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Supplement

Methods

Anxiety symptom severity

To ascertain group differences in current anxiety symptoms, we administered the child- and parent-report versions of the Screen for Child Anxiety Related Emotional Disorders (SCARED) within one month of the task. The SCARED includes 41 items pertaining to anxiety-related symptoms or behaviors; each item is rated on a 3-point Likert-type scale (0=not true, 2=very true). The average of the child- and parent-reported SCARED total scores were used in analyses to reduce reporter discrepancies.

Thermal Calibration

Possible temperatures ranged from 34°C to 48°C (increments of 0.5°C). Participants rated subjective pain following each period of pain delivery using the FACES pain scale. For all participants, two initial temperatures of 34°C and 36°C were applied to the right arm to acclimate participants to the procedure. During the calibration, heat stimulation was applied to 4 skin sites over 18 trials. The first six trials were always

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34°C, 36°C, 38°C, 41°C, 44°C, and 47°C, which provided a linear rating by temperature curve. The three arm sites with the highest rating accuracy (lowest average residuals from curve) were used in the task.

Importantly, as noted in the main text, only 6 out of 64 subjects (9.4%) who started the task aborted, indicating relatively good tolerability of the pain stimulus among youth despite its aversiveness.

Task

After cue-contingency instruction and prior to the start of the task itself, we verified that participants understood the contingencies. This was done by having the participants complete a short training (24 trials) in which they used the computer mouse to identify whether a given shape predicts low or high pain; successful identification in at least 20 trials was required to proceed to the task.

The task design in terms of number of trials per combination of cue and temperature delivered is depicted in Table S1. Within each block, the order of trials was randomized.

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E-Prime (Psychology Software Tools, Sharpsburg, PA) was used to deliver visual stimuli and trigger stimulation.

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<thead>
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<th>Cue Temp.</th>
<th>Trials</th>
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<tbody>
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<tr>
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<tr>
<td></td>
<td>High Medium</td>
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*Instructed Reversal*

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<th>Trials</th>
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<td></td>
<td>Low High</td>
<td>2</td>
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**Table S1.** Experimental Design of the task, demonstrating block structure in terms of combinations of cue (low-pain, high-pain)

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and temperature delivered (low-pain, medium-pain, high-pain), and number of trials per combination.

Behavioral and psychophysiology data analysis

Pain anticipation. Analyses of participants’ ratings of expected pain level following each cue tested for Cue\times Group interactions on participants’ pre-reversal ratings, with Cue (Original High Cue, Original Low Cue) as a within-subject factor and Group (Anxious, Healthy) as a between-subjects factor.

Pain experience. Additional analyses examined the Trial Type\times Group interaction within just the medium-heat trials with Trial Type (LM, HM) as a within-subject factor and Group (Anxious, Healthy) as a between-subjects factor.

Instructed reversal. Our primary aim was to test for associations among anxiety, pain anticipation, and experience. A secondary aim was to examine whether anxiety moderates updating of cue contingencies following instructed reversal. This is potentially relevant to exposure therapy, which includes explicit elements designed to target threat-association updating\(^6,7\). We hypothesized that youth with anxiety would update

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responses more slowly than healthy youth following instructed cue-contingency reversal. Analyses of participants’ ratings of expected pain levels following each cue tested for Cue×Phase×Group interactions on participants’ ratings, with Cue (Original High Cue, Original Low Cue) and Phase (Pre-Reversal, Post-Reversal) as within-subject factors and Group (Anxious, Healthy) as a between-subjects factor.

Analyses of participants’ anticipatory SCR by reversal phase tested the Cue×Phase×Group interactions on SCR. Analyses of participants’ response to heat pain by reversal phase tested the Trial Type×Phase×Group interactions on SCR and on pain ratings.

In addition to these analyses, we also conducted a series of exploratory analyses to delineate more specific effects of reversal on anticipatory biasing of heat experience, to comprehensively inform future studies focusing on this specific aspect of the study. These analyses tested the anticipatory effect specifically on the medium-heat trials, testing the Cue×Phase×Group interactions on participants’ SCR to the heat, with Cue (Original High Cue, Original Low Cue) and Phase (Pre-Reversal, Post-Reversal) as within-subject factors and Group

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(Anxious, Healthy) as a between-subjects factor. Additional exploratory analyses tested for the effect of instructed vs. experienced reversal on anticipatory responding. This was carried out by testing the Group×Cue×Phase interaction on anticipatory SCR during the trials immediately before and after the experienced reversal (i.e., block 5 vs. block 7), but following the instructed reversal, with Cue (Original High-Pain Cue, Original Low-Pain Cue) and Experience (Pre Experienced Reversal, Post Experienced Reversal) as within-subject factors and Group (Anxious, Healthy) as a between-subjects factor. We also tested for the effect of reinforcement on anticipatory biasing on response to heat by testing the Group×Cue×Phase interaction on SCR to medium heat in the blocks before and after the experienced reversal (i.e., block 5 vs. block 7) but following the instructed reversal.

Analyses on psychophysiology and ratings were carried out using multilevel linear mixed-effects models implemented in R (lme4 package⁸), with subject as a random intercept. Significant interactions were followed up by lower-order tests using the testinteractions function (phia package⁹).
Imaging data processing and analysis

MRI scans were acquired on a 3-Tesla MR750 GE scanner with a 32-channel head coil at the National Institute of Mental Health Functional Magnetic Resonance Imaging Core Facility. Participants completed a T1-weighted magnetization-prepared rapid conditioning gradient-echo scan (MPRAGE) with the following parameters: 176 slices; 256x256 matrix; 1mm³ isotropic voxels; flip angle = 7°; repetition time (TR) = 8.1ms, echo time (TE) = 3.58ms.

The number of days separating the MRI scan visit and the threat anticipation task visit varied considerably (MED = 103 days, SD = 111). This reflects the challenges of research in youth, whereby some participants had to wait until their orthodontic braces were removed before scanning, and some families had limited availability for participating in multiple research visits. For patients with delays of more than a month, diagnostic status was reconfirmed prior to testing. To account for variability due to this factor, all analyses testing for associations between brain structure and task measures were

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Repeated while covarying the number of days between visits.

Findings did not change when this covariate was included in models.

**Image Processing.** To facilitate reproducibility, we are including the imaging analysis pipeline, including commands and references to documentation, at the end of this document.

Scans were processed using FreeSurfer’s ‘recon-all’ function (version 6.0.0; [http://surfer.nmr.mgh.harvard.edu/](http://surfer.nmr.mgh.harvard.edu/)) and then visually inspected. Surface-based analysis followed methodology described in prior work. T1-weighted images were corrected for magnetic field inhomogeneities, affine-registered to the Talairach-Tournoux atlas, and then skull-stripped. Location, intensity, and intensities of neighboring voxels were used to identify white matter. A mesh of triangular faces was constructed using two triangles for each exposed voxel face, which was then smoothed based on local intensity in the original images using trilinear interpolation. Next, we ran a second smoothing iteration, which resulted in a representation of gray-white matter interface. The external cortical surface was produced by identifying a point where tissue contrast is
maximal, maintaining constraints on smoothness and possibility of self-intersection\textsuperscript{10}.

The subcortical volume-based processing stream is designed to automatically preprocess MRI volumes and label subcortical tissue classes\textsuperscript{14,15}. First, images were affine-registered to the MNI305 space. Then, initial volumetric labeling was conducted and variation in intensity due to the B1 bias field was corrected. Finally, a nonlinear volumetric alignment to the MNI305 atlas was performed, and structures were labeled. These structures included bilateral cerebellum, amygdala, hippocampus, thalamus, caudate, putamen, pallidum, and nucleus accumbens, as well as midbrain. Permutations tests corrected for the number of structures tested (see below).

Bias-corrected images from FreeSurfer were segmented into gray matter, white matter, and cerebrospinal fluid using the FAST module of FSL. The outputs of FAST are images with voxel values corresponding to the proportion of the volume of the voxel that is occupied by each of these tissue classes\textsuperscript{16}. We tested for effects on gray matter volume and on total volume.

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**Analysis.** PALM (Permutation Analysis of Linear Models\(^ {17}\)) software was used to conduct permutation tests based on 2000 permutations, using an approximation to the tail of the permutation distribution of the maximum statistic using a generalized Pareto distribution\(^ {18}\). Analyses included global whole-brain estimates as nuisance variables, as recommended in previous work\(^ {19,20}\). Subcortical volumes analyses controlled for total intracranial volume, while cortical analyses controlled for global average thickness. Whole-brain cortical analyses utilized a mask that allowed us to use only the vertices that are represented in the cortex, masking out a sub-callosal region of each hemisphere. ROI-based cortical analyses used a mask that only included vertices where cortical thickness was found to be inversely associated with anticipatory physiological responses in previous work\(^ {20}\). None of the participants in the current study took part in this previous study.

As mentioned in the main text, additional exploratory analyses were conducted to further investigate the relationship between pain tolerance and the psychophysiological response to pain as they relate to brain structure. Pain tolerance was defined as the temperature corresponding to a reported pain
Thermal Calibration

All participants underwent a calibration procedure prior to the task, as reported in the main text. Healthy and anxious groups did not differ in mean temperature (degrees Celsius) corresponding to low pain (level 2; M[SD] = 38.20 [2.12] and M[SD] = 37.2 [2.51], respectively), medium pain (level 5; M[SD] = 42.32 [1.86] and M[SD] = 40.90 [2.89], respectively), or high pain (level 8; M[SD] = 46.28 [2.30] and M[SD] = 45.58 [2.11], respectively), or in reliability of the temperature-pain

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relationship (R²; M[SD] = 0.72 [0.13] and M[SD] = 0.75 [0.14], respectively), all ps>0.05 (corrected).

Pain anticipation

Expectancy Ratings. We tested the Cue×Group interaction on pre-reversal expectancy ratings. We observed a significant main effect of Cue, F₁,₄₄₈=2091.96, p<0.001, such that participants expected more pain following the High-Pain Cue than the Low-Pain Cue (see Fig. S1). No other effects were observed.

Pain experience

Psychophysiological response. As noted in the main text, there was a non-significant, trend-level main effect of Group, suggesting that anxiety patients tended to generally respond more to the heat than healthy participants. Since the groups significantly differed in anticipatory response to the cues preceding the heat, we repeated this analysis while controlling for the magnitude of anticipatory responding (by covarying the SCR to the cue preceding heat delivery). Controlling for anticipatory responding further diminished the difference between the groups, F₁,₄₇=2.51, p=0.12, suggesting that a trend

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for higher psychophysiological response to the heat in anxious patients was dependent on their anticipatory response. No other effects on SCR were observed.

In an exploratory analysis on SCR to the medium heat only, we observed a significant main effect of Cue, $F_{1,748}=18.16$, $p<0.001$, showing that participants across groups responded more to the same level of heat when it followed the high-pain cue than when it followed the low-pain cue. We also observed a significant effect of Group in this analysis, $F_{1,48}=4.26$, $p=0.044$. As before, when controlling for the magnitude of anticipatory responding, the effect of Group was no longer significant, $F_{1,47}=2.42$, $p=0.13$.

Instructed Reversal

Cue-based pain anticipation. Mean pain expectancy ratings by cue, group, and phase are shown in Fig. S1. We observed a significant main effect of Cue on expectancy ratings, $F_{1,944}=10.60$, $p=0.001$, such that participants expected more pain following the High-Pain Cue than the Low-Pain Cue throughout the task. This main effect was qualified by a significant Cue×Phase

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interaction, $F_{1,944}=3276.92$, $p<0.001$. Follow-up tests indicate that participants expected a higher level of pain following the high-pain cue than the low-pain cue before reversal, $b=4.72$, $p<0.001$, and reversed this pattern following instruction, $b=4.21$, $p<0.001$, indicating successful updating of expectations. No other effects were observed.

![Pain Expectancy Ratings](image)

**Figure S1.** Pain expectancy ratings. (A) Participants’ mean expected pain ratings by Cue (Low-Pain, High-Pain) and Group (Healthy, Anxious) before (A) and after (B) instructed reversal.

*Note:* Error bars denote one standard error of the mean. ***, $p<0.001$. 
Mean SCR by cue, group, and phase is presented in Fig. S2. We noted a significant Phase×Cue interaction on anticipatory psychophysiological response to the cues, $F_{1,3344}=83.26, p<0.001$. Follow-up tests indicated that participants showed higher SCR to the high-pain cue than to the low-pain cue before reversal, $b=0.33, p<0.001$, and reversed this pattern following instruction, $b=0.18, p<0.001$, indicating successful reversal of anticipatory responding. This effect was qualified by a significant three-way Cue×Phase×Group interaction, $F_{1,3344}=7.18, p=0.007$; whereas before reversal, anticipatory response to cues differed by group (see main text), following reversal, patterns of response to cues did not differ by group, $p=0.34$, with both groups showing comparable reversal of anticipatory responses, $ps<0.05$. In addition, we found a significant Phase×Group interaction, $F_{1,3344}=5.81, b=0.13, p=0.016$, such that patients showed higher responses prior relative to after reversal, $b=0.13, p=0.002$, whereas healthy participants did not respond differently between phases, $p=0.93$. There was also a significant main effect of Group, $F_{1,48}=5.21, p=0.027$, such that anxious participants responded more overall than healthy participants. There was also a main effect of Cue, $F_{1,3344}=6.97, p=0.008$, such

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that all participants responded more to the high-pain cue relative to the low-pain cue across the task. Finally, there was also a main effect of Phase, $F_{1,3344}=5.21$, $p=0.023$, such that participants showed higher responses before relative to after reversal.

**Figure S2. Instructed reversal effects on skin conductance response to cues.** (A) Participants’ mean skin conductance response by Cue (Low-Pain, High-Pain) and Group (Healthy, Anxious) before (A) and after (B) instructed reversal.

*Note: Error bars denote one standard error of the mean. *, $p<0.05$, **, $p<0.01$, ***, $p<0.001$.*

**Anticipatory modulation of pain experience.** Mean SCR to the
We observed a significant Trial Type×Phase interaction on SCR to the heat, $F_{3,3336}=4.22$, $p=0.005$. While pairwise tests between all Trial Types were significant before the reversal (see main text), follow-up tests indicate that after instructed reversal, participants no longer showed differential responses in LL and LM trials, ($p=0.79$, corrected). Pairwise tests between all other combinations of Trial Types after the reversal were significant ($bs>0.22$, $ps<0.005$, corrected), showing the overall pattern of $HH>HM>LM=LL$. There was also a significant effect of Group on SCR, $F_{1,48}=4.24$, $p=0.045$. As before, when we controlled for the magnitude of anticipatory responding (by covarying the SCR to the cue preceding heat delivery), the main effect of group was no longer significant, $F_{1,48}=3.29$, $p=0.08$.

Mean pain ratings by trial type, group, and phase, are presented in Fig. S3B. We noted a significant Trial Type×Phase interaction, $F_{3,3336}=8.54$, $p<0.001$. Follow-up pairwise tests between all trial types within each phase were all significant, $bs>1.15$, $ps<0.001$, indicating successful reversal of anticipatory modulation of pain experience. In addition, there was a main effect of Trial Type, $F_{3,3336}=2741.08$, $p<0.001$. Follow-

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Follow-up pairwise tests between all combinations of trial types were significant (ps<0.001, corrected) and followed the pattern HH>HM>LM>LL. We also observed a Trial Type×Group interaction, $F_{3,3336}=7.34$, $p<0.001$. However, follow-up tests comparing the groups within each trial type showed no significant effects (ps>0.58). No other effects were observed.

Of note, we did not observe significant main effects of Phase on SCR or pain ratings, ps>0.05, indicating no habituation to the heat stimulus over time.

### Instructed Reversal Effects on Response to Pain

#### A. Skin Conductance Response

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<tr>
<td><strong>Anxious</strong></td>
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#### B. Self-Reported Pain

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**Figure S3.** (A) Participants’ mean skin conductance response to the heat by Trial Type (HH, HM, LM, LL) and Group (Healthy, Anxious) before reversal (left) and after reversal (right); (B) Participants’ mean pain ratings of the heat by Trial Type (HH, HM, LM, LL) and Group (Healthy, Anxious) before reversal (left) and after reversal (right).

*Note:* Error bars denote one standard error of the mean.

***, p<0.001 (Bonferroni corrected). HH= High-Pain Cue + High-Pain Temperature, HM= High-Pain Cue + Medium-Pain Temperature, LM= Low-Pain Cue + Medium-Pain Temperature, LL= Low-Pain Cue + Low-Pain Temperature.

**Exploratory analyses: immediate effects of instructed reversal.** For completeness, we also report on exploratory analyses that examined immediate effects of instructed reversal on anticipatory responding, prior to experiencing the reversed contingencies, by testing the Cue×Phase×Group interaction on anticipatory SCR in trials in the blocks immediately before and after the instructed reversal. We observed a significant Phase×Cue interaction on anticipatory psychophysiological response, $F_{1,744}=10.74$, $p=0.001$, with participants successfully
reversing their anticipatory response to the cues, showing higher SCR to the original safety (now threat) cue than to the original threat (now safety) cue, $b=0.28, p<0.001$. This effect was not moderated by group, $p=0.51$.

We also tested for immediate effects of instructed reversal on anticipatory modulation of mildly aversive heat by testing the Cue×Phase×Group interaction on SCR to medium heat in the blocks immediately before and after the instructed reversal. A similar effect was noted on immediate effects of reversal. We observed a significant Phase×Cue interaction on participants’ SCR to the medium-level heat, $F_{1,744}=14.29, p<0.001$. Follow-up tests indicate that, prior to reversal, participants responded more to the medium-level heat when it came after the High-Pain Cue than when it came after the Low-Pain Cue ($b=0.19, p=0.03$), and this pattern reversed after the reversal ($b=0.28, p=0.003$), indicating immediate reversal of anticipatory modulation of pain experience. This effect did not differ between groups (Phase×Cue×Group interaction: $F_{1,744}=0.42, p=0.52$). No other effects were observed.

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**Exploratory analyses: effects of experienced reversal**

We found a significant Cue×Phase×Group interaction on participants’ SCR to the cue in the blocks before and after reinforcement of the reversal, $F_{1,746}=4.49$, $p=0.034$. Follow-up tests indicate that, prior to reinforcement, responses to the Cues did not differ by Group, $b=0.01$, $p=0.95$, and both healthy and anxious participants showed a significant difference in their anticipatory response to each cue ($b=0.28$, $p=0.007$, and $b=0.27$, $p=0.009$, respectively). Following reinforcement, there was a significant Cue×Group interaction, $b=0.44$, $p=0.003$; follow-up analyses, however, showed that both anxious participants ($b=0.23$, $p=0.03$) and healthy participants ($b=0.21$, $p=0.05$) still showed a significant difference in their response to each cue.

In addition to the three-way interaction, we also observed a significant Cue×Phase interaction, $F_{1,746}=10.75$, $p=0.001$. While participants showed a significant difference overall in response to the cues prior to reinforcement ($b=0.28$, $p<0.001$), this difference was no longer significant after reinforcement, $b=0.02$, $p=0.88$. Additionally, we noted a significant Group×Phase interaction, $F_{1,745}=4.86$, $p=0.028$. Follow-up tests indicate that
while there was no significant effect of Group prior to reinforcement \((b=0.28, p=0.08)\), anxious participants responded more to the cues overall than healthy participants following reinforcement \((b=0.38, p=0.035)\). We also noted a Group\(\times\)Cue interaction, \(F_{1,748}=8.52, p=0.004\). Follow-up tests indicated that while anxious participants showed differential response to the cues overall \((b=0.25, p=0.001)\), healthy participants did not \((b=0.04, p=0.61)\). We also noted a significant main-effect of Group, \(F_{1,86}=11.46, p=0.001\), such that anxious participants responded more overall than healthy participants. No other effects were observed.

When testing the effect of reinforcement on participants’ response following the medium heat trials, we found a main effect of Group, \(F_{1,90}=5.07, p=0.027\), such that anxious participants responded more to the medium heat overall compared to healthy participants. We also found a main effect of Phase, such that participants responded more overall to the medium heat before reinforcement than after, \(F_{1,745}=5.69, p=0.017\). No other effects were observed.
Brain imaging

Additional exploratory analyses examined links between brain structure, psychophysiological response to pain, and individual pain tolerance. Psychophysiological response to pain was positively correlated with pain tolerance, $r(39)=0.46$, $p=0.003$. The main text reported an association between left posterior insula and SCR to heat. When accounting for participants’ pain tolerance, no clusters demonstrated this association, suggesting that pain tolerance plays a role in the association between insula structure and response to pain.

Analyses testing for associations between brain structure and pain tolerance did not reveal significant clusters. However, when controlling for SCR to pain, a cluster in the right somatosensory cortex emerged (Fig S3; peak: $p=6.6\times10^{-6}$, 82 vertices), such that decreased thickness in this region predicted a higher pain tolerance.

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**Figure S3. Brain structure correlates of pain tolerance.** A right-hemisphere cluster depicting a significant negative association between cortical thickness and pain tolerance (level-8 temperature determined during pre-task calibration procedure), when controlling for mean skin conductance response to delivered heat (during the task).

*Note:* Results are for a whole-brain analysis using a cluster-forming threshold of $p=0.005$ and a cluster-extent threshold of $p_{FWE}=0.05$. Colors reflect $p_{FWE}$ of the cluster.

In addition, we examined whether thickness in the dLPC ROI was associated with severity of anxiety symptoms as assessed by the

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SCARED. To this end, we calculated the mean thickness within the ROI by participant and calculated a partial correlation between thickness and total SCARED scores, while controlling for mean global thickness (as in the primary analyses). This correlation was not significant, \( r(38)=0.20, p=0.22 \), suggesting that the association between SCR in anticipation of the painful stimulus and DLPFC thickness is unrelated to severity of anxiety symptoms.

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**Analysis pipeline for imaging data**

1. Run FreeSurfer for each participant to align, register, and segment the brain images:
   ```bash
   recon-all -subjid subj -i output/subj.nii.gz -all
   ```
3. Run `mris_preproc` to smooth and put all participants in the same common grid for between-subject comparisons:
   ```bash
   e.g.: mris_preproc subj --hemi rh --meas thickness -out rh.thickness.mrispreproc.mgh --nocleanup --fwhm-src 20 --target fsaverage5
   ```
4. Merge hemispheres to allow multiple testing correction across both hemispheres (bh):
   ```bash
   palm_hemimerge lh* rh* (documentation: https://github.com/andersonwinkler/PALM/blob/master/palm_hemimerge.m)
   ```
5. Extract volumes of subcortical structures from the outputs of FreeSurfer:

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```
6. Compute the amount of gray matter within each subcortical structure, using asegpve, which in turn uses FSL FAST for segmentation into GM/WM/CSF:

   asegpve -s subj (documentation: https://github.com/andersonwinkler/toolbox/blob/master/bin/asegpve)

7. Prepare design matrices and contrast files for PALM analysis.
While this could have been accomplished manually, a MATLAB script was created:
```
% Load the demographic variables
D = strcsvread(fullfile(rootdir,'derivatives','demographics_MRI.csv'));

% Get the SCR variables, save
SCR_Cue_Mean = cell2mat(D(2:end,strcmp(D(1,:), 'SCR_Cue_Mean')));
SCR_Heat_Mean = cell2mat(D(2:end,strcmp(D(1,:), 'SCR_Heat_Mean')));
csvwrite(fullfile(palmdir,'SCR_Cue_Mean.csv'),SCR_Cue_Mean);
csvwrite(fullfile(palmdir,'SCR_Heat_Mean.csv'),SCR_Heat_Mean);

% Get age and center
age = cell2mat(D(2:end,strcmp(D(1,:), 'Age')));
age = bsxfun(@minus,age,mean(age));

% Get the diagnostic group (0 is HV, 1 is ANX) and center
dx = D(2:end,strcmp(D(1,:), 'Dx'));
dx = cell2mat(dx);
```

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```matlab
dx = bsxfun(@minus,dx,mean(dx));

% Get the sexes and center
sex = D(2:end,strcmp(D(1,:),'Sex'));
sex = cell2mat(sex);
sex = bsxfun(@minus,sex,mean(sex));

% Create an intercept and a dummy
I = ones(size(age));
dummy = I*9999;

% Load the global variables
G = strcsvread(fullfile(rootdir,'derivatives','globals.csv'));
Globals = cell(3,1);
Globals(1) = cell2mat(G(2:end,strcmp(G(1,:),'bh.MeanThickness')));
Globals(2) = cell2mat(G(2:end,strcmp(G(1,:),'EstimatedTotalIntraCranialVol')))/1e6;
Global_names = ('globalthk','globalicv');

% Subcortical imaging data:
Img = ('avggm', 'vols');
for i = 1:numel(Img)
    img = load(fullfile(rootdir,'palm',sprintf('aseg19rois_%s.cvs',Img(i))));
    csvwrite(fullfile(palmdir,sprintf('%s.csv',Img(i))),img);
    csvwrite(fullfile(palmdir,sprintf('%s.dx.csv',Img(i))),img.*dx);
end
mask = ones(1,size(img,2));
csvwrite(fullfile(palmdir,'mask.csv'),mask);

% Cortical imaging data:
Img = ('thickness');
for i = 1:numel(Img)
    x = palm_miscread(fullfile(rootdir,'palm',sprintf('bh.%s.mgz',Img(i))));
```

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```matlab
img = permute(x.data,[4 1 2 3]);
x.data = permute(img,[2 3 4 1]); x.filename = fullfile(palmdir,sprintf('bh.%s',Img(i)));
palm_miscwrite(x,false);
    x.data = permute(img.*dx,[2 3 4 1]); x.filename = fullfile(palmdir,sprintf('bh.%s.dx',Img(i)));
palm_miscwrite(x,false);
end

% Compute the average area per vertex, to be used for spatial statistics
x = palm_miscread(fullfile(rootdir,'palm','bh.area.mgz'));
x.data = mean(x.data,4);
x.filename = fullfile(palmdir,'bh.avg_area_per_vertex');
palm_miscwrite(x,false);

% Create the designs
M = [I ... % intercept (1)
dummy ... % imaging data (2)
age ... % age (3)
dx ... % dx (group) (4)
sex ... % sex (5)
dummy]; % img*dx (7)
csvwrite(fullfile(palmdir,'design_not_including_global.csv'),M)
for g = 1:numel(Globals)
csvwrite(fullfile(palmdir,sprintf('design_%s.csv',Global_names(g))),horzcat(M,Globals(g)))
end

% Create the contrast files (6 columns)
C = [...
    0 +1 0 0 0 0;
    0 -1 0 0 0 0;
    0 0 0 0 +1;
    0 0 0 0 -1]
csvwrite(fullfile(palmdir,'contrasts_not_including_global.csv'),C);
C = horzcat(C,zeros(size(C,1),1));
csvwrite(fullfile(palmdir,'contrasts_withglobal.csv'),C);
```

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8. Run PALM (documentation: https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/PALM):

   PALM -i predicted_var.csv -d
design_incl_global_globalthickness.csv -t
contrasts_incl_global.csv -evperdat bh.thickness.mgz 2 1 -
evperdat bh.thickness.dx.mgz 6 1 -m
bh.FS.ic5.aparc.mask.dpv -s bh.white.srf
bh.avg_area_per_vertex.mgz -C 2.58 -designperinput -logp -
nouncorrected -approx tail -n 2000

9. Split output files in merged hemispheres format into left and right hemispheres:

   palm_hemisplit bh* (documentation: https://github.com/andersonwinkler/PALM/blob/master/palm_hemisplit.m)

10. Figures were generated by hand using Surf Ice:

    https://www.nitrc.org/projects/surfice/

References


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