Resting State Functional Connectivity of the Periaqueductal Gray Area (PAG) in Association to Threat Bias in Anxiety Disorders

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Introduction

The periaqueductal grey area (PAG) is highly involved in processing pain and fear. It receives input from the prefrontal cortex and projects to the spinal cord for pain modulation. Previous functional magnetic resonance imaging (fMRI) studies have reported PAG activation when people faced threat, and such activation was higher when threat was in shorter distance to the person. PAG was also functionally connected with regions associated with pain modulation and executive function, including the basal ganglia, when participants faced threat. Specifically, the PAG-basal ganglia connectivity was attenuated with higher pain intensity. Although the PAG is receiving attention in pain research, little is known about the differential functional connectivity of PAG between healthy controls (HC) and patients with anxiety related disorders (PAD), as well as its association with response to threats.

This study explored the resting state functional connectivity (rsFC) of the PAG in HC and PAD, and its correlation with performance in a dot probe task, a common task to measure attentional bias. We expected a disruptive PAG-basal ganglia connectivity with threat bias in PAD.

Methods

Data Set:

- Data obtained from the Nathan Kline Institute - Rockland Sample.
- 70 healthy adults; 30 patients with anxiety related disorders.
- Participants performed a dot-probe task outside the scanner.
- Also completed a 5-minute resting fMRI scan.

Dot-Probe Task:

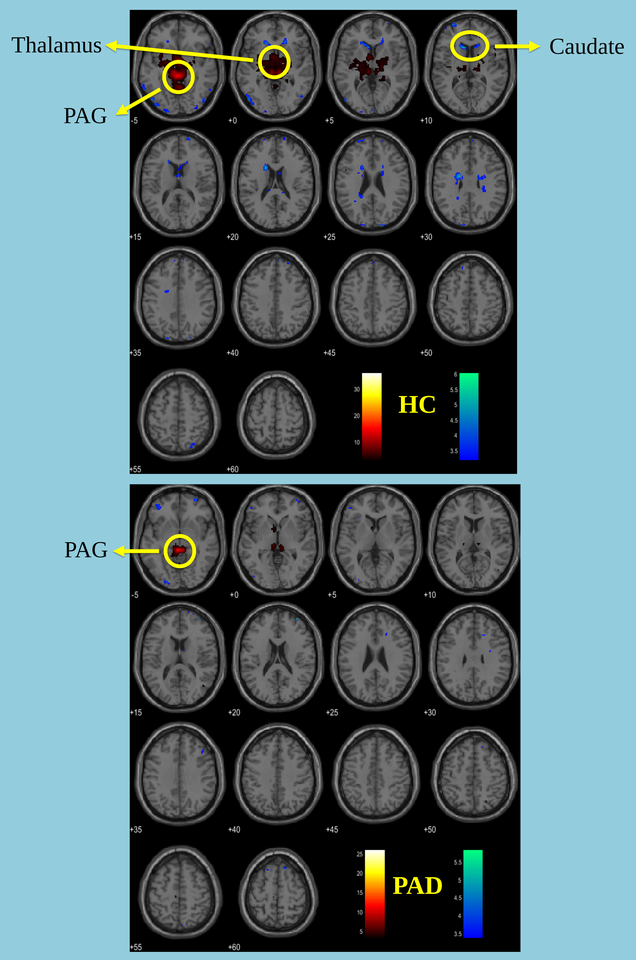
- Two faces (happy, threatening, or neutral) appeared on screen.
- A dot replaced one face eliciting a button press to that location.
- Threat Bias = difference in reaction time (RT) between the dot replacing the neutral faces and the threatening faces (i.e., RT in neutral – RT in threat).
- Positive threat bias indicates more attention towards threat and possibly increased anxiety induced by stimuli.

Imaging Analysis:

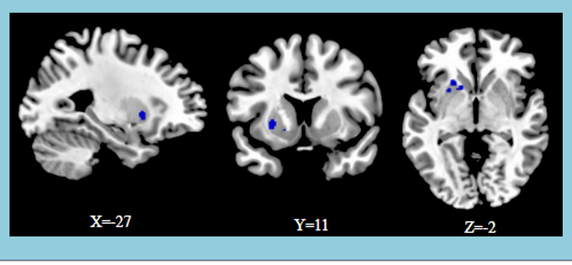
- Whole brain resting state functional connectivity (rsFC) was computed using PAG as a seed region in each group.
- Regression of PAG rsFC with Threat Bias in each group.
- All results survived at $p<0.05$ Family Wise Error (FWE) level.

Results

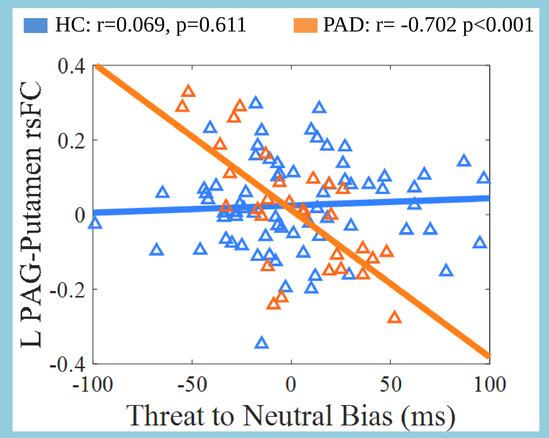
Whole brain rsFC of PAG in HC and PAD are shown below. Two sample t test revealed no significant group differences in PAG rsFC. Red: positive connectivity; Blue: negative connectivity.



Regression analysis showed a significant and negative correlation between the left PAG-putamen rsFC and Threat Bias in PAD but not in HC.



Results



The correlation between PAG-Putamen rsFC and threat bias was significantly different between the HC and PAD ($t=4.757$, $p<0.001$).

Conclusions

- Results indicate a negative correlation between PAG-putamen rsFC and Threat Bias in patients with anxiety disorders; however, this correlation was absent in HC.
- This negative correlation suggests a disruptive coupling between PAG and putamen, a structure in the basal ganglia, associate with the potential higher pain and anxiety accompanied by higher threat bias.
- This suggests that the PAG-putamen connectivity could serve as an important neural indicator of pain and anxiety regulation.
- Our results underscore the importance of a healthy PAG-basal ganglia coupling in anxiety disorders and provides biological foundation for developing targeted treatments in clinical psychology and neurology.
- Future studies should evaluate this relationship in each type of anxiety-related disorders to decrease the confound introduced by multimorbidity.

Acknowledgements

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