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Neural correlates of emotional processing in panic disorder

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ABSTRACT

Background: Deficits in emotional processing are conceptualized in prevailing models of anxiety to underpin key symptoms of panic disorder (PD). Neuroimaging studies show evidence of aberrant neural functioning in PD patients during emotional processing, however little is understood about how non-conscious emotional processing impacts neural processes.

Method: We examined activation and functional connectivity differences in brain regions involved in emotional processing between PD and healthy controls (HC) during subliminal and supraliminal presentations of facial emotions. Twenty-two PD and 33 HC participants were shown happy, sad, neutral, fear, anger and disgust facial expressions during functional magnetic resonance imaging using a 3T MRI scanner. We performed voxelwise ROI analyses at FWE-corrected $p < 0.05$ for main effects of group and group*emotion interactions.

Results: There was less pregenual anterior cingulate cortex (pgACC) activation to subliminal presentations of happy and sad faces in PD compared to HC participants (group*emotion). In addition, PD patients had less pgACC - right amygdala connectivity than HC participants during sad and fear subliminal processing (group*-emotion). PD patients also exhibited lower right cerebellum activity across all supraliminal presentations of facial expressions compared to HC.

Conclusion: These findings suggest that there is aberrant neural processing in PD patients during both conscious and preconscious processing of both positive and negative stimuli, suggesting impaired recruitment of implicit regulatory networks during affective processing. It appears that PD patients may experience deficits in key regulatory connections between inhibitory and emotional neural networks at very early stages of processing of negative affective states.

1. Introduction

Panic disorder (PD) is an anxiety condition that is characterized by fear of ongoing panic attacks and the harm they may do the individual. Panic attacks involve rapid intense occurrence of anxiety accompanied by several physiological changes in the body such as accelerated heart rate, shortness of breath, shaking, and chest pain (American Psychiatric Association, 2013). PD is one of the most common anxiety conditions, affecting approximately 6% of the population (Thibaut, 2017). Major models of PD emphasize the aberrant nature of emotional processing in PD patients, including preattentive and excessive attention to potential threat stimuli (Rachman, 1980). This emphasis on emotional processing has been supported by considerable research that people with PD have abnormalities in processing emotional information, and this is thought to underpin the symptomology of PD (Baker et al., 2004; Mogg et al., 2012; Reinecke et al., 2013). Underlying much of the aberarrant emotional processing in PD is excessive attention to threat, exemplified by PD individuals being more likely to perceive non-angry facial emotions as angry (Kessler et al., 2007) and preferentially attending to fearful faces relative to healthy controls (HC; Reinecke et al., 2011).

Consistent with clinical and behavioral findings, neuroimaging studies show evidence of aberrant functioning in the neural networks

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involved in emotional processing for people with PD. For example, PD patients show amygdala hypoactivation to presentations of happy, angry, fearful and neutral facial expressions compared to healthy controls (Demenescu et al., 2013; Pillay et al, 2006). Hypo-responsivity in the anterior cingulate cortex (ACC) and cingulate cortex to fearful faces has also been observed in PD patients, when compared to HC (Pillay et al., 2006) which may underlie reduced capacity in regulating emotional responses to the emotionally expressive faces. This pattern may also reflect hyper-arousal in PD patients (Zugliani et al., 2017), an effect which reduces their capacity to process new emotional information (Pillay et al., 2006). ACC hyper-responsivity to happy faces has also been found in PD patients (Pillay et al., 2007), possibly indicating that PD individuals attribute greater salience to emotional information compared to HC (Pillay et al., 2007). Furthermore this greater sensitivity to threatening emotions is also reflected in studies that have observed that PD is associated with hyperactivity in the right insula to anger and fearful faces relative to HC (Fonzo et al., 2015).

The aforementioned studies focused on examining the neural networks involved in conscious processing of facial emotions in PD. It is important to also investigate neural activations in PD during non-conscious processing of emotional stimuli. From an evolutionary perspective, being able to detect rapid changes in the environment is needed to protect oneself, and various subcortical regions, such as the amygdala, nucleus accumbens, superior colliculus, and pulvinar have been implicated in the processing subliminal emotional information (Adolphs, 2002; Tamietto & de Gelder, 2010). The relevance of pre-conscious processing of emotional stimuli is relevant to PD because of evidence that PD patients process subliminally presented threat stimuli preferentially relative to HC (Lim and Kim, 2005; Lundh et al., 1999). To date, there is only one neuroimaging study that has examined subliminal processing of emotional stimuli in PD; this study showed that PD patients were characterized by lower bilateral amygdala activation to subliminal presentations of fearful faces relative to HC (Ottaviani et al., 2012). A limitation of this study was that it focused specifically on amygdala responses to subliminal processing of fearful faces, and accordingly a broader investigation of preconscious processing of emotions in PD is needed. To this end, this study investigates neural responses to supraliminal and subliminal presentations of anger, disgust, happy, sad, fear and neutral faces. We also extend on previous work by evaluating functional connectivity between key regions of the emotion processing (amygdala, insula) and regulatory (anterior cingulate, dorsolateral prefrontal cortices) brain networks. Based on prior findings (Demenescu et al., 2013; Ottaviani et al., 2012; Pillay et al, 2006; Pillay et al., 2007), we hypothesized that patients with PD would show lower recruitment of key brain regions involved in both these processes, particularly the amygdala and anterior cingulate brain regions, during both supraliminal and subliminal processing of facial emotions. Also, considering that functional connectivity between these regions is critical in successful processing and regulation of emotions, we expected amygdala-cingulate connectivity to be altered in PD.

2. Material and method

2.1. Participants

The sample comprised 55 participants [22 panic disorder (PD) and 33 healthy controls (HC)] who were recruited from public advertising to participate in a study on brain functioning. The clinical sample was assessed for diagnosis of PD according to the DSM-IV criteria using the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998). Exclusion criteria included history of psychosis, neurological disorder, or current substance dependence. PD and HC were matched on sex and age. The protocol permitted participants to be on prescribed medication if they were on a stable dosage for at least two months prior to the scan.

2.2. Clinical measures

Participants were assessed for comorbid Axis I disorders, including generalized anxiety disorder, major depressive episode, obsessive compulsive disorder, social phobia and agoraphobia using the MINI (Sheehan et al., 1998). Participants also completed the following self-report questionnaires: 1) Beck Depression Inventory (BDI-II; Beck et al., 1996), a 21-item measure of depressive symptoms, 2) Agoraphobic Cognitions Questionnaire (ACQ; Chambless et al., 1984), a 14-item questionnaire used to assess fear-related thoughts commonly associated with PD, specifically agoraphobic concerns, and 3) Beck Anxiety Inventory (BAI; Beck et al., 1988), which is a 21-item assessment of the physiological symptoms of anxiety .

2.3. Procedure

The study was approved by the Western Sydney Area Health Service Human Ethics Committee and participants provided written informed consent prior to taking part in the study.

2.4. Emotional faces processing task

The emotional faces processing task was used to assess brain regions involved in subliminal and supraliminal processing of fear, anger, disgust, happy, sad and neutral faces in two separate task runs and has been previously described in Korgaonkar et al., 2013. Participants were shown emotional faces and asked to focus on the emotion portrayed by each face without requiring any response. Each face was shown for either 16.7 ms (subliminal task) or 500 ms (supraliminal task). These parameteres were chosen based on psychophysiological evidence that emotional faces can be differentiated at $\leq$ 20 ms (Korgaonkar et al., 2013) and explicitly identified at $\geq$ 330 ms (Williams et al., 2004). For the subliminal task, each emotional face was superceded by a 150 ms neutral face that was randomly oriented one degree from the two dimensional plane to reduce conscious discrimation based on facial features. Each task run comprised of 30 stimuli blocks with five blocks for every emotion type. Each emotion block contained eight different faces (4 males nad 4 females) portraying the same emotion. The blocks were shown in a pseudorandom order with total 240 faces across the task. We used a 1233.3 ms interstimulus interval for the subliminal task, and a 750 ms interstimulus interval for the supraliminal task. The same faces were used for both tasks. The subliminal task was always presented first to reduce priming effects induced by conscious viewing of faces (supraliminal conditon) on processing of subliminal faces. Face stimuli were chosen from a standardized set of emotional faces modified to be centrally positioned at eye level (Gur et al., 2002).

2.5. Imaging acquisition

Functional task images were acquired with the 3 T GE Signa HDx scanner (eight channel head coil; GE Healthcare, Milwaukee, Wisconsin) using echo planar imaging MR sequence specifications: TR = 2500 ms, TE = 27.5 ms, Flip angle = 90°; FOV = 24 cm, matrix size = 64 × 64). For each participant, three dummy volumes were taken before acquiring data for the emotional faces task to evaluate stableness of the scanner's magnetization. During every scan, we obtained 40 continuous slices of 120 functional T2*-weighted volumes aligned with the inter-commissural line (voxel volume: 3.75 mm × 3.75 mm × 3.5 mm). We also generated 180 slices of T1-weighted anatomical structural images (1 mm^3 isotropic voxel resolution) in the sagittal plane to allow scans to be normalized to standard space by utilizing a 3D spoiled gradient echo sequence (parameters TR = 8.3 ms; TE = 3.2 ms; flip angle = 11°; TI = 500 ms; NEX = 1; ASSET = 1.5; Frequency direction: S/I; matrix size = 256 × 256).

2.6. fMRI data analysis

fMRI analyses were carried out using SPM8, and post-hoc analyses were completed with IBM SPSS Statistics 24 and have been described in detail in our previous work (Breukelaar et al., 2021, Korgaonkar et al., 2020). Neural data was pre-processed, which involved image realignment and warping, normalization, and signal estimation via extraction of white matter and ventricles. Participants exceeding a movement threshold of ≥ 30 (out of 120 scans), corresponding to the number of scans with movement spikes identified based on participant's head motion from one volume to the next was >0.3 mm (frame wise displacement) or had a difference in scaled signal intensity (global signal variance) >10, as well as the two volumes before and one after, were excluded from the study. Finally, images were smoothed (8 mm Gaussian Kernel).

During first level analyses, neural data from each emotion block were transformed into a Blood Oxygenation Level-Dependent (BOLD) response using a hemodynamic response within a general linear model framework. Contrast images were generated for each emotion versus implicit rest baseline. These images were used to investigate neural differences associated with emotional processing between PD and HC groups at the second-level of analysis. This analysis was carried out voxelwise using a 2 × 6 flexible factorial repeated measures ANOVA design with group as a between-subjects factor and emotion type as a within subject variable. A region of interest (ROI) analysis approach was used. The following ROIs were selected based on their involvement in emotional processing from existing literature and as used in our previous work (Bryant et al., 2020): the bilateral amygdala and bilateral insula, were generated using the Automated Anatomical Labelling (AAL) atlas (Tzourio-Mazoyer et al., 2002), whereas the dorsal, pregenual and subgenual anterior cingulate cortex, dACC: 0 24 38; pgACC: 0 42 4, sgACC: 0 24 –8; Kober et al., 2008), and the bilateral dorsolateral prefrontal cortex (DLPFC, L: −36 20 26, R: 46 30 18; Fusar-Poli et al., 2009) were constructed using a 8 mm radius sphere from *meta*-analyses of fMRI studies on emotional processing for greater and consistent activation for emotion processing versus baseline (either fixation cross or neutral). We performed post-hoc *t*-tests on significant clusters for group*emotion interaction effects to elucidate the direction of neural differences for each emotion type between groups. To do this, we extracted parameter estimates for significant clusters using MarsBaR 0.42 (Brett et al., 2002). In addition, we conducted generalized psychophysiological interaction (gPPI) connectivity to explore functional connectivity differences between groups with significant activation seeds. The same ROIs from activation analyses were used for functional connectivity analyses. All fMRI analyses controlled for the family wise error rate (FWE) at $p = 0.05$. Bivariate correlation analyses were also performed to assess the association between neural measures of significant clusters (using mean parameter estimates and also voxelwise) and ACQ, BDI and BAI scores. These analyses were also controlled for multiple comparisons using a family wise error rate of $p < 0.05$.

3. Results

3.1. Participant characteristics

Table 1 shows the participant characteristics. Groups did not differ on age ($t(53) = -0.015$, $p > 0.05$) or sex ($\chi^2 = 1.85$, $p > 0.05$). As expected, PD participants scored higher on the ACQ ($t(47) = 9.98$, $p < 0.001$), BAI ($t(46) = 13.52$, $p < 0.001$) and BDI ($t(46) = 9.08$, $p < 0.001$) compared to HC.

3.2. Neural activations and connectivity during emotional processing

For supraliminal face processing, there were no significant differences between the groups for our selected ROIs. However, at the whole brain level, we found a main group effect of reduced right cerebellum

Table 1
Participant characteristics.

	PD	HC
	(*n* = 22)	(*n* = 33)
Age, mean (SEM)	39.09(2.58)	33.58(2.14)
Female, *n* (%)	16(72.72)	18(54.55)
Medication use		
SSRI, *n* (%)	5(22.72)	0
SNRI, *n* (%)	4(18.18)	0
Anti-psychotics, *n* (%)	2(9.09)	0
Comorbid Diagnoses		
Major Depressive Disorder, *n* (%)	14(63.64)	1(4.55)
Social Phobia *n* (%)	11(50.00)	0
Agoraphobia, *n* (%)	14(63.64)	2(6.06)
PTSD *n* (%)	1(4.55)	0
Generalised Anxiety Disorder, *n* (%)	14(63.64)	0
Obsessive Compulsive Disorder, *n* (%)	4(18.18)	0
ACQ* (SEM)	35.3(1.97)	17.45(0.61)
BDI* (SEM)	27.76(2.66)	4.78(0.84)
BAI* (SEM)	28.7(1.93)	3.43(0.78)

* indicates significant difference between Panic Disorder and Control groups at $p < 0.05$. Abbreviations: ACQ, Agoraphobic Cognitions Questionnaire; BAI, Beck Anxiety inventory; BDI, Beck depression inventory; SEM, standard error of the mean; SSRI, Selective serotonin reuptake inhibitors; SNRI, Serotonin–norepinephrine reuptake inhibitors.

Table 2
Neural activation and connectivity differences in brain regions involved in emotional processing between PD and HC groups during supraliminal and subliminal presentations of emotional faces.

Brain region	Peak MNI Coordinates (x, y, z)	Cluster size (cor.)	Peak z-score	*p*-value (FWE cor.)	Direction
		Activation			
Supraliminal – whole brain analysis					
R Cerebellum	8, −64, −44 14, −64, −50	68	4.94 4.65	0.009 0.032	PD < HC
Subliminal – whole brain analysis n.s. Supraliminal – ROI analysis n.s. Subliminal – ROI analysis					
pgACC	−4, 36, 2	13	294	0.027	PD < HC Happy Faces PD < HC Sad Faces
		Connectivity			
Supraliminal – whole brain analysis n.s. Subliminal – whole brain analysis n.s. Supraliminal – ROI analysis n.s. Subliminal – ROI analysis					
pgACC – R Amygdala	34, −2, −28	8	3.01	0.026	PD < HC Sad Faces PD < HC Fear Faces

activity in PD relative to HC (FWE $p < 0.05$; Table 2; see Supplementary Material for figures).

During subliminal face processing, SPM second level ROI analysis showed a significant group × emotion interaction for the pgACC (FWE $p < 0.05$). Post-hoc tests indicated that the PD group had less activation in the pgACC during the presentation of happy and sad faces (Table 2; Fig. 1) compared to HC. No group differences in neural activity were identified for the subliminal face processing condition at the whole brain level (all FWE $p > 0.05$; see Supplementary Material).

Functional connectivity analyses showed that there was a connectivity difference between groups for the subliminal task. A group*-emotion effect for the pgACC to right amygdala connection was significant and was primarily driven by lower pgACC – right amygdala connectivity in the PD group during subliminal sad and fear emotional presentations compared to HC (Table 2; Fig. 2). There were no connectivity differences for the other emotions. To rule out any impact of medication use, we replicated both the activation and connectivity analyses using only the unmedicated patient cohort; our results were consistent with the primary analyses described above (see Supplementary Material). Additionally, we also observed pgACC activation differences for the neutral faces and pgACC-right amygdala connectivity to be additionally reduced for the happy and neutral subliminal faces for the unmedicated PD group relative to HC.

3.3. Correlations between clinical measures and neural activity

Mean beta estimates from significant activation and connectivity clusters were correlated with ACQ, BAI and BDI scores for PD and HC groups separately using bivariate and pooled controlling for group membership using partial Pearson correlations. There were no correlation between the clinical measures and mean values for neural activity or connectivity for any of the significant clusters for both PD and HC groups (all $p > 0.05$). However at the voxel-wise level, we observed significant (FWE $p < 0.05$) positive correlations between supraliminal activation for the right cerebellum with ACQ (for anger and fear emotions) and BDI (anger, sad, disgust and neutral emotions) scores (Table 3). There were no significant correlations for subliminal activation for any of the emotions in the pgACC and symptoms scores. For functional connectivity for pgACC- right amygdala for the subliminal task, there were significant positive correlations between connectivity for disgust faces and ACQ scores and negative correlations between connectivity for disgust faces and BDI scores (Table 3; see supplementary section for scatterplots). There were no significant associations for connectivity related to sad and fear faces that distinguished the PD and HC groups.

4. Discussion

This study represents the first study to investigate neural responding in PD during both supraliminal and subliminal processing of faces depicting a range of different emotions. The major findings were that PD was characterized by (a) less activation in the pgACC during subliminal happy and sad processing, and (b) less connectivity between the pgACC and right amygdala during subliminal sad and fear processing. While we did not observe any differences between groups for supraliminal processing of emotions in the primary processing and regulatory emotion brain regions, we did find that PD had less overall activation than controls in the cerebellum.

The finding of reduced pgACC activation in PD during processing of both happy and sad faces can be understood in light of much evidence that the pgACC is involved in emotional processing, and particularly in emotion regulation and emotion conflict (Egner et al. 2008; Eippert et al., 2009; Etkin et al., 2006). The involvement of the pgACC in regulation of emotional states suggests that the observed reduced pgACC activation in PD may reflect these individuals are less capable in regulating emotional responses to the emotionally expressive faces. Regarding the finding that this pattern was observed in response to happy faces suggests that PD participants did not engage the appropriate network in regulating this emotion in a similar manner as they responded to sad faces. Meta-analysis indicates that the pgACC is activated during processing of positive emotions (Wager et al., 2008), which can also serve to down-regulate negative emotional states (Etkin et al., 2011). Reinforcing this central role of the pgACC in anxiety is *meta*-analytic evidence that the pgACC grey matter volume is consistently reduced in anxiety disorders (Shang et al., 2014). Taken together, the reduced pgACC activation in PD participants may reflect their under-engagement in emotional regulation of affective states, which can apply to both positive and negative emotional processing.

The other major finding was the reduced connectivity between the pgACC and right amygdala in PD participants. There is considerable evidence for the central role of ACC and amygdala connectivity in down-regulating limbic-based emotional states (Etkin et al., 2011; Mansouri et al., 2009), and how this disrupted connectivity may underlie anxiety disorders (Etkin, 2010). Meta-analytic studies of resting state connectivity indicate that pgACC-amygdala connectivity is strongly associated with the internalizing spectrum of symptoms (Marusak et al., 2016), which are core to anxiety and PD. The reduced connectivity of the pgACC-amygdala may reflect that PD is characterized by poor down-regulation of affective states, regardless of the affective state.

Our results were observed only during the subliminal emotion processing task. We did not observe any neural differences in the primary emotion processing and regulatory brain regions between the panic

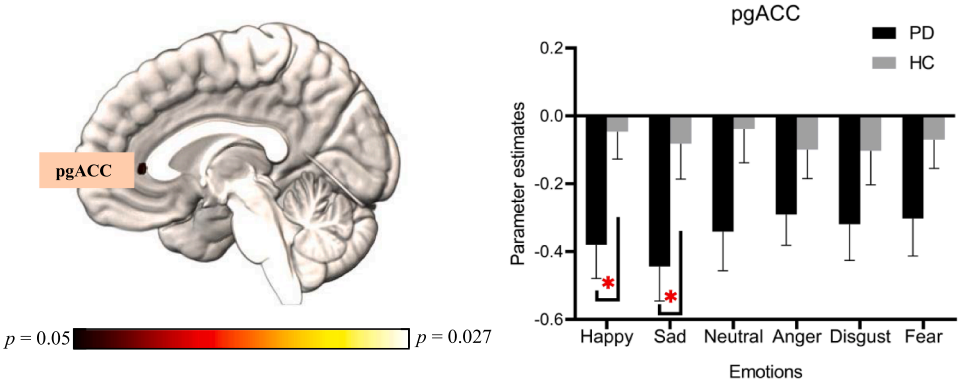

Fig. 1. BOLD differences in the pgACC between PD and HC during the subliminal emotional face processing task. The figure shows that PD individuals had less pgACC activity (subliminal condition) compared to HC (group*emotion interaction at FWE $p < 0.05$) for happy and sad faces. Activation differences between groups for all emotions were calculated using extracted beta estimates. The colour bar indicates the corrected FWE *p*-value for individual voxels in the pgACC.

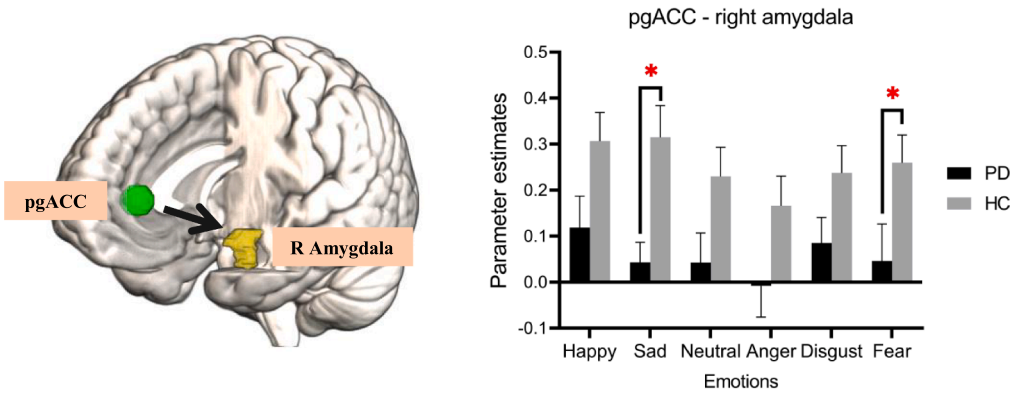

Fig. 2. Between group differences in terms of pgACC connectivity to the right amygdala during subliminal presentation of emotional faces. The 3D canonical brain (MRIcroGL; Rorden, 2021) shows the pgACC to right amygdala pathway where connectivity differences exist between PD and HC. Post-hoc comparisons using mean beta estimates show that this difference is driven by reduced PD connectivity for this pathway relative to controls during subliminal processing of fear and sad emotions.

Table 3
Cluster table corresponding to voxel-wise level correlational analyses conducted to determine the association between clinical measures and neural measures that distinguish PD from HC (FWE $p = 0.05$ corrected level).

ROI	Peak MNI Coordinates (x, y, z)	Cluster size (cor.)	Peak z-score	*p*-value (cor.)	Emotion	Clinical Measure	Direction
Supraliminal Task							
R cerebellum activation	24–44 −52	1	3.4	0.049	Anger	ACQ	Positive
	24–42 −54	2	3.45	0.041	Fear	ACQ	Positive
	32–38 −44	2	3.63	0.024	Disgust	BDI	Positive
	32–40 −44	7	3.68	0.021	Anger	BDI	Positive
	32–38 −44	1	3.44	0.043	Sad	BDI	Positive
	32–38 −44	4	3.57	0.027	Neutral	BDI	Positive
Subliminal Task							
pgACC activation				*n.s.*			
pgACC-R Amygdala connectivity	24 2–18	11	3.01	0.029	Disgust	ACQ	Positive
	26 4–28	4	2.97	0.032	Disgust	BAI	Negative

Abbreviations: ROI, region of interest; R, right; pgACC, pregenual anterior cingulate cortex; cor, corrected; ACQ, Agoraphobic Ccognitions Questionnaire; BAI, Beck Anxiety Inventory.

disorder group relative to controls in supraliminal processing of facial emotion. This is inconsistent with results from previous studies that have observed hypoactivation of the amygdala and ACC brain regions in individuals with panic disorder for processing of happy, angry, fearful emotions (Demenescu et al., 2013; Pillay et al., 2006). It is likely that this may be due to methodological or cohort differences between the studies. Both these previous studies have relied on relatively smaller sized cohorts as compared to our study. We did observe that PD group had lower activation in the cerebellum across emotions compared to controls for the supraliminal task. Although the cerebellum was not our predefined ROI, these results are in line with the functional involvement of the cerebellum in fear and anxiety disorders (Moreno-Rius, 2018) and previous findings of reduced resting connectivity in this region in PD (Ni et al., 2021). Furthermore, greater activation of the cerebellum in PD was significantly correlated with worse depressive (BDI) and fear of bodily symptoms associated with anxiety and panic (ACQ). However the direction of association of this finding was unexpected considering that PD group demonstrated reduced cerebellar activity compared to controls.

The subliminal task is designed to tap into bottom up mechanisms of emotion processing that are engaged fairly early in the temporal processing of emotions. The finding of both abnormal activation and connectivity related to pgACC during preconscious processing of emotions indicates that PD is characterized by deficient regulation at a very early stage of emotion processing. Studies using tasks designed to specifically test emotion regulatory brain circuits e.g. conscious reappraisal of negative emotions are required to fully understand the neural deficits in conscious level of emotion processing in PD.

In the context of symptoms observed in panic disorder, it is also important to consider that the overall reduced activation observed in both the supraliminal and subliminal tasks could possibly be due to hyperventilation or panic attacks due to claustrophobia experienced in the MRI scanner. Respiratory alterations due to increased anxiety are known to reduce cerebral blood flow (and hence the BOLD fMRI signal effects) that are independent of task-related neural activation (Giardino et al., 2007). While the participants in our study did not report any incidents of panic attacks during scanning, the impact of respiratory alterations on the neural signal cannot be ruled out. Also, our PD cohort was highly comorbid with depressive symptoms and it is likely that the neural deficits observed could be an effect of depression. However, it is important to note that only supraliminal activation in the cerebellum was found to be associated with severity of depression (BDI scores) in our study and we did not observe significant associations between depressive symptom scores and activation in the pgACC or connectivity between pgACC and right amygdala for subliminal processing of emotions that distinguished PD from controls in our study.

A few limitations should be considered. Our study relies on facial expression of emotions and generalizability of findings should be testing using other forms of affective stimuli and also nuanced features of emotion regulations e.g. emotion conflict processing or reappraisal. The sample size used in our study is relatively low and findings should be replicated using larger cohorts - particularly the lack of findings for conscious processing of emotions. Future work should also focus on evaluating causal relationships between brain regions to fully understand the neural dynamics of emotion processing underlying this disorder. Also, deficits in the neural circuitry underlying emotion processing has been observed across other forms of anxiety disorders such as PTSD and social phobia (Killgore et al., 2014). Whether these deficits are specific to panic disorder cannot be concluded based on this work. Studies that formally compare emotion deficits across several

forms of anxiety disorders are required. Although we measured fear of bodily symptoms (ACQ questionnaire) in our study, assessment of panic attacks and panic disorder symptom severity (e.g. using the PDSS, panic disorder severity scale Shear et al., 1997) would have provided a thorough assessment of severity of panic symptoms and test associations with neural measures.

5. Conclusion

In conclusion, our study provides evidence of deficits in regulatory brain networks at very early stages of affect processing in PD. Individuals with PD seem to be less capable of engaging the regulatory control of brain regions involved in emotion processing and this is reflected in hypoactivation and hypoconnectivity of the pregenual anterior cingulate cortex in particular. This mechanism could potentially underlie the excessive pre-attention to threat which is a characteristic feature of this disorder and could be a potential target mechanism for treatments.

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CRediT authorship contribution statement

Mayuresh S. Korgaonkar: Methodology, Software, Writing – original draft, Writing – review & editing, Supervision. **Jenny Tran:** Data curation, Writing – original draft, Writing – review & editing. **Kim L. Felmingham:** Methodology, Writing – review & editing, Supervision. **Leanne M. Williams:** Methodology, Resources, Writing – review & editing, Funding acquisition. **Richard A. Bryant:** Conceptualization, Methodology, Resources, Writing – review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2021.102902.

References

American Psychiatric Association, 2013. Diagnostic and statistical manual of mental disorders, 5th ed. Author, Arlington, VA.

Adolphs, R., 2002. Recognizing emotion from facial expressions: psychological and neurological mechanisms. Behav. Cogn. Neurosci. Rev. 1 (1), 21–62. https://doi.org/10.1177/1534582302001001003.

Baker, R., Holloway, J., Thomas, P.W., Thomas, S., Owens, M., 2004. Emotional processing and panic. Behav. Res. Ther. 42 (11), 1271–1287. https://doi.org/10.1016/j.brat.2003.09.002.

Breukelaar, I.A., Bryant, R.A., Korgaonkar, M.S., 2021. The functional connectome in posttraumatic stress disorder. Neurobiol. Stress 14, 100321. https://doi.org/10.1016/j.ynstr.2021.100321.

Bryant, R.A., Erlinger, M., Felmingham, K., Malhi, G.S., O'Donnell, M.L., Williams, L.M., Korgaonkar, M., 2020. Differential neural predictors of treatment response for fear and dysphoric features of posttrraumatic stress disorder. Depression Anxiety 37, 1026–1036. https://doi.org/10.1002/da.23061.

Beck, A.T., Epstein, N., Brown, G., Steer, R.A., 1988. An inventory for measuring clinical anxiety. Psychometric properties. J. Consult. Clin. Psychol. 56, 893–897. https://doi.org/10.1037/0022-006X.56.6.893.

Beck, A.T., Steer, R.A., Brown, G.K., 1996. Beck Depression Inventory-Second Edition. The Psychological Corporation, San Antonio, TX.

Brett, et al., 2002. Marseille region of interest toolbox (Version 0.42). [Computer software]. SourceForge. http://marsbar.sourceforge.net/.

Chambless, D.L., Caputo, B., Bright, P.O., Gallagher, R., 1984. Assessment of fear of fear in agoraphobics: The body sensations questionnaire and the agoraphobics cognitions questionnaire. J. Consult. Clin. Psychol. 52, 1090–1097. https://doi.org/10.1037/0022-006X.52.6.1090.

Demenescu, L.R., Kortekaas, R., Cremers, H.R., Renken, R.J., van Tol, M.J., van der Wee, N.J.A., Veltman, D.J., den Boer, J.A., Roelofs, K., Aleman, A., 2013. Amygdala activation and its functional connectivity during perception of emotional faces in social phobia and panic disorder. J. Psychiatr. Res. 47 (8), 1024–1031. https://doi.org/10.1016/j.jpsychires.2013.03.020.

Egner, T., Etkin, A., Gale, S., Hirsch, J., 2008. Dissociable neural systems resolve conflict from emotional versus nonemotional distracters. Cereb. Cortex 18 (6), 1475–1484. https://doi.org/10.1093/cercor/bhm179.

Eippert, F., Bingel, U., Schoell, E.D., Yacubian, J., Klinger, R., Lorenz, J., Buchel, C., 2009. Activation of the opioidergic descending pain control system underlies placebo analgesia. Neuron 63 (4), 533–543. https://doi.org/10.1016/j.neuron.2009.07.014.

Etkin, A., 2010. Functional neuroanatomy of anxiety: a neural circuit perspective. Curr. Top. Behav. Neurosci. 2, 251–277. https://doi.org/10.1007/7854_2009_5.

Etkin, A., Egner, T., Kalisch, R., 2011. Emotional processing in anterior cingulate and medial prefrontal cortex. Trends Cogn. Sci. 15 (2), 85–93. https://doi.org/10.1016/j.tics.2010.11.004.

Etkin, A., Egner, T., Peraza, D.M., Kandel, E.R., Hirsch, J., 2006. Resolving emotional conflict: A role for the rostral anterior cingulate cortex in modulating activity in the amygdala. Neuron 51 (6), 871–882. https://doi.org/10.1016/j.neuron.2006.07.029.

Fonzo, Gregory A., Ramsawh, Holly J., Flagan, Taru M., Sullivan, Sarah G., Letamendi, Andrea, Simmons, Alan N., Paulus, Martin P., Stein, Murray B., 2015. Common and disorder-specific neural responses to emotional faces in generalised anxiety, social anxiety and panic disorders. Br. J. Psychiatry 206 (3), 206–215. https://doi.org/10.1192/bjp.bp.114.149880.

Fusar-Poli, P., Placentino, A., Carletti, F., Landi, P., Allen, P., Surguladze, S., et al., 2009. Functional atlas of emotional faces processing: A voxel-based meta-analysis of 105 functional magnetic resonance imaging studies. J. Psychiatry Neurosci. 34, 418–432.

Giardino, Nicholas D., Friedman, Seth D., Dager, Stephen R., 2007. Anxiety, respiration, and cerebral blood flow: implications for functional brain imaging. Compr. Psychiatry 48 (2), 103–112.

Gur, Ruben C., Sara, Radim, Hagendoorn, Michiel, Marom, Oren, Hughett, Paul, Macy, Larry, Turner, Travis, Bajcsy, Ruzena, Posner, Aaron, Gur, Raquel E., 2002. A method for obtaining 3-dimensional facial expressions and its standardization for use in neurocognitive studies. J. Neurosci. Methods 115 (2), 137–143.

Kessler, Henrik, Roth, Julia, von Wietersheim, Joern, Deighton, Russell M., Traue, Harald C., 2007. Emotion recognition patterns in patients with panic disorder. Depression Anxiety 24 (3), 223–226. https://doi.org/10.1002/(ISSN)1520-639410.1002/da.v24:310.1002/da.20223.

Killgore, William D.S., Britton, Jennifer C., Schwab, Zachary J., Price, Lauren M., Weiner, Melissa R., Gold, Andrea L., Rosso, Isabelle M., Simon, Naomi M., Pollack, Mark H., Rauch, Scott L., 2014. Cortico-limbic responses to masked affective faces across ptsd, panic disorder, and specific phobia. Depression Anxiety 31 (2), 150–159. https://doi.org/10.1002/da.2014.31.issue-210.1002/da.22156.

Kober, Hedy, Barrett, Lisa Feldman, Joseph, Josh, Bliss-Moreau, Eliza, Lindquist, Kristen, Wager, Tor D., 2008. Functional grouping and cortical-subcortical interactions in emotion: A meta-analysis of neuroimaging studies. NeuroImage 42 (2), 998–1031. https://doi.org/10.1016/j.neuroimage.2008.03.059.

Korgaonkar, M.S., Grieve, S.M., Etkin, A., Koslow, S.H., Williams, L.M., 2013. Using standardized fMRI protocols to identify patterns of prefrontal circuit dysregulation that are common and specific to cognitive and emotional tasks in major depressive disorder: first wave results from the iSPOT-D study. Neuropsychopharmacology 38 (5), 863–871. https://doi.org/10.1038/npp.2012.252.

Korgaonkar, Mayuresh S., Goldstein-Piekarski, Andrea N., Fornito, Alexander, Williams, Leanne M., 2020. Intrinsic connectomes are a predictive biomarker of remission in major depressive disorder. Mol. Psychiatry 25 (7), 1537–1549. https://doi.org/10.1038/s41380-019-0574-2.

Lim, S.L., Kim, J.H., 2005. Cognitive processing of emotional information in depression, panic, and somatoform disorder. J. Abnorm. Psychol. 114 (1), 50–61. https://doi.org/10.1037/0021-843X.114.1.50.

Lundh, L.G., Wikstrom, J., Westerlund, J., Ost, L.G., 1999. Preattentive bias for emotional information in panic disorder with agoraphobia. J. Abnorm. Psychol. 108 (2), 222–232. https://doi.org/10.1037//0021-843x.108.2.222.

Mansouri, F.A., Tanaka, K., Buckley, M.J., 2009. Conflict-induced behavioural adjustment: a clue to the executive functions of the prefrontal cortex. Nat. Rev. Neurosci. 10 (2), 141–152. https://doi.org/10.1038/nrn2538.

Marusak, H.A., Thomason, M.E., Peters, C., Zundel, C., Elrahal, F., Rabinak, C.A., 2016. You say 'prefrontal cortex' and I say 'anterior cingulate': meta-analysis of spatial overlap in amygdala-to-prefrontal connectivity and internalizing symptomology. Transl. Psychiatry 6 (11), e944. https://doi.org/10.1038/tp.2016.218.

Mogg, K., Wilson, K.A., Hayward, C., Cunning, D., Bradley, B.P., 2012. Attentional biases for threat in at-risk daughters and mothers with lifetime panic disorder. J. Abnorm. Psychol. 121 (4), 852–862. https://doi.org/10.1037/a0028052.

Moreno-Rius, J., 2018. The cerebellum in fear and anxiety-related disorders. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 85, 23–32. https://doi.org/10.1016/j.pnpbp.2018.04.002.

Ni, Ming-Fei, Zhang, Bing-Wei, Chang, Yi, Huang, Xiao-Feng, Wang, Xiao-Ming, 2021. Altered resting-state network connectivity in panic disorder: an independent ComponentAnalysis. Brain Imag. Behav. 15 (3), 1313–1322. https://doi.org/10.1007/s11682-020-00329-z.

Ottaviani, Cristina, Cevolani, Daniela, Nucifora, Valeria, Borlimi, Rosita, Agati, Raffaele, Leonardi, Marco, De Plato, Giovanni, Brighetti, Gianni, 2012. Amygdala responses to

masked and low spatial frequency fearful faces: a preliminary fMRI study in panic disorder. Psychiatry Res. 203 (2-3), 159–165. https://doi.org/10.1016/j.pscychresns.2011.12.010.

Pillay, S.S., Gruber, S.A., Rogowska, J., Simpson, N., Yurgelun-Todd, D.A., 2006. fMRI of fearful facial affect recognition in panic disorder: the cingulate gyrus-amygdala connection. J. Affect. Disord. 94 (1–3), 173–181. https://doi.org/10.1016/j.jad.2006.04.007.

Pillay, S.S., Rogowska, J., Gruber, S.A., Simpson, N., Yurgelun-Todd, D.A., 2007. Recognition of happy facial affect in panic disorder: an fMRI study. J. Anxiety Disord. 21 (3), 381–393. https://doi.org/10.1016/j.janxdis.2006.04.001.

Rachman, S., 1980. Emotional processing. Behav. Res. Therapy 18 (1), 51–60. https://doi.org/10.1016/0005-7967(80)90069-8.

Reinecke, A., Cooper, M., Favaron, E., Massey-Chase, R., Harmer, C., 2011. Attentional bias in untreated panic disorder. Psychiatry Res. 185 (3), 387–393. https://doi.org/10.1016/j.psychres.2010.07.020.

Reinecke, A., Waldenmaier, L., Cooper, M.J., Harmer, C.J., 2013. Changes in automatic threat processing precede and predict clinical changes with exposure-based cognitive-behavior therapy for panic disorder. Biol. Psychiatry 73 (11), 1064–1070. https://doi.org/10.1016/j.biopsych.2013.02.005.

Rorden, C., 2021. MRIcroGL (Version 1.2.20210317). [Computer software]. NITRIC: Neuroimaging tools and & resources collaboratory. https://www.nitrc.org/projects/mricrogl.

Shang, Jing, Fu, Yuchuan, Ren, Zhengjia, Zhang, Tao, Du, Mingying, Gong, Qiyong, Lui, Su, Zhang, Wei, Chen, Huafu, 2014. The common traits of the ACC and PFC in anxiety disorders in the DSM-5: meta-analysis of voxel-based morphometry studies. PLoS ONE 9 (3), e93432. https://doi.org/10.1371/journal.pone.009343210.1371/journal.pone.0093432.g00110.1371/journal.pone.0093432.t00110.1371/journal.pone.0093432.t00210.1371/journal.pone.0093432.t00310.1371/journal.pone.0093432.t00410.1371/journal.pone.0093432.t00510.1371/journal.pone.0093432.s001.

Shear, M.K., Brown, T.A., Barlow, D.H., Money, R., Sholomskas, D.E., Woods, S.W., Gorman, J.M., Papp, L.A., 1997. Multicenter collaborative panic disorder severity scale. Am. J. Psychiatry 154, 1571–1575.

Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Dunbar, G.C., 1998. The Mini-International Neuropsychiatric Interview (MINI): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J. Clin. Psychiatry 59, 22–33.

Tamietto, M., de Gelder, B., 2010. Neural bases of the non-conscious perception of emotional signals. Nat. Rev. Neurosci. 11 (10), 697–709. https://doi.org/10.1038/nrn2889.

Thibaut, F., 2017. Anxiety disorders a review of current literature. Dialogues Clin. Neurosci. 19 (2), 87–88. https://doi.org/10.31887/DCNS.2017.19.2/fthibaut.

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., Joliot, M., 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage 15 (1), 273–289. https://doi.org/10.1006/nimg.2001.0978.

Wager, T., Barrett, L.F., Bliss-Moreau, E., Lindquist, K.A., et al., 2008. The neuroimaging of emotion. In: Lewis, M. (Ed.), Handbook of emotion, 3rd ed. Guilford, New York.

Williams, Leanne M., Liddell, Belinda J., Rathjen, Jennifer, Brown, Kerri J., Gray, Jeffrey, Phillips, Mary, Young, Andy, Gordon, Evian, 2004. Mapping the time course of nonconscious and conscious perception of fear: an integration of central and peripheral measures. Hum. Brain Mapp. 21 (2), 64–74. https://doi.org/10.1002/(ISSN)1097-019310.1002/hbm.v21:210.1002/hbm.10154.

Zugliani, M.M., Martin-Santos, R., Nardi, A.E., Freire, R.C., 2017. Personality Traits in Panic Disorder Patients With and Without Comorbidities. J. Nervous Menalt Disease 205 (11), 855–858. https://doi.org/10.1097/NMD.0000000000000745.