with various chronic pain disorders [16,17]. Inclusion criteria included: ages 10–24 years, pain lasting for more than 3 months, and a confirmed diagnosis of endometriosis for the patient cohort. General exclusion criteria included significant cognitive impairment, severe psychiatric disorder, positive pregnancy and/or drug screening test, claustrophobia, and MRI incompatible implants. In addition, the same exclusion criteria were applied to the age-matched healthy controls, but they had no current or past history of chronic pain (symptoms present for more than 3 months) and identified as female. All procedures and protocols were approved by the Boston Children's Hospital Institutional Review Board and conducted in accordance with the Declaration of Helsinki. Participants and legal guardians provided a written informed consent/assent before inclusion in the study.

2.2. Clinical measures

Participants self-reported age in years and their average pain intensity on a 10-point Likert scale (average pain during the past week; 0 = *no pain*, 10 = *worst possible pain*). Pain duration was calculated in months from the time patients reported onset of their pain to the date of the study visit. In addition, the day of menstrual cycle at the time of the scan visit and the length of menstrual cycle were assessed by using two items from the Pubertal Development Scale (PDS; [18]: the date of the

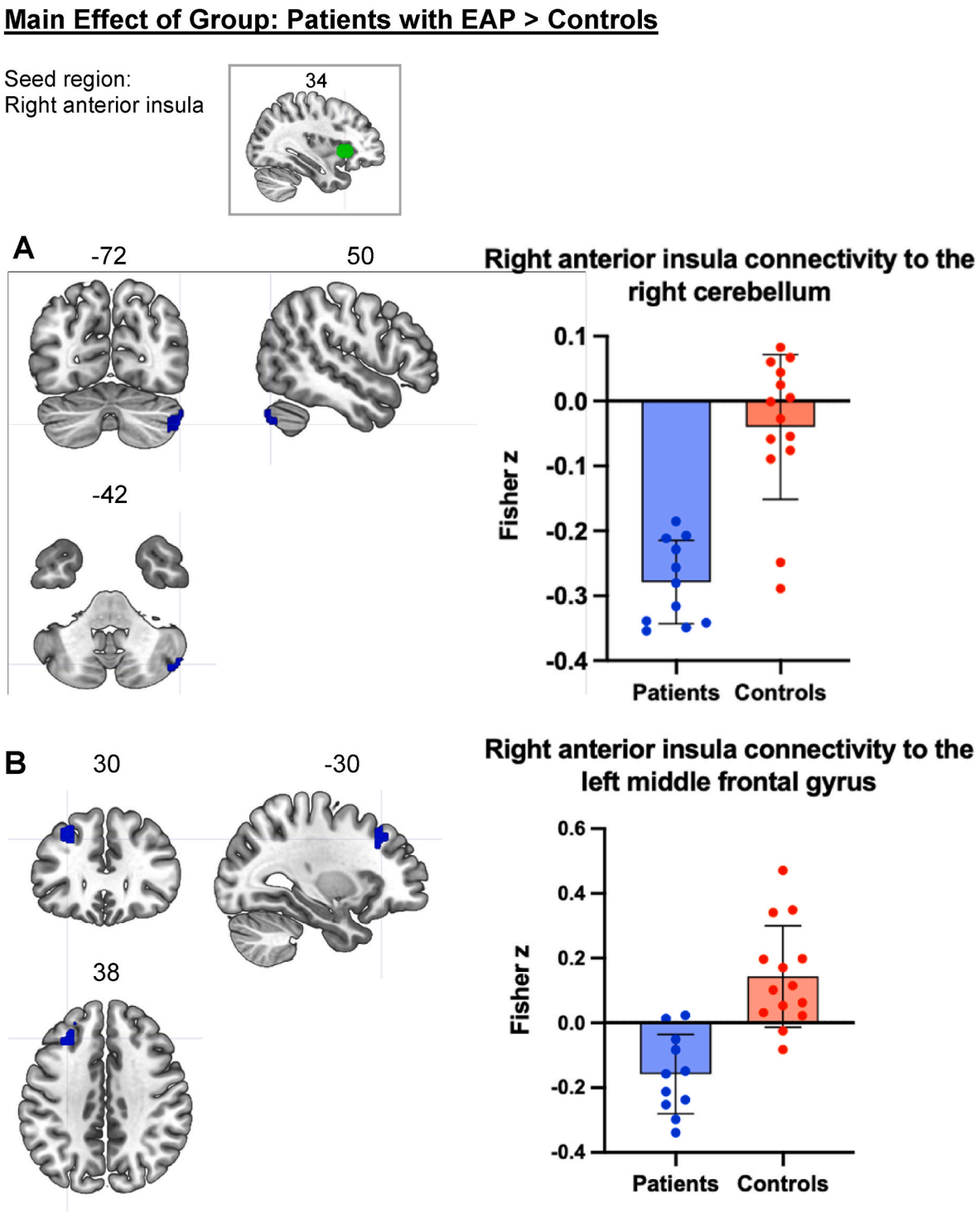

Fig. 1. Altered resting-state functional connectivity between the right anterior insula and the rest of the brain in patients with endometriosis-associated pain (EAP) compared to healthy controls. The right anterior insula demonstrated significantly decreased functional connectivity to the right cerebellum (crus I and crus II) (**A**), and left middle frontal gyrus (**B**) in EAP patients. Coordinates are in Montreal Neurological Institute (MNI) space (coronal, sagittal, and axial views of the brain). Functional connectivity maps are corrected at pFDR<0.05. Bar graphs indicate average and individual Fisher's z-transformed connectivity values. Error bars represent standard error of mean.

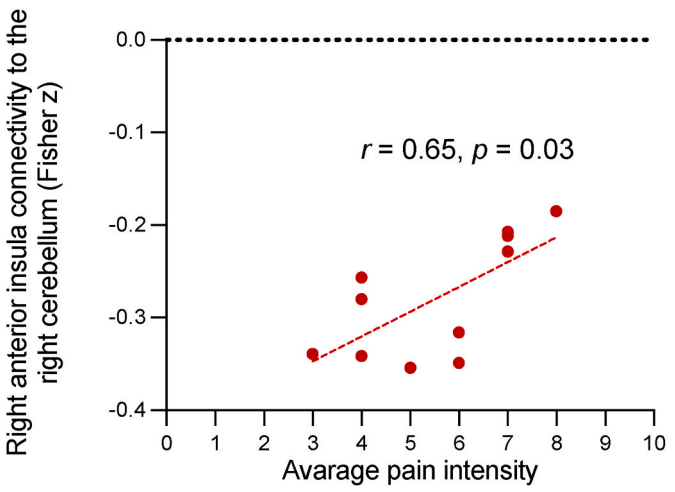

Fig. 2. In patients with endometriosis-associated pain (EAP), right anterior insula connectivity to the right cerebellum was positively correlated with average pain intensity. Connectivity values are Fisher's *z*-transformed.

Table 3
Significant correlations in resting-state functional connectivity of the right anterior insula with fear of pain (negative) and state anxiety (positive) in patients with endometriosis-associated pain (EAP).

Cluster	Cluster size	Peak MNI coordinates			Cluster *p* (FDR)	Cluster *p*-*uncorr*
		x	y	z		
Fear of pain (negative correlation)						
Right superior frontal gyrus/frontal pole	80	22	38	36	0.036	0.0015
State Anxiety (positive correlation)						
Left supplementary motor area	75	−2	−10	62	0.029	0.0020
Right superior frontal gyrus/frontal pole	73	24	6	48	0.029	0.0023
Left superior frontal gyrus/frontal pole	68	−20	6	74	0.029	0.0030
Left middle frontal gyrus	68	−32	8	56	0.029	0.0030

Note. Clusters are significant at *p*FDR < 0.05 following an initial cluster defining threshold of $p < 0.001$. Coordinates are in Montreal Neurological Institute (MNI) space.

first day in the last period and the date of the first day of the second to last period. Painful days per month and the current use of contraceptives were also recorded.

2.3. Psychosocial functioning

2.3.1. Pain Catastrophizing Scale for Children

Pain catastrophizing was assessed by the Pain Catastrophizing Scale for Children (PCS–C; [19]. The PCS-C includes 13 items that are rated on a 5-point scale ranging from 0 = *not at all true* to 4 = *very true*. Higher scores indicate higher levels of negative thinking about pain (Cronbach's α was 0.87 in the present sample).

2.3.2. Fear of Pain Questionnaire for Children

Pain-related fear was measured by the Fear of Pain Questionnaire for Children (FOPQ-C; [14]. The FOPQ-C consists of 24 items, each item scored on a 5-point scale from 0 = *strongly disagree* to 4 = *strongly agree* (Cronbach's α in the present sample was 0.93).

2.3.3. Functional Disability Inventory

The Functional Disability Inventory (FDI; [20] was used to assess difficulty in physical and psychosocial functioning due to pain. The instrument consists of 15 items that are rated on a 5-point scale ranging from 0 = *no trouble* to 4 = *impossible* (Cronbach's α in the present sample was 0.92).

2.3.4. State-Trait Anxiety Inventory for Children

Anxiety symptoms were assessed using the State-Trait Anxiety Inventory for Children (STAI-C; [21]. STAI-C consists of two 20-item scales that measure state and trait anxiety scored on a 5-point and 3-point scale (STAI-S: e.g., 0 = *not calm*, 4 = *very calm*; STAI-T: 0 = *hardly ever* to 2 = *often*). Higher scores indicate higher severity of symptoms (Cronbach's α values were STAI-S α = 0.72 and STAI-T α = 0.91 in the present sample).

2.3.5. Children's Depression Inventory-2

Children's Depression Inventory-2 (CDI-2; [22] was applied to measure depressive symptoms. CDI-2 is a 28-item questionnaire, and the response options for each item are rated on a 3-point scale (0 = *no symptom*, 2 = *definite, marked symptom*) (Cronbach's α was 0.82 in the present sample). It is interpreted using *t*-scores based on age and sex-based norms.

2.4. Data analysis

Demographic data and clinical measure scores were analyzed with SPSS version 23.0 software (SPSS, Inc., Chicago, IL, USA). Independent *t*-tests or Mann-Whitney U tests were performed to determine whether patients with EAP and healthy controls differed in age, pain catastrophizing, fear of pain, pain related functional disability, anxiety, and depressive symptoms (pain duration and intensity data were available for the patient group only). In addition, chi square ($\chi 2$) tests were conducted to compare hormonal contraceptive use. Significance levels were set at $p < 0.05$. Cronbach's alpha coefficients were calculated for all self-report measures.

2.5. Imaging

2.5.1. Image acquisition

Anatomical and functional imaging was performed using a 3 T MR scanner (Siemens Magnetom TrioTim syngo MR B17) with a 12-channel head coil. Resting-state functional images were acquired using a T2*-weighted echo-planar-imaging (EPI) sequence with multi-band acceleration (simultaneous multi-slice or SMS) as follows: 51 axial slices (3 mm isotropic) covering the entire cortical volume, repetition time (TR) = 1110 ms, echo time (TE) = 30 ms, flip angle = 70°, field of view (FOV) = 228 × 228 mm, slice acceleration factor = 3. In total, 425 functional volumes were acquired with eyes open while viewing a black screen. An additional 8 functional volumes recorded with the same parameters, but reverse phase encoding direction were collected. T1-weighted anatomical data were also acquired from each patient using a 3D multi-echo magnetization-prepared rapid gradient-echo (ME-MPRAGE) sequence with the following parameters: 176 slices, 1 mm isotropic, TR = 2520 ms, TE1 = 1.74 ms, TE2 = 3.6 ms, TE3 = 5.46 ms, TE4 = 7.32 ms, flip angle = 7°, FOV = 240 × 240, GRAPPA acceleration factor = 2.

2.5.2. Imaging data analysis

Preprocessing and denoising were performed as part of the larger project (see also [17]. Preprocessing of the resting-state fMRI data included geometric distortion estimation and correction. From the pairs of images with reversed phase-encoding directions (distortions going in opposite directions), the susceptibility-induced off-resonance field was estimated using a method similar to that described in Ref. [23] (topup

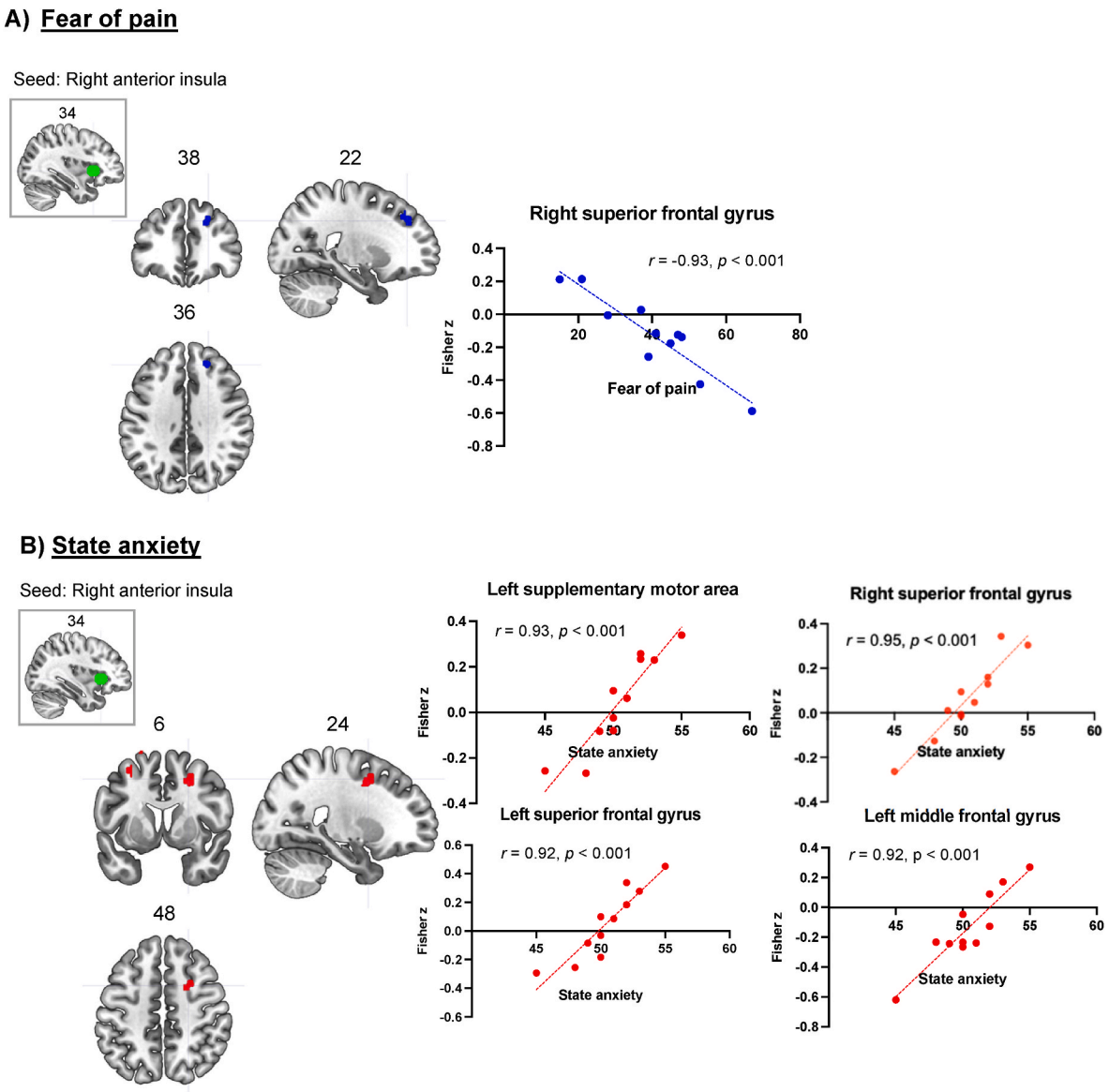

Fig. 3. In patients with endometriosis-associated pain (EAP), resting-state functional connectivity of the right anterior insula was negatively related to fear of pain in the right superior frontal gyrus (**A**), and positively related to state anxiety in the left supplementary motor area, bilateral superior frontal gyrus and left middle frontal gyrus (**B**). Coordinates are in Montreal Neurological Institute (MNI) space (coronal, sagittal, and axial views of the brain). Functional connectivity maps are corrected at *p*FDR < 0.05. Connectivity values are Fisher's *z*-transformed.

Table 4
Significant correlations in resting-state functional connectivity of the left medial prefrontal cortex with state anxiety (positive and negative) in patients with endometriosis-associated pain (EAP).

Cluster	Cluster size	Peak MNI coordinates			Cluster *p* (FDR)	Cluster *p-uncorr*
		x	y	z		
State Anxiety						
Left cerebellum (positive correlation)	147	−32	−60	−40	0.029	0.000004
Left precuneus cortex (negative correlation)	157	−12	−42	62	0.001	0.000008

Note. Clusters are significant at *p*FDR < 0.05 following an initial cluster defining threshold of $p < 0.001$. Coordinates are in Montreal Neurological Institute (MNI) space.

tool implemented in FMRIB Software Library [FSL]; [24]. Images were distortion corrected in the full resting-state dataset by using FSL's applytopup. Undistorted images were preprocessed in CONN [25] including the following steps: 3D head motion correction, segmentation into white matter (WM), grey matter (GM) and cerebral spin fluid (CSF), normalization to Montreal Neurological Institute (MNI) space and spatial smoothing (using a 6 mm full-width at half-maximum [FWHM] Gaussian kernel).

Denoising steps involved regression of motion parameters and their first derivatives (12 parameters) and WM/CSF noise components (derived by the anatomical component-based noise correction method, aCompCor [26]; 2 × 5 parameters), linear trend removal, as well as simultaneous band pass filtering (0.005–0.1 Hz). Quality assurance was carried out to detect outliers, and two healthy controls were excluded from the analysis due to head movement (data with motion >3 mm/degrees). First-level analysis was performed for estimation of bivariate correlation coefficients between the a priori defined regions-of-interest (ROIs) or seeds and the rest of the brain.

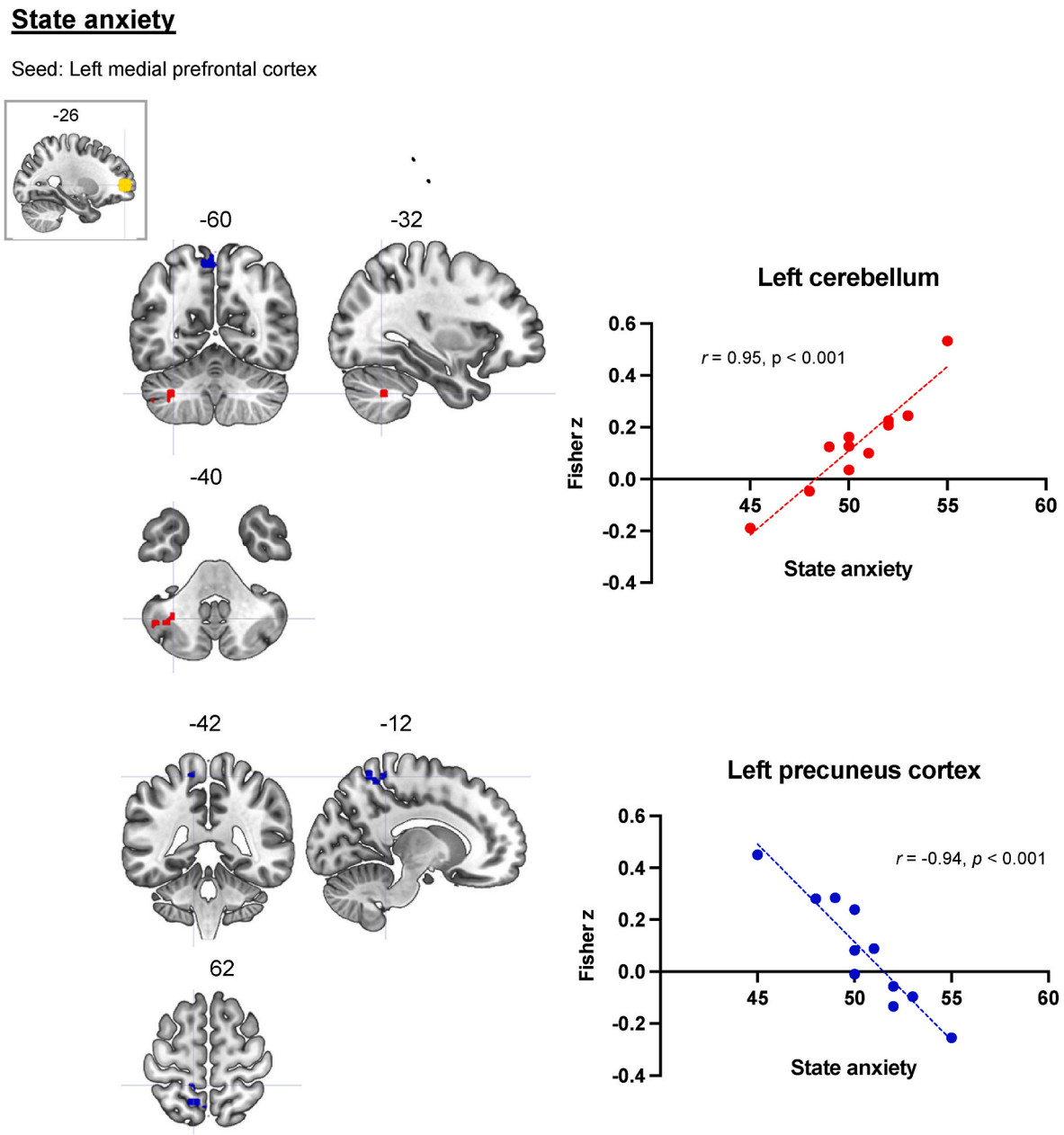

Fig. 4. In patients with endometriosis-associated pain (EAP), resting-state functional connectivity of the left medial prefrontal cortex was positively related to state anxiety in the left cerebellum (crus I and crus II), and negatively related to state anxiety in the left precuneus cortex. Coordinates are in Montreal Neurological Institute (MNI) space (coronal, sagittal, and axial views of the brain). Functional connectivity maps are corrected at *p*FDR < 0.05. Connectivity values are Fisher's *z*-transformed.

The anterior insula and the medial prefrontal cortex were used as ROIs. These seed locations were selected based on previous findings of resting-state functional connectivity changes in adult women with EAP [8]. The right anterior insula and the left medial prefrontal cortex ROIs were generated as spheres with a radius of 10 mm (peak MNI coordinates from Ref. [8]: 34; 19; 0 and −26; 54; 4, respectively).

Functional connectivity between each ROI and the rest of the brain was tested with the seed-to-voxel approach in CONN [25]. In the second-level analyses, differences were assessed between patients and controls in the anterior insula and medial prefrontal cortex functional connectivity using group as a between-subject factor. Main effects of group were examined at a cluster-level threshold of $p < 0.001$, and subsequent cluster-level false discovery rate (FDR) corrected $p < 0.05$. For significant findings, estimated bivariate correlation coefficients were averaged across the voxels of each cluster, extracted, and transformed using Fisher's z transformation for further analyses. To investigate the association between the resting-state functional connectivity results and the clinical measurements in the patient group (not across the entire sample), Pearson correlation was employed using SPSS. In this way, we aimed to assess whether the group results can be further explained by other clinical and psychological factors. In addition, independent of group differences, correlations of the resting-state functional connectivity in the relevant seeds with the clinical measurements were further explored in the patient group. Again, the significance level was set at a cluster-level threshold of $p < 0.001$, and subsequent cluster-level FDR corrected $p < 0.05$. Anatomical locations of the significant clusters were identified using the Harvard-Oxford cortical and subcortical structural atlases [27]. Results were visualized on the MNI 152 template brain provided in MRIcroGL software (https://www.mccauslandcenter.sc.edu/mricrogl/).

3. Results

3.1. Participants' characteristics

Out of the 28 participants included in this study (12 patients with EAP and 16 healthy controls), two controls had to be excluded for movement artifacts (criteria described above), and one patient for technical reasons resulting in a total of 25 participants (*M* age = 16.8 *SD* = 2.4). Thus, the final sample consisted of 11 patients with EAP (13–21 years old, *M* age = 17.1, *SD* = 1.9) and 14 age- and sex-matched healthy controls (13–21 years old, *M* age = 16.6, *SD* = 2.7).

Clinical data of participants are shown in Table 1. Patients with EAP reported significantly higher levels of pain-related fear and functional disability, and marginally higher pain catastrophizing compared to healthy controls. Of note, on average, the patient cohort endorsed moderate levels of pain catastrophizing, fear of pain, and disability, and patients also endorsed mild to severe levels of pain severity in the past week. Furthermore, there were no significant differences between groups in anxiety and depressive symptoms. At the time point of the study all patients with EAP and 27% of the healthy controls used hormonal contraceptives. The rest of the controls were naturally cycling women (in this group the day of menstrual cycle at the time of the scan visit and the length of menstrual cycle were also assessed, see Table 1). In general, patients had an average pain duration of over 3 years (36.55 months; *SD* ± 32.61) and the average number of painful days per month was 18.55 ± 11.77 days.

3.2. Functional connectivity results

Compared to healthy controls, patients with EAP showed significantly decreased resting-state functional connectivity between the right anterior insula and two clusters located in the right cerebellum (posterior lobe, crus I and crus II) and the left middle frontal gyrus (Table 2, Fig. 1). For the medial prefrontal cortex seed, the comparison between the two groups revealed no significant findings.

Additionally, correlation analysis revealed that in patients with EAP, the functional connectivity strength between the right anterior insula seed and the right cerebellum was positively correlated with the average pain intensity ($r = 0.65$, $p = 0.03$) (Fig. 2) but not with the other clinical and psychosocial factors (disease duration, pain catastrophizing, fear of pain, functional disability, anxiety and depression). Functional connectivity between the right anterior insula and middle frontal gyrus did not correlate significantly with these measures.

Independent of group differences, in patients with EAP, the functional connectivity of the right anterior insula showed negative correlation with fear of pain in the right superior frontal gyrus, and positive correlation with state anxiety in the left SMA, bilateral superior frontal gyrus and left middle frontal gyrus (Table 3, Fig. 3). The functional connectivity of the left medial prefrontal cortex demonstrated negative correlation with state anxiety in the left precuneus cortex, and positive correlation with state anxiety in the left cerebellum (Table 4, Fig. 4).

4. Discussion

This pilot study is the first, of our knowledge, to report brain alterations in adolescent and young women with EAP using resting-state fMRI. Here, we report two main findings. First, reduced right anterior insula connectivity was observed with the right cerebellum and left middle frontal gyrus/frontal pole in young women with EAP compared to healthy controls of similar age. Second, the functional connectivity pattern between the right anterior insula and cerebellum was associated with greater pain intensity in the patient group. These results indicate that functional brain changes connected to EAP are also present in a younger age group (13–21 years) and give further support for the involvement of CNS in endometriosis.

4.1. Decreased anterior insula - middle frontal gyrus functional connectivity in EAP

Evidence suggest that the anterior insula plays a pivotal role in acute and chronic pain, and mediates different aspects of pain [28]. As part of the salience network, this region detects and integrates information about salience and mediates goal-directed cognitive control [29,30]. Our results revealed that in patients with EAP the right anterior insula demonstrated decreased functional connectivity with the left middle frontal gyrus, a region shown to be implicated in both the dorsal and ventral attentional networks (top-down and bottom-up controlled attention, respectively) [31,32,33], and known to be affected in different pain conditions (including irritable bowel syndrome, fibromyalgia and migraine; [34,35,36]. Pain processing depends on bottom-up (e.g., stimulus intensity) and top-down effects (e.g., expectations). In the chronic pain state, these modulatory circuits seem to be disrupted contributing to the onset and maintenance of enhanced pain experience [37,38,39].

Of particular importance, decreased GMV was also observed in the left middle frontal gyrus in adult women with EAP [7] giving further support to the significance of this region in the development and maintenance of pain states in endometriosis. Crucially, the middle frontal gyrus is part of the dorsolateral prefrontal gyrus (DLPFC). Given that the DLPFC is generally associated with pain suppression and maintenance of pain inhibition [40,41,42], particularly the left side [43], it is reasonable to believe that the decreased connectivity between the middle frontal gyrus/DLPFC and the anterior insula may indicate altered pain modulation in EAP [44,41,45]. In line with this, the right anterior insula has a critical role in switching between network states (i.e., central executive network and default mode network), and it affects and projects to the central executive network, of which the DLPFC is a crucial part [46,47,48,45]. Altered connectivity between these networks is frequently reported in chronic pain conditions [49,9,50,51,52].

4.2. Decreased anterior insula – cerebellum functional connectivity in EAP

Patients with EAP also showed reduced right anterior insula connectivity with the right posterior cerebellum (particularly, crus I and crus II) compared to controls. Although the cerebellum is commonly activated during nociceptive processing and it seems to have a dominantly inhibitory role in pain modulation [53,54,55], studies also reported cerebellar activations during affective and aversive-sensory stimulation [56,57,58,59,60,61,62,63] leading to the proposed role of cerebellum in affective pain processing [64]. Notably, crus I and crus II (of lobule VII) could be a prominent cerebellar hub where emotional and cognitive information is gathered and sent to other brain regions [64]. Specifically, these cerebellar sub-regions have demonstrated overlapping activity between aversive emotional and painful heat stimulation [60], and they seem to be functionally coherent with the salience network [65].

Taken together, our observation could be interpreted that the anterior insula is disrupted in terms of integrating and modulating signals from pain-related regions due to its diminished functional connectivity. Similarly, reduction in functional connectivity related to dysregulated pain inhibition was also observed among patients with fibromyalgia (often considered the prototypical centralized pain disorder) [66,67] and patients with various chronic pain conditions [68].

4.3. Relationship between pain intensity and functional connectivity, differences in adult vs. adolescent women with EAP

We found that the connectivity strength of the right anterior insula with the cerebellum increased with self-report pain intensity suggesting a link between heightened pain experience and greater coupling of brain areas implicated in physical, affective and cognitive-evaluative

components of pain, and in the salience network [64,69,65,54,70]. In line with our results, previous studies have shown that greater activation in the anterior insula is related to the magnitude of painful stimuli rating [71,72,73], and this region is central for the subjective evaluation of internal conditions/body states, such as pain [69]. Although this finding could be attributed to the ongoing salient and painful sensations possibly underpinning central sensitization in patients with EAP, further studies with longitudinal design are needed to confirm whether this link between subjective pain intensity and changes in functional connectivity reflects either an adaptive mechanism or an atypical condition that predisposes young women to chronic pain.

Based on the present and previous results, we can conclude that brain changes related to the EAP may be represented differently in the developing brain. That is, in adult women increased anterior insula functional connectivity was found within regions of the medial prefrontal cortex (part of the default mode network) [8], while we found decreased connections with the middle frontal gyrus and cerebellum. Connectivity differences between adult and younger patients with complex regional pain syndrome have also been reported before [9,74] suggesting a potentially important age related and developmental difference of the underlying brain mechanisms and connections (especially in the frontal areas) [75,76], or it could relate to the different manifestations of the symptoms in younger women with EAP (e.g., lesions often present differently; both cyclic and non-cyclic pelvic pain is common in adolescents) [77,78]. During adolescence, repeated pain is likely accompanied by enhanced neuroplasticity in which networks of the brain, including those underlying pain processing, undergo significant development (for a review, see Ref. [79]. It should be noted that the central executive network is not fully developed until adulthood (maturation of the prefrontal cortex is fully accomplished around the age of 25 years [80,81]; suggesting that pain-related experiences might be dominated by emotionally-driven responses and the engagement of the salience network in a younger age group [76]. Recent evidence has also showed that in adolescent females (compared to adult women) pain-evoked activation was increased in limbic brain areas and in regions mainly involved in the bottom-up attentional mechanism and self-referential processing [82]. This imbalance in the brain development could play an important role in the bottom-up and top-down processing of pain suggesting a less effective top-down control system during adolescence (as compared to adulthood) [81]. Adolescents may process emotional distress and affective pain in similar areas of the brain. 'Social pain', the experience of pain resulting from interpersonal rejection or loss [83,84], relies on some of the same brain regions that process physical pain including the anterior insula. The anterior insula seems to be involved in the distressing experience and affective component of pain and could be associated with physical and mental health problems [85].

Lastly, independent of group differences, in patients with EAP, the functional connectivity of the right anterior insula showed positive correlation with state anxiety in the bilateral superior and left middle frontal gyrus, and in the left SMA. Besides the involvement of the middle frontal regions in pain (as discussed above), activation of the SMA is consistently reported during pain processing in healthy controls and patients with fibromyalgia [34,66,86,87,88], and it has been proposed that the SMA might be more involved in the affective function of pain [87]. In line with this, state anxiety was also related to enhanced functional connectivity between the left medial prefrontal cortex and left cerebellum (crus I and crus II) further supporting the cerebellar involvement in pain, and emotional and affective functions [64,60]. Interestingly, the connectivity of the left medial prefrontal cortex showed negative correlation with state anxiety in the left precuneus (components of the default mode network) indicating altered functional connections underlying attentional processes and emotional states in young patients with EAP [89,90].

Although in adult patients with EAP [8], functional connectivity was positively correlated with both clinical anxiety and depression, in our pilot study, patients did not show increased anxiety and depressive symptoms relative to controls but they did report higher levels of pain-related fear, catastrophizing, and functional disability, which could suggest an increased risk of developing mood disturbances later in life. Of note, fear of pain was associated with weakened functional connectivity of the anterior insula in the right superior frontal gyrus, implicating that pain-related fear may contribute to the diminished or ineffective pain inhibition in young women with EAP [91].

4.4. Limitations and future directions

First, since this was a pilot study, results must be interpreted cautiously due to the small sample size. Nevertheless, it seems that age-related alterations may occur with the endometriosis disease; however, future studies are needed to compare across different age groups (i.e., adolescents, young adults, and adult women with endometriosis). Second, while all patients used hormonal contraceptives, most of the healthy participants did not, and endogenous hormones may be potential mediators of brain states [92]. There does not seem to be consistency or consensus of what phase of the menstrual cycle is ideal for neuroimaging studies and adolescent participants may have variable cycle lengths [93,94,95] making it difficult to ascertain cycle phase by day alone; a confirmation hormonal assay would be ideal [96]. Third, we only assessed resting-state (task-free) functional connectivity differences between patients with EAP and controls. Future studies should aim to include endometriosis patients without pain and patients with other types of chronic pain. In addition, no studies have explored brain responses to painful or other stressful stimuli in women with EAP. For example, offset analgesia (OA) is an increasingly used method to measure inhibitory pain mechanism [97,98] and while previous studies do provide evidence for attenuated OA responses (i.e., a disproportionately large reduction in pain perception after a small decrease in temperature during noxious stimulation [99]; in patients with various chronic pain conditions, this is unknown in EAP [100].

5. Conclusion

Our results support that endometriosis-related pain is likely due to dysfunction in the CNS pain regulatory system, an area of investigation understudied in this population. Since most women report symptoms of endometriosis during adolescence, and there is a risk of chronification of pain, this would be a crucial time to intervene [101]. Also, studies need to further explore whether neural alterations are normalized by therapy or laparoscopic surgery. Detecting early "normalization" of atypical brain changes could be an important biomarker for predicting pain chronification, treatment response, and for developing centrally mediated treatments in endometriosis.

Funding

Research reported in this study was funded by an NIH R01 grant awarded to LS (R01HD083270). CBS and DB are funded by an Investigator Initiated Award – Partnering PI Option from the Department of Defense (W81XWH1910560).

Declaration of competing interest

The authors report no conflict of interest.

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