fMRI-based machine learning analysis of neural substrates of pediatric anxiety: Temporal Pole and emotional face-responses.

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Abstract

A prominent cognitive aspect of anxiety is dysregulation of emotional interpretation of facial expressions, associated with neural activity from the amygdala and prefrontal cortex. We report machine learning analysis of fMRI results supporting a key role for a third area, the temporal pole (TP) for childhood anxiety in this context. This finding is based on differential fMRI responses to emotional faces (e.g., angry versus fearful faces) in children with one or more of generalized anxiety, separation anxiety, and social phobia (n = 22) compared with matched controls (n = 23). In our machine learning model, the right TP distinguished anxious from control children (accuracy = 81%). Involvement of the TP as significant for neurocognitive aspects of pediatric anxiety is a novel finding worthy of further investigation.

Keywords — Pediatric anxiety, Task-based fMRI analysis, Temporal pole, Facial emotional processing

Introduction

Clinical anxiety is associated with inability to control or autoregulate one’s autonomic response and is the most common mental illness among children and young adults (ages
18–40\textsuperscript{2}, with a lifetime prevalence rate of 28.8\%\textsuperscript{3,4}. The median age onset for all anxiety disorders, at 11 years old, marks this as the earliest among all psychiatric disorders\textsuperscript{5} and over 30\% of pediatric cases meet criteria for two or more subtypes\textsuperscript{2}. Despite high prevalence and possible early onset, these disorders are often under-reported because of conflation of normal developmental-behavioral patterns with anxiety symptoms. Assessment is typically limited to diagnostic interviews and questionnaires to produce a diagnostic label, which comes with its own validity issues\textsuperscript{3,4,6}. Anxiety and related symptoms may have profound effects on neurological functioning in a child’s rapidly developing brain\textsuperscript{7} and, over extended periods of time, may lead to cognitive, social, and emotional deficit\textsuperscript{4}. For example, adolescents with high trait anxiety exhibit an attentional bias (i.e., pay greater attention) to negatively valenced faces\textsuperscript{8,9}. Although socio-emotional circuits in the brain have been implicated in numerous psychiatric disorders, including anxiety\textsuperscript{10}, such cognitive deficits have rarely been used as an indication of brain mechanisms underlying psychopathology.

Cognitive models of anxiety suggest that negative biases exist for performance on information-processing task\textsuperscript{11} — in particular, anxious individuals allocate greater attention to negative or threatening stimuli\textsuperscript{5} and may find threatening words more salient and remember them more often than non-threatening words\textsuperscript{9,12}. Emotional facial expressions are often perceived as more negative or threatening (even if they are typically judged as neutral), and this is associated with activation of affective brain circuits\textsuperscript{8,14}. These attentional and perceptual biases are thought to be an important feature underlying the etiology of anxiety disorders, a view supported by functional neuroimaging studies. Despite the likely clinical significance of these biases, few studies have focused on the adolescent population during a facial emotional processing task\textsuperscript{15–17}, and rarely have machine learning methods been applied to assess if neural signatures underlying such biases may be used to identify individual children suffering from anxiety.

Functional neuroimaging measurements during facial processing tasks have helped reveal neurological underpinnings of emotional regulation. Overall, there is evidence of dysregulated fear-circuitry related regions, including the amygdala and prefrontal cortex (PFC)\textsuperscript{18}. Children with panic disorder (PD) or generalized anxiety disorder (GAD) may exhibit exaggerated amygdala responses to fearful faces, compared to non-anxious or depressed children\textsuperscript{18}. In adults, hyperactivity has been observed in several limbic brain regions in separation anxiety disorder (SAD) patients when responding to fearful faces, including the fusiform gyrus (associated with facial recognition), and there is evidence of increased connectivity between the fusiform gyrus and amygdala, as well as the fusiform gyrus and superior temporal sulcus\textsuperscript{20}. Also, abnormal neural responses to emotional faces have been reported for adults with GAD, PD and SAD, with greater right amygdala activation reported in response to fearful versus happy faces\textsuperscript{21}. From these studies, similar amygdala activation patterns to happy faces were reported for both patients and controls, indicating that this area is also responsive to positively valenced facial expressions. Increased responses in the superior temporal sulcus, an important area for deriving social and emotional information, were observed for SAD and PD patients viewing fearful faces. The findings mentioned above have focused mainly on between group differences or similarities. In recent years, advanced data analysis methods such as machine learning, have enabled accurate prediction on an individual basis\textsuperscript{22}. This approach holds the potential to enable improvement of clinical decision making (such as diagnostic assessments), and
Fig. 1: Processing pipeline for the primary analysis. Voxels from 959 Talairach regions were individually trained on a super learner (SL) classifier to determine which regions could best distinguish between anxious and non-anxious children. The SL included a nested cross-validation process to hypertune parameters for an AdaBoost model. The region with the highest average accuracy was selected for our analysis. Note: each time produced its own prediction; we labeled each person with the majority vote over the time points for that subject.

to provide evidence-based determination of which brain regions display the largest differences between individuals in different classes (e.g., diagnosis cases vs. no-diagnosis), based on fMRI data, while the participants perform passive or active tasks. In this study, we explore whether machine learning analysis of data in the facial recognition paradigm, may allow us to identify, with higher precision, which children will suffer from anxiety.

Conventional neuroimaging analysis of two different populations (i.e., anxious versus non-anxious) involves comparing neural activation of various regions between the groups, anticipating that comparing the blood oxygenation level-dependent response (BOLD) at specific voxels will show significant differences. However, this analysis mainly focuses on univariate and group-level statistics and may not lead to predictions for individual cases, due to the overlap of neural responses at any given voxel. Multivoxel pattern classification (MVPA) applies machine learning algorithms to fMRI BOLD signals to produce predictive models. These models can categorize brain patterns into distinct stimulus conditions (i.e., emotional faces) or groups based on spatial and temporal discriminative neural signatures from high dimensional neuroimaging data. This analysis can also reveal which brain regions differ the most between two groups or stimulus conditions. Neural signatures can be further clarified with advanced alignment techniques such as a probabilistic shared response model (SRM), aligning patterns of neural responses across subjects into a common, lower-dimensional space. Here, we demonstrate that MVPA can be used to decode brain patterns related to the disease state of adolescent children. MVPA may also indicate which brain regions are
Fig. 2: Preprocessing pipeline for negative stimuli analysis. Voxels from the selected region (from the primary analysis) were used to predict the stimulus label for each timepoint (fear versus anger). We used a probabilistic shared response model (SRM) to transform all functional images into a shared common space. Thereafter, a linear SVM was trained on the functionally aligned data, which were used to predict a facial stimulus for each time point, for each subject. Model metrics include mean accuracy and standard error from 5-fold CV.

Key aspects for altered functional connectivity in anxious children in this context.

Using a publicly available dataset [https://openneuro.org/datasets/ds000144](https://openneuro.org/datasets/ds000144) comprising task-based fMRI data from children with anxiety disorders such as SAD, SP and GAD: (1) We applied a data driven approach to determine a combination of brain regions to distinguish anxious versus non-anxious children with above chance accuracy based on facial-emotional processing. (2) We examined neural correlates of angry and fearful faces to distinguish those stimuli using similar techniques. Figures 1 and 2 illustrate the analysis pipeline for these research questions (refer to the online methods for a full description of the study).

Our approach is based on task-based fMRI data, rather than resting-state MRI. A key question is whether task-based fMRI derived regions can be linked to various resting-state networks in this context. Many reports indicate that a functional imbalance in large scale networks, such as the default mode network (DMN), the salience network, or the affective network, play a crucial role in anxiety disorders. However, we found that intrinsic resting-state network activity may not differ significantly from task evoked responses, in accordance with several sources suggesting that task-based responses are related to modest changes compared to intrinsic activity. If certain regions arise as significant predictors of childhood anxiety using machine learning analysis for the task-based approach, it will be important to compare them with components of resting-state networks previously associated with anxiety.
Research has not yet established a clear link between brain-behavioral function and clinical diagnosis in children, which is problematic. The hope is that, research into developmental psychopathology will bridge the gap between psychiatric practice and neuroscience. Our current approach may enable us to relate functional brain measures to pediatric diagnoses in anxiety disorders and may also help to generate new therapeutic insights.

To date, we are not aware of published attempts to use machine learning to validate psychiatric disorders in young children (in this case 5-10 years old) using task-based fMRI data. We propose that distinguishable neural substrates in anxious vs. non-anxious children can be identified with our machine learning approach to task-based paradigm fMRI analysis, for individual predictions on a case by case basis.

Results

Clinical and demographic statistical analysis

Table 1 shows the demographic and clinical data from the 22 anxious and 23 non-anxious children in our sample, including comorbidities and overlap between various anxiety disorders. Note, we compare non-anxious subjects against each of the anxious groups. When testing for group difference in age, a two-tailed t-test revealed a significant difference between the anxious and non-anxious group ($t_{(43)} = 2.03, p < 0.05$) and the SP cohort ($t_{(32)} = 2.36, p < 0.02$). When measuring functional impairment and diagnosis, the anxious groups differed significantly from the non-anxious group ($p < 0.005$). No statistical differences were found when comparing sex, ethnicity, handedness, IQ, or socioeconomic status between any of the groups.

Anxious versus non-anxious classification analysis

Machine Learning analysis

Using the Talairach atlas (2mm), we segmented the brain into 959 regions, then applied a super learner (SL) to each individual region to determine which returned the best mean accuracy. Here, the SL used nested cross validation (CV) (5-CV on the outer and inner loop) to partition and fine tune hyper-parameters. Our SL used AdaBoost (logistic regression as a base estimator) to model the neural signatures. Figure illustrates the machine learning pipeline for this section. Talairich region #41 (MNI: $x = 40, y = 11, z = -35$) (Right temporal pole, right Cerebrum, Superior Temporal Gyrus, Brodmann area #38) returned the highest accuracy with 81% (STE +/- 1.46%). When examining differences between other top regions, the accuracy of Region #41 was not statistically different than region #664 (MNI: $x = 10, y = -50, z = 20$) (Right cerebrum, Limbic lobe. Posterior cingulate white matter) ($t_{(21)} = 0.16, p = 0.87$) or Region #720 (MNI: $x = -52, y = -19, z = 7$) (Left Cerebrum, Transverse temporal gyrus, Brodmann area 38) ($t_{(21)} = 0.18, p = 0.85$).
Table 1: A summary table of demographic and clinical symptom scores of participants. The 3 anxiety groups are not mutually exclusive. Mean values and standard deviations are reported for all 4 groups. Significant difference from non-anxious children at \( ^*p < 0.05, ^{**}p < 0.005 \).

| Demographics       | Non-anxious (N=23) | Anxious (N=22) | Generalized Anxiety (N=15) | Separation Anxiety (N=10) | Social Phobia (N=11) |
|--------------------|--------------------|----------------|---------------------------|--------------------------|----------------------|
| Age at scan        | 7.48 (1.04)        | 6.86 (0.99)    | 6.86 (1.06)               | 7.00 (1.33)              | 6.63 (0.81)          |
| Female             | 13                 | 16             | 12                        | 7                        | 8                    |
| Ethnicity          | 12                 | 10             | 8                         | 6                        | 3                    |
| Below poverty      | 4                  | 6              | 5                         | 5                        | 2                    |
| Handedness (right) | 16                 | 18             | 14                        | 7                        | 8                    |
| IQ                 | 104.48 (14.02)     | 103.86 (10.81) | 103.52 (11.51)            | 103.20 (10.63)           | 106.18 (9.54)        |
| Symptoms           |                    |                |                           |                          |                      |
| Impairment (0-10)  | 0.74 (1.09)        | 3.5 (2.35)**   | 3.93 (2.66)**             | 3.80 (2.62)**            | 3.28 (1.68)**        |
| Emotional symptoms (0-14) | 2.17 (1.99) | 6.54 (2.91)** | 7.26 (3.13)**             | 8.40 (2.91)**            | 5.81 (2.40)**        |
Classification performance was measured using accuracy (percentage of correctly classified participants), precision, sensitivity (i.e., recall), and F1-score. Using our SL, we achieved an accuracy of 81% an overall precision of 80% as seen in Figure 4A, recall at 80% and an F1-score of 80%. Table S1 reveals the detailed results of our SL.

**Statistical analysis of Talairach region #41**

Here, we conducted a high level, between-group ROI analysis for region #41 to examine activation differences between anxious and non-anxious children. Using the beta values from our second level, grouped Bayesian representational similarity analysis (GBRSA), we compared activation in this region by using a mask to confine our analysis. Figure 5 (left) shows the region-based beta values for both anxious and non-anxious children. We compared all 685 pairs of voxels in this region using a Mann Whitney U-test (two-tailed). This statistical test revealed a significant difference in voxels for region #41 ($U = 215017.00, p < 0.005$).

**Fully connected network with region #41**

We examined the most correlated regions (top 30%) with our ROI using absolute Pearson correlations for anxious and non-anxious children. Twenty-six brain regions were correlated with Talairach region #41 for anxious children but only 16 brain regions for non-anxious children as seen in Figure 4 (right side) and Table 2. For anxious children, the highest correlated regions to Talairach region #41 were the right superior temporal gyrus (STG), the left STG and the right inferior frontal gyrus. For non-anxious children, the most correlated regions were the right STG, left STG and the left Brodmann area #38 (BA38). Notable differences between connected regions included right amygdala being correlated with Talairach region #41, Brodmann area #9 (which includes the prefrontal cortex) and the inferior frontal gyrus in anxious, but not control children. Please refer to the online methods to learn about the fully connected network analysis.

**Negative stimuli classification**

**Model classification of fearful versus angry faces**

We trained a linear Support Vector Machine (SVM) to predict whether a participant (either anxious or not) was viewing a fearful or an angry face at a given time, using only region #41. We applied a probabilistic shared response model (SRM) to functionally align the shared feature space across all subjects as seen in Figure 2. Using 5-fold CV, with this new representational space, we achieved an accuracy of 97.1% (STE +/- 0.43%) with a precision of 97.5%, a recall of 97.1%, and an F1 score of 97.1% when classifying fearful and angry faces. Please refer to Table S2 for evaluation metrics. When we trained the same model without functional alignment, we only achieved an accuracy of 49.4% (STE +/- 0.81%), the precision of 45.1%, a mean recall of 49.4%,
Table 2: **Talairach regions most correlated with region #41.** These values represent the Pearson correlation between different Talairach regions and region #41 (threshold to above 0.6). Twenty-six regions show a Pearson correlation with region #41 above 0.6 for anxious children, but only 16 for non-anxious children. Abbreviations: STG: Superior temporal gyrus, ITG: Inferior temporal gyrus, MTG: Medial temporal gyrus, WMT: White matter tract, IFG: Inferior frontal gyrus, VAN: Ventral anterior nucleus, SOG: Superior occipital gyrus, SFG: Superior frontal gyrus.

| Brain Regions correlated with Region #41          | Non-anxious | Anxious |
|-------------------------------------------------|-------------|---------|
| R. Temp. lobe, STG                              | 0.87        | 0.9     |
| L. STG, Brodmann 38                             | 0.83        | <0.60   |
| R. ITG, Brodmann 21                             | 0.65        | <0.60   |
| R. MTG, Brodmann 21                             | 0.71        | <0.60   |
| L. STG                                           | 0.74        | 0.75    |
| L. Fusiform Gyrus                               | <0.60       | 0.63    |
| L. Fusiform Gyrus, Brodmann 20                  | <0.60       | 0.66    |
| L. Fusiform Gyrus, WMT                          | <0.60       | 0.66    |
| L. Parahippocampal Gyrus, Brodmann 36           | <0.60       | 0.66    |
| L. Fusiform Gyrus, Brodmann 36                  | <0.60       | 0.68    |
| R. Amygdala                                      | <0.60       | 0.67    |
| L. Front. lobe, IFG                             | <0.60       | 0.67    |
| R. Front. lobe, IFG                             | <0.60       | 0.83    |
| R. IFG Brodmann 47                              | <0.60       | 0.72    |
| R. Font. lobe, IFG, WMT                         | <0.60       | 0.74    |
| R. Parahippocampal Gyrus, Brodmann 20           | <0.60       | 0.69    |
| R. Parahippocampal Gyrus, Brodmann 38           | 0.72        | <0.60   |
| R. Frontal lobe, STG                            | <0.60       | 0.72    |
| R. Temp. lobe, IFG                              | 0.73        | 0.71    |
| L. Sub-Gyrnal                                    | 0.64        | <0.60   |
| R. Temp. Sub-Gyrral Brodmann 13                 | 0.66        | <0.60   |
| R. Temp. Sub-Gyrnal                             | 0.73        | <0.60   |
| R. Front. Lobe, Sub-Gyral Brodmann 47           | <0.60       | 0.63    |
| R. Brainstem Extra-Nuclear WMT                  | <0.60       | 0.64    |
| R. Cerebrum Extra-Nuclear WMT                   | <0.60       | 0.66    |
| L. Temp. Lobe, Insula Brodmann 13               | 0.64        | <0.60   |
| L. Front. Lobe, IFG Brodmann 45                 | <0.60       | 0.73    |
| R. Front. Lobe, IFG Brodmann 45                 | <0.60       | 0.74    |
| R. Front. lobe, SFG                             | 0.71        | <0.60   |
| R. Thalamus, VAN                                | 0.64        | <0.60   |
| R. Front. lobe, Precentral Gyrus                | <0.60       | 0.7     |
| R. Front. Lobe, IFG Brodmann 44                 | <0.60       | 0.71    |
| Cuneus                                          | 0.7         | <0.60   |
| L. Occip. Lobe, Cuneus Brodmann 19              | 0.65        | <0.60   |
| L. Temp. Lobe, SOG                              | 0.66        | <0.60   |
| R. Front. Lobe, IFG, Brodmann 9                 | <0.60       | 0.63    |
| L. Occip. Lobe, SOG Brodmann 39                 | <0.60       | 0.64    |
A) Non-anxious

B) Anxious

Fig. 3: **Left** Grouped Bayesian representational similarity analysis of region #41. A between-group ROI analysis was used to examine activation differences for anxious versus non-anxious children. In our statistical comparisons, 685 pairs of mean beta values in region #41 were compared between each group using a Mann Whitney U-test (two-tailed). (U=215071.00, \( p < 0.005 \)). **Right** Fully connected network analysis of Talairach region #41 with anxious versus non-anxious children. A visual representation of regions connected with region #41. Dots represent the 38 regions with absolute correlation thresholds greater than 0.6, each connected with a red line to region #41. A) Fully connected network for non-anxious children. B) Fully connected network for anxious children.

and an F1 score of 42.7% as seen in Table S2. Figure 4B reveals the precision of the SVM with functional alignment (SRM) and without functional alignment.

**Four-class classification**

This final classification model coupled the predictions from our class label and negative stimuli classification models into a four-class performance task. For each time point, our ensemble model predicts which group the subject was from (anxious versus non-anxious), and what type of stimuli he/she was viewing at that time (anger versus fearful faces). Our model was able to achieve a balanced accuracy of 73% (STE +/- 0.06%) which is an improvement from baseline (26%). Mean precision, recall, and F1 scores were also 73%. Non-anxious children viewing angry faces revealed the highest recall at 76%, and non-anxious children viewing fearful faces revealed the highest precision at 75% as seen in Figure 4C and Table S3. No significant differences were found between the 4 classes with respect to their precision, recall, or F1 scores.
Fig. 4: Precision tables for both anxious versus non-anxious and negative stimuli classification analysis. a) Precision table for anxious versus non-anxious AdaBoost classification model. b) Precision table for fearful versus angry faces linear SVM with and without functional alignment. c) Precision table for four-class classification model of negative stimuli and disease state. All error bars represent the standard error of the precision across outer-CV folds.

**Discussion**

This study illustrated that a data-driven, machine learning approach can be used to distinguish anxious children from non-anxious children and identify which regions may be important for this performance task. Talairach region #41 (aka, Brodmann’s area 38, right temporal pole, planum polare, or area TG) can be used to distinguish anxious children from non-anxious children based on their brain scans as they view negative facial stimuli. We used machine learning to demonstrate that task-based fMRI activity related to this anatomical area is sufficient to achieve a relatively high accuracy. In our primary analysis, we trained a super learner for each individual Talairach brain region. Region #41 (the temporal pole) returned the highest mean accuracy with 81%.

Additionally, we examined the functional connectivity between region #41 and other areas and found that anxious children showed similar correlational patterns between several regions that make up the affective network. In addition, anxious children also exhibited more and stronger correlational patterns to other brain regions compared to non-anxious children. This network is a distributed neuronal network related to mood regulation and affective processing. However, very little research has been conducted on this particular region in relation to pediatric anxiety.

In our negative stimuli analysis, we examined how neural signatures differed between fearful and angry faces in both anxious and non-anxious children. We were able to achieve an accuracy of 97% with a linear SVM, but only after applying functional alignment (probabilistic SRM) to the brain scans of all children. This suggests that fearful and angry faces are highly dissociable when projected onto a common shared space. Functional alignment can provide enhanced predictive power because it automatically reduces the feature space while aligning the vectors between subjects to a shared common representational space. We then trained a new model to make individual predictions from both of our previous models in a four-class classification task that predicted the disease state and the type of facial stimuli simultaneously. Here,
we achieved an accuracy of 73%, suggesting that we can accurately identify both neural signatures of anxious children and how they process fear and angry faces.

Due to the diverse structure and connectivity to a number of regions, the putative role of the TP has been inconsistent and subject to significant debate\cite{10,34,35}. The TP has been proposed as a social-emotional cognition hub that receives various sensory inputs from limbic structures to organize social processes\cite{34}. Emotional facial processing is a particular social process, and young children suffering from anxiety seem to show functional dysregulation in related key limbic structures such as the amygdala and the PFC. Our results showed that the TP also plays a crucial role in facial processing, but we wanted to examine this in children to better understand the psychopathology of anxiety disorder. Using only the neural correlates in the TP, we were able to make individualized predictions about which children suffered from anxiety using a non-linear machine learning model. This suggests that altered functionality exists in this region during a facial processing task involving negative or threat provoking stimuli. This a novel finding in relation to pediatric cases of anxiety.

**Neuroanatomy of the Temporal Pole (TP)**

The TP lies between the O-PFC and the amygdala\cite{10}, sitting near the anterior end of the temporal lobe, rostral to the perirhinal cortex. It has significant neural connections with the amygdala and PFC via the uncinate fasciculus, making it a paralimbic region\cite{10,36}. Although it is known for processing language, functionality surrounding the TP has also been linked to facial, emotional, and social processing, but it still remains largely understudied\cite{37}. Below, we present findings neuroanatomical studies in macaque monkeys, showing patterns of connectivity similar to those exhibited in human brain\cite{38–40}. Additionally, in the human brain, the TP is anatomically close to (and highly connected to) other areas related to facial and socio-emotional processing\cite{10}.

**Evidence of socio-emotional processing in the temporal pole**

Using data from macaque monkeys, Kondo et al. (2005) hypothesized that the TP modulates emotional functions related to salient perceptual stimuli based on anatomical connectivity\cite{39,41}. The ventral region receives input from visual processing centers and is considered to be an endpoint in visual processing in macaques\cite{42}. Neurons in this region respond to complex stimuli and change in activity related to visual memory tasks\cite{39}. In humans, neuroimaging tasks have shown that neurons in the TP also respond to complex visual stimuli such as faces. Additionally, studies of visually evoked negative emotions such as fear and anger, have observed changes in activity of the right-ventral region of TP\cite{33,34}. Right-lateralized regions of TP have been implicated in high-level sensory representations with emotional and social experiences while left-lateralized regions of TP have been associated with linking semantic memory to high-level representations such as faces\cite{10}. Specifically, damaged left TP studies revealed deficits in proper naming abilities and face-name associative learning tasks\cite{35,36}. Additionally, epileptic damage to the right TP has resulted in higher prevalence of anxiety and depression disorders compared to the left TP\cite{37}. Here, it is evident that the TP plays a role in processing emotionally balanced facial expressions. In childhood
anxiety, this cognitive process is compromised. Research remains focused largely on amygdalocentric systems, but our results suggest that the activity of right TP alone enables distinctions between anxious and non-anxious children.

As outlined above, research into neural aspects of socio-emotional processing has focused mainly on areas such as the amygdala and the prefrontal cortex, not the TP. Perhaps as the TP is a paralimbic region, it has not received the same attention as the amygdala and PFC in emotion studies. In addition, the awkward anatomical placement of TP near the air-tissue boundaries of the sinuses is associated with weaker BOLD signals, making it difficult to draw consistent and statistical significance from fMRI measures. Nevertheless, in our study, the TP fMRI data revealed neural differences in socio-emotional processing of facial stimuli in anxious and non-anxious children.

Implications in Childhood anxiety

Since 2000, a number of neuroimaging studies have found deficiencies in facial-emotion recognition among individuals suffering from anxiety. In most cases, research has focused on two brain regions — amygdala and PFC — when examining distinct functional differences in anxious individuals while viewing emotional faces. Cognitive schema theories suggest that negative or threatening faces receive preferential and early processing advantages through these parts of the brain. It is known that rapid, direct processing of rudimentary sensory stimuli from the thalamus can reach the amygdala in short succession, and the amygdala also receives sensory input from indirect pathways such as the PFC, where it assigns significance to the sensory stimuli based on context and prior experiences. This pathway reaches the amygdala in a slower fashion but conveys higher-order representations and is relevant for memory consolidation. Top-down modulation of this pathway may exert inhibitory influences on the amygdala. In adolescent anxiety, modulatory pathways may become dysregulated, allowing the amygdala to become hyperactive. Numerous studies have cited the PFC-amygdala network in emotional facial processing tasks. While this area is relatively well-known to be implicated in childhood anxiety, it is not the only area where functional differences may be observed.

In trying to conceptualize the functional relationship between anxiety and facial emotional processing, the TP should be considered. A reviewer of a 2016 meta-analysis involving fear conditioning noted that it would “be a great favor if the [neuroscience] community would finally put away the amygdalocentric view on human fear conditioning and emphasize the role of other higher cortical structures.” Few studies have focused on paralimbic regions such as the TP and its connectivity to the amygdala, perhaps due to its later, high-level processing onset of complex stimuli. As mentioned earlier, the TP is (1) heavily connected with the amygdala, (2) responsible for processing complex visual and auditory stimuli, and (3) has been shown to integrate social and emotional significance to said stimuli. Together, these areas are a part of a larger-scale, resting-state brain network known as the affective network. This network has been implicated in various anxiety disorders where individuals are characterized by hyper-arousal, heightened worry states, increased sensory processing and poor emotional regulation. Our connectivity analysis provides strong evidence that the
affective network is at play in adolescent children in a task-based design. Not only was
the TP a strong predictor of childhood anxiety, but it also showed strong correlational
patterns with other affective network regions such as the amygdala, STG, the orbital
frontal cortex (OFC), and the border of the insula (Brodmann area #45). In addition,
anxious individuals exhibited strong correlations for neural activity between the TP
and visual cortical areas such as the occipital cortex and the fusiform gyrus. These
regions have been linked to the perception of emotion in facial stimuli. Although the
affective network domain is based on resting state brain paradigms, similar regions in
our task based study were identified by our model. Regions within the affective network
seem to show the greatest discriminative power between anxious and non-anxious
children. This only reinforces the notion that the TP must be examined in more detail,
as it is part of a larger affective network that regulates emotional and perceptual
stimuli.

Various brain studies have focused on functional and structural differences
in the bilateral TP between different populations during emotional stimulus tasks.
While none have emulated the paradigm we have presented, certain parallels exist
to confirm our findings. From a social and emotional standpoint, several fMRI and
PET studies have shown activation of the TP in such tasks. Bilateral activation of
the TP has been seen in negatively valenced films inducing sadness and right
TP activation has also been noted in viewing sad and angry faces. Recalling past
anxious and angry experiences have shown bilateral activation as well. This suggests
that emotionally valenced stimuli do operate within the TP. In our study, we applied
functional alignment techniques to better distinguish between various emotional stimuli
such as fear and anger in anxious and non-anxious children. Our goal here was to
further examine whether types of emotional stimuli differ in their neural signatures
for anxious and non-anxious children in the TP. We successfully classified time-points
of either fearful or angry faces across all subjects with 97% accuracy. Using only this
region, we were able to distinguish diagnostic labels using the emotional stimuli of
fearful and angry faces. This implies that anxious children process fearful and angry
faces differently from each other and they also process these emotions differently from
non-anxious children.

While few studies have been conducted on children with anxiety, there are
a few sources that cite the TP in clinical anxiety. A study focusing on group-level
differences between SP and GAD in young adults with SP showed increased BOLD
activity in the TP and the amygdala when responding to fearful faces compared to young
adults with GAD and the control group. The GAD group showed increased activity
for angry faces in Brodmann area #10 (which includes part of the PFC) and the middle
frontal gyrus but showed a decrease in activity for the amygdala compared to the SP
and the control groups. The authors concluded that the amygdala was not a sufficient
enough area alone to distinguish group and stimulus level differences in young adults
with SP and GAD, recommending that other areas be examined as well. Another
study examined mood disorders in adults who suffered from temporal lobe epilepsy.
The authors found that 29 of the 44 patients presented a major mood disorder (mainly
anxiety) 6 months before their surgery. A major trend revealed that most of these
patients had their epileptic seizures propagated from the right TP compared to the left.
Lastly, a resting-state MRI study that analyzed the functional connectivity between the
amygdala and the TP in GAD patients revealed some interesting caveats. Compared
to the control group, GAD patients revealed an increase in functional connectivity
between these regions. They contend that this altered connection may contribute to
the etiology of GAD in older patients. Our study confirms the same findings, except for
children. Based on our connectome analysis, anxious children had a higher correlation
between the right TP and the amygdala as well as the PFC, while non-anxious children
did not. This may reveal that innervation’s between the TP and other limbic regions
may manifest in young children, and remain into adulthood.

Currently, there is no validation or diagnostic procedure that involves any
component other than clinical signs and symptoms via psychiatric assessment. Although
neuroendocrine, cognitive, genetic, and neuroanatomical correlates exist, there is no
available biological test for diagnosis. Here, we used a facial processing fMRI task to
not only classify anxious from non-anxious children, but to also distinguish between the
affective stimuli presented. Instead of using a multi-variate strategy to examine whole-
brain neural patterns, we focused on one particular region which has been implicated
but understudied in anxiety and socio-emotional processing. The TP served as an
anatomical region that could predict which children suffered from anxiety based on the
neural correlates of fearful and angry faces.

Limitations and future work

One future consideration is to conduct a meta-analysis to other studies of anxious
children or adults. As mentioned, there are few papers focusing on the temporal pole
as a region that could be implicated in anxiety. If data is available, validating our
model on adult cases could yield interesting findings. Another consideration is to test
our model on a separate cohort dataset with more subjects. Ideally, evaluating the
performance of our proposed approach could benefit from a more homogeneous target
group. Since our target group contained children with 3 different types of anxiety
disorders (co-morbid disorders as well), the variance between the neural signatures of
these children may have differed significantly. There is evidence that SP, GAD, and
SAD show different neurological and behavioral patterns between each other[59,62,63].
Thus, confounding effects may exist within the anxious group that could affect the
overall performance accuracy. However, comparing SP, GAD, and SAD is out of the
scope of this paper. Another limitation may be that functional alignment could result
in high accuracies in other areas than the TP for our secondary analysis. The TP
was critical for the primary analysis classification, but was comparable to other brain
regions in the secondary analysis after functional alignment was applied. Another
future consideration could involve transfer learning, a machine learning technique that
involves training with one type of labeled data (e.g., only train a model using GAD
participants), then applying that model on other classes (e.g., SP or SAD children) to
examine whether the model can correctly distinguish cases based on the prior knowledge
of only GAD children. Another potential limitation was the absence of other facial
stimuli in the task. Carpenter, K.L., Angold, A., Chen, N.K., Copeland, W.E., Gaur,
P., Pelphrey, K., Song, A.W. and Egger, H.L. (2015) only released functional scans
with fearful and angry faces for the purposes of their study[63]. Thus, we had to focus
on negative stimuli only, and although we successfully distinguished fear from angry
faces in the brain, other facial stimuli may offer further insights into how emotion is
processed in the brain of anxious and non-anxious children. We may extend our study
to the other related, publicly available datasets that have other types of (visual/facial)
In summary, the goal of this study was to use a data-driven approach to classify anxious versus non-anxious children using emotional facial stimuli. Here, we used a non-linear super learner (AdaBoost with logistic regression as a base estimator) to target the Talairach regions that could best distinguish anxious from non-anxious children. Our model achieved an accuracy above 81% for this task. Subsequently, we examined how different negative emotional faces would be processed in both groups. We found that fear and angry faces could clearly be distinguished in the TP, but only after functional alignment was applied to the brain scans of all subjects. This study illustrates the power of task-based fMRI designs to predict disease states and stimulus conditions. It also indicates that the TP is a region that should be further examined in pediatric anxiety. Cognitive processes such as emotional facial processing may be compromised in anxious children. We have demonstrated that machine learning analysis of face-processing, task-related fMRI data may be used to distinguish anxious from non-anxious children. This may enable further understanding of neural underpinnings of pediatric anxiety and help to extend and validate diagnostic labels used by psychiatrists and other clinicians.

Author Contributions

Jeff Sawalha: Investigation, data analysis, writing — original manuscript, editing.
Muhammad Yousefnezhad: Project organizer, investigation, data analysis, writing — original manuscript, editing.
Alessandro Selvitella: Statistical analysis, review and editing.
Bo Cao: Reviewing and editing.
Andrew J. Greenshaw and Russell Greiner: Principal investigators, project supervisors, final review and editing.

Competing Interests Statement

The authors declared no competing interests.

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Methods

Data

This paper analyzed data provided by Carpenter, K.L., Angold, A., Chen, N.K., Copeland, W.E., Gaur, P., Pelphrey, K., Song, A.W. and Egger, H.L. (2015), who posted their data-set on [https://openneuro.org](https://openneuro.org). The link to the data repository is [https://openneuro.org/datasets/ds000144](https://openneuro.org/datasets/ds000144). Their data was made publicly available on 2018-03-26.

Recruitment

Secondary analysis of existing data was obtained from Carpenter, K.L., Angold, A., Chen, N.K., Copeland, W.E., Gaur, P., Pelphrey, K., Song, A.W. and Egger, H.L. (2015). Children were initially recruited from the Duke Preschool Anxiety Study (DPAS), which was a longitudinal, multi-phase study. The last phase was entitled “Learning about the Developing Brain study” (LABD), where 208 children who participated in previous phases of the DPAS were recruited to take part in this study which examined brain development in children suffering from anxiety. Of the 208 children, 155 were eligible to participate in the neuroimaging phase. Children who met the criteria for generalized anxiety disorder, SP, and/or SAD were recruited into the “case” group, and children who did not meet the criteria for an anxiety disorder were recruited as the comparison group. Children in the LABD were not excluded for comorbid non-anxiety disorders or for taking psychotropic medications.

Parents completed the Preschool Age Psychiatric Assessment (PAPA) for children involved in this study. The PAPA is a diagnostic instrument for assessing psychopathology of children aged 2-9, and it is based on the parent version of the Child and Adolescent Psychiatric Assessment. Frequency, duration, and the onset of symptoms are collected to determine whether the child meets the diagnostic criteria for anxiety disorders in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). The PAPA assesses symptom severity during the previous 3 months, as shorter recall periods have been shown to reflect more accurate recall. A composite score of GAD, SP, SAD, and depression symptoms were obtained from the PAPA and was used as a measure of school-age emotional symptomatology.

This study was approved by the Duke University Medical Center Institutional Review Board, and was carried out in accordance to U.S regulatory requirements related to the protection of human research participants, which include the Accreditation of Human Research Protection Program (AAHRPP) and the Health Insurance Portability and Accountability Act (HIPAA) guidelines. Verbal assent from the child and informed consent from the parent were obtained after a full description of the study was presented. Children and parents were financially compensated with gifts or money vouchers.
Participants

Children eligible for the fMRI study had to meet 3 requirements: (1) They completed the first phase of the DPAS study, (2) they must be older than 5 and half years old, (3) have successfully completed a mock scan session in the MRI machine. Children were placed into one of two groups. The first group involved anxious children, who met the criteria for GAD, SP SD, or some combination of the 3 using the PAPA questionnaire, and non-anxious children who served as a control group. Of the 155 children initially recruited, only 45 had usable data due to a number of reasons including parents or child refusal to take part, absences, excessive motion in the scanner, and lower IQ.

Of those 45 children, 22 were in the anxious group and 23 were in the non-anxious group. Within the anxious group, 15 children met the criteria for GAD, 11 for SP, and 10 for SAD. Twelve out of 22 anxious children met the criteria for more than one anxiety disorder. The age range of both groups was between 5.5-9.5 years old as seen in Table 1. Impairment and emotional symptoms were recorded prior to the start of the fMRI study and were representative of psychiatric symptoms that interfere with daily functioning. Impairment scores were assessed using the World Health Organization’s International Classification of Functioning, Disability, and Health. Emotional symptoms were measured on a composite scale that accounted for both anxiety and depressive symptoms.

Functional MRI task

The fMRI task was a block design, emotion face processing task. Facial stimuli from the NimStim Stimulus Set were selected (45), but only angry and fearful faces were used according to Carpenter et al (2015). Each subject completed 2 blocks. At the beginning and end of each run, there was a 16-second fixation block and 15-second task blocks were stationed in between and separated by 12-second baseline fixation blocks which consisted of a colored star in the center of the screen. Faces were shown for 1.25 seconds with no inter-stimulus interval. Each run contained 3 blocks of fearful and angry faces exclusively, with the order of the emotional faces randomized. To make sure the children were staying engaged, they were instructed to press a button whenever a face with glasses was shown on screen. These faces were randomly placed throughout the blocks and expressed the same emotion as the other pictures within the block. The average task accuracy was 83.33% for non-anxious children and 82.29% for anxious children.

MRI acquisition

MRI acquisition was completed on two different 3T GE scanners. Of the 45 participants, 15 (8 anxious, 7 non-anxious) were scanned using the EXCITE HD system, and 30 participants (14 anxious, 16 non-anxious) were scanned on the MR750 system. Parameters and pulse sequences were congruent between the two systems, and calibration metrics such as spatial accuracy and dynamic signal stability were validated using an agar phantom (soft tissue mimic). In both systems, scans lasted 5 minutes and 44 seconds and 172 functional images were generated during the task. For each
run, between 34-39 slices were generated which were parallel to the AC-PC plane using a BOLD-sensitive EPI sequence (Voxel size: 4mm$^3$; Repetition time: 2000ms; Echo time: 27ms; Field-of-view: 24cm; Flip-angle: 77; Interleaved-odd acquisition). Co-registering the functional images was done in conjunction with a high resolution T1-weighted anatomical scan using the 3D-FSPGR sequences with SENSE (Voxel size: 1mm$^3$; Repetition time: 8.096ms; Echo time: 3.18ms; Inversion time: 450ms; Field-of-view: 25.6cm; Interleaved-odd acquisition). Batch effects were recorded as a covariate in the machine learning analysis to ensure manufacturing differences between the two systems were not a cause of functional differences.

**Pre-processing**

Data was analyzed using Easy fMRI (Version 1.8B8800) and FMRIB Software Library (FSL Version 6.0.3). We have used the “fMRIPrep” pipeline — including brain extraction, registration to standard space, motion correction, slice time correction, normalization, and spatial smoothing. To prepare the images for registration, we first used the Brain Extraction Tool (BET) to eliminate non-brain tissues such as the scalp and brain marrow. We then registered all the subject’s brain images to a common reference coordinate system using the MNI-152, 2mm resolution (T1 weighted) standard space. To anatomically align the brain images, we used an affine (12 degrees of freedom, 12 DOF) transformation to rotate, translate, and scale the images into alignment. Motion correction was also handled in this affine transformation. Because of movement in the scanner, we needed each voxel to correspond to a consistent anatomical point for each point in time. Here, we chose to use the first image in the time frame to reference all other volumes at other time points. Fortunately, the dataset we acquired already removed excess motion subjects. Carpenter, K.L., Angold, A., Chen, N.K., Copeland, W.E., Gaur, P., Pelphrey, K., Song, A.W. and Egger, H.L. (2015) removed relative and absolute motion and intensity jumps greater than three standard deviations from the run mean as part of their scrubbing protocol. The mean of runs was determined by taking the absolute deviation relative to the mean of runs after each voxel was passed through a high pass filter to remove low-frequency drifts (1/60 Hz). Task blocks were removed from analysis if two volumes were removed from the start of the block or more than 3 volumes in total were removed from the block. Additionally, the entire run was excluded from subsequent analyses if more than one block of emotional stimuli was removed. Next was spatial smoothing, Spatial smoothing is a method used to increase the signal to noise ratio in fMRI brain volumes. Smoothing was done by using a 3D convolution with a gaussian kernel to replace voxel intensities with a weighted average of neighboring intensities. We specified our Full-Width-Half-Maximum (FWHM) kernel to be 5.0mm. After, we applied a global intensity normalization between subjects and sessions. Lastly, we used temporal filtering, which is a removal of high and or low frequencies in the raw signal of voxel intensities via bandpass filters. In a time series of each voxel, there may be scanner related or physiological signals that cause high-frequency noise.
Analysis: Anxious versus non-anxious classification

Machine learning analysis

Using the Talairach atlas (with 2mm voxel size), we segmented the brain into 959 regions, then applied a super learner (SL) to examine which areas were closely related to our diagnostic labels. This was a brain-wide regional analysis to test our hypothesis against other brain regions. The SL would make a prediction on every time point for each subject, which means 35 predictions were within each subject. The final prediction for a subject was a majority vote of the class label, regardless of task stimuli. Figure 1 illustrates the full machine learning pipeline for our primary analysis. The SL was a nested cross-validation process, whereby the outer CV process used \( \frac{4}{5} \) of the participants for a training set (balanced for diagnostic labels), and \( \frac{1}{5} \) for a testing set. Within the training set, another 5 fold-CV was used to fine tune the hyper-parameters within the SL. An ensemble classifier (AdaBoost) with a logistic regression base estimator was used to make the predictions on each participant. We used three hyperparameters to tune our classifier within the inner CV. First, we used a different number of estimators [n_estimators = 10, 50, 100, 150] to determine the maximum number of estimators at which boosting is terminated. Second, we adjusted the learning rate [learning_rate = 0.05, 1, 2]. Third, we changed the number of max iterations completed by the SL [max_iterations = 100, 500, 1000]. Lastly, we tuned the type of regularization performed by the logistic regression estimator [penalty = L1, L2, none]. This was also coupled with the regularization penalty variable [C = 0.5, 1, 2]. We evaluated the performance of our results by using the accuracy, which was computed as the average accuracy across the folds in the outer CV. We selected the topic region based on the highest mean accuracy from the outer folds. Additionally, we used precision, recall and F1-score to evaluate the model.

Statistical analysis of top region(s)

We conducted a high level, between-group analysis for the ROI selected to examine activation differences for anxious versus non-anxious children. Instead of using a regular classification analysis, we conducted a grouped Bayesian representational similarity analysis (GBRSA) that can compare the (dis)similarities between different cognitive states across multiple participants. Traditional RSA has been widely adopted in cognitive neuroscience but suffers from some confounding factors. Mainly, similarity metrics tend to be much higher when neural patterns are in close temporal proximity. Secondly, RSA is subject to overestimation of the variance and underestimation of the correlation between true patterns may exist due to the condition-by-condition covariance matrix of the spatial patterns. In GBRSA, this temporal and covariance bias is reduced by learning the covariance structure as a hyper-parameter of the trained model. By reducing the unknown activity patterns across anxious and non-anxious children, a direct estimation can be made from the covariance matrix. Once generated, we measured neural activity in the TP to determine whether either group differed from each other using a Mann-Whitney U test, which does not assume normality assumes a non-normal distribution of the neural activity.
Fully connected network analysis

Lastly, we wanted to look at a fully connected network analysis between the highest selected region and all other regions. To do this, we first partitioned the raw neural activities between anxious and non-anxious children. Next, neural activities were further partitioned based on 959 regions of the Talairach atlas. We then averaged the neural activities within each Talairach region across all voxels — which resulted in a vector with the same size as our time points. After, we compared each of these vectors by calculating the absolute value of the correlation in a similarity matrix. We then applied a threshold to examine the most correlated regions (top 30%). Finally, we visualized both of the anxious and non-anxious networks and only showed the top connections with our highest selected region. This was done to examine whether our ROI showed different neural connections to different areas of the brain in anxious and non-anxious children, regardless of facial stimuli.

Analysis: Negative facial stimuli

Model classification of fearful versus angry faces

We also sought to distinguish fearful versus angry faces among the neural activity of all children with our ROI. For between-subject comparisons, tasks such as pattern classification or RSA yield lower accuracies because the representational spaces are highly dimensional, the functional topography may be different between subjects and anatomical brain structures vary between participants. Thus, a recent method known as functional alignment has been proposed to align patterns of neural responses across subjects into a common, lower-dimensional space. One important assumption is that we assume all human brains have similar neural activity for experiencing the same categorical stimuli. Here, we used a probabilistic shared response model (SRM) to functionally align neural activity for fearful and angry faces for all subjects only in our region of interest. SRM uses the training data to learn the mappings for each subject’s data shared feature space. Then these learned mappings are projected onto the held-out data for each subject into a shared feature space. One of the main distinctions in SRM is that the model directly estimates that the selected shared features are significantly less than the number of voxels it is selecting from. This is different from other methods where the number of features usually equals the number of voxel. The machine learning pipeline for our negative stimuli analysis can be seen in Figure. Once we obtained the functionally aligned dataset for the facial stimuli, we trained a linear SVM classifier on the ROI. Again, 5-fold CV was used, but with no internal CV approach this time. Also, no majority vote was used for final predictions. Instead, each time point was individually predicted, and metrics such as accuracy, precision, recall, and F1-score were averaged across each time point between all subjects in the testing folds.
Multi-class classification

Taking the final predictions from both our analysis models, we sought to make a four-class classification model that predicts the diagnostic stimuli (anxious versus non-anxious) and the type of stimuli (fearful versus angry faces) in a post-hoc analysis. Using the final predictions from the trained AdaBoost classifier (anxious versus non-anxious) and the linear SVM (fearful versus angry faces), we generated new prediction labels based on the original class and stimuli labels and compared them to the observed labels. A one way ANOVA was conducted to examine differences in precision between the 4 classes. This can be seen in Figure 4C.

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Supplementary Materials

Table S1: **Primary analysis super learner model results.** This table reveals the results from the highest region-based model (region #41) and from our super learner. The standard error on the accuracy is computed across the number of folds in the cross-validation process.

| Classifier | Class     | Precision | Recall | F1 Score | Accuracy |
|------------|-----------|-----------|--------|----------|----------|
| AdaBoost   | Non-anxious | 80.0%     | 79.0%  | 80.0%    | 80.0% (+/- 4.0%) |
|            | Anxious    | 79.0%     | 80.0%  | 79.0%    | 80.0% (+/- 4.0%) |
|            | Overall    | 80.0%     | 80.0%  | 80.0%    | 80.0% (+/- 4.0%) |

Table S2: **Secondary analysis model results.** This table reveals the results from the highest region-based model (region #41). Our model achieved a 97.1% accuracy for distinguishing fearful from angry faces in both class groups. The standard error on the accuracy is computed across the number of folds in the cross-validation process. A t-test between the two models revealed a non-significant difference ($t_{(21)} = 0.81$, $p > 0.05$).

| Classifier  | Class | Precision | Recall | F1 Score | Accuracy |
|-------------|-------|-----------|--------|----------|----------|
| Linear SVM  | Fear  | 97.9%     | 97.1%  | 97.1%    | 97.1% (+/- 0.5%) |
|             | Angry | 97.1%     | 97.0%  | 97.1%    | 97.1% (+/- 0.5%) |
|             | Overall | 97.5%    | 97.1%  | 97.1%    | 97.1% (+/- 0.5%) |

Table S3: **Four-class ensemble classification results.** This final classification model coupled the predictions from our group and negative stimuli classification models into a four-class performance task. Our models achieved a balanced accuracy of 73% compared to baseline which was 26%.

| Classifier       | Class             | Precision | Recall | F1 Score | Accuracy |
|------------------|-------------------|-----------|--------|----------|----------|
| Four-class ensemble model | Non-anxious angry | 74.0%     | 76.0%  | 75.0%    | 73.0% (+/- 5.4%) |
|                  | Non-anxious fear  | 75.0%     | 72.0%  | 73.0%    |          |
|                  | Anxious angry     | 74.0%     | 71.0%  | 73.0%    |          |
|                  | Anxious fear      | 70.0%     | 74.0%  | 72.0%    |          |
|                  | Overall           | 73.0%     | 80.0%  | 80.0%    | 73.0% (+/- 5.4%) |