

RESEARCH ARTICLE

Trait anger modulates neural activity in the fronto-parietal attention network

Nelly Alia-Klein^{1*}, Rebecca N. Preston-Campbell², Scott J. Moeller³, Muhammad A. Parvaz¹, Keren Bachi¹, Gabriela Gan⁴, Anna Zilverstand¹, Anna B. Konova⁵, Rita Z. Goldstein¹

1 Departments of Psychiatry and Neuroscience, Icahn School of Medicine at Mount Sinai, New York, New York, United States of America, **2** Battelle Public Health Research & Translational Science, St. Louis, Missouri, United States of America, **3** Department of Psychiatry, Stony Brook University School of Medicine, Stony Brook, New York, United States of America, **4** Department of Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Heidelberg, Germany, **5** Center for Neural Science, New York University, New York, New York

* nelly.alia-klein@mssm.edu



OPEN ACCESS

Citation: Alia-Klein N, Preston-Campbell RN, Moeller SJ, Parvaz MA, Bachi K, Gan G, et al. (2018) Trait anger modulates neural activity in the fronto-parietal attention network. *PLoS ONE* 13(4): e0194444. <https://doi.org/10.1371/journal.pone.0194444>

Editor: Alessio Avenanti, University of Bologna, ITALY

Received: August 16, 2017

Accepted: March 2, 2018

Published: April 19, 2018

Copyright: © 2018 Alia-Klein et al. This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability Statement: The data is available upon request. Because IED and aggression data are sensitive, and in compliance with our research's approval from the IRB of SUNY Stony Brook, New York, we will make the data and associated documentation available to users only under a data-sharing agreement. Data requests can be addressed to nelly.alia-klein@mssm.edu.

Funding: This work was supported by a grant from the National Institute of Health (nih.gov; R01MH090134 to N.A.K.) and grants from the

Abstract

Anger is considered a unique high-arousal and approach-related negative emotion. The influence of individual differences in trait anger on the processing of visual stimuli is relevant to questions about emotional processing and remains to be explored. Using functional magnetic resonance imaging (fMRI), we explored the neural responses to standardized images, selected based on valence and arousal ratings in a group of men with high trait anger compared to those with normative to low anger scores (controls). Results show increased activation in the left-lateralized ventral fronto-parietal attention network to unpleasant images by individuals with high trait anger. There was also a group by arousal interaction in the left thalamus/pulvinar such that individuals with high trait anger had increased pulvinar activation to the high-arousal (versus low arousal) unpleasant images as compared to controls. Thus, individual differences in trait anger in men are associated with brain regions subserving executive attentional and sensory integration during the processing of unpleasant emotional stimuli, particularly to high arousal images.

Introduction

Anger is considered to be an approach-related emotional state incorporating physiological, affective, cognitive, and behavioral components which occur in response to unpleasant or undesired events [1–4]. The experience and expression of anger is demonstrated as high-arousal emotional reactivity to negatively valenced stimuli [2–8]. Some individuals are prone to experiencing anger, reflecting an enduring trait pattern of response [6, 9, 10]. Evidence has shown that individuals with elevated levels of anger demonstrate reduced self-control [11] while attributing disproportionate salience and preferentially attending particularly to negatively valenced stimuli or threatening cues [9, 12–14].

National Institute on Drug Abuse (drugabuse.gov; 5T32DA007135-32 to R.P.-C., K01DA037452 to S. J.M., F32DA033088 to M.A.P.).

Competing interests: The authors have declared that no competing interests exist.

Functional neuroimaging studies have implicated a network of brain regions subserving the processing of emotional stimuli encompassing the amygdala, insula, and prefrontal cortical (PFC) areas [e.g., medial and lateral PFC, and the orbitofrontal cortex (OFC)] [15–20]. Further, emotional processing of visual stimuli involves the visuospatial-attentional processing network, including the visual cortex, parietal cortex [21], dorsolateral prefrontal cortex (DLPFC), and thalamus [22]. These networks are also involved in motivated attention to the significance, or sensory distinctiveness of the stimuli, and are modulated by both stimulus valence (i.e., pleasant or unpleasant) and arousal levels [23, 24]. The neural processing of arousal, or the intensity of the experience of an emotion, which can range from calming to exciting or agitating [25], has been associated with activation in the amygdala, insula, ventrolateral PFC, and dorsomedial PFC [25–28].

Currently, the relationship between elevated trait anger and neural activity during emotion processing is not well understood. It is postulated that the approach motivation in anger, modulates the evaluative response to salient stimuli [1, 2, 29]. This motivational theoretical model suggests that cortical regions are asymmetrically involved in approach and avoidance motivation, and that approach-related anger [30], associated with increased levels of left lateralized brain activity [31, 32] and decreased levels of right frontal activity [2] reflects a bias or selective attention to negatively valenced stimuli. These network functions may share characteristic patterns in externalizing psychopathology. For example, individuals with intermittent explosive disorder (IED) and cocaine addiction show hyper-reactivity to error commission and left DLPFC positivity correlated with increased trait anger expression [33]. Others vulnerable to externalizing psychopathology have demonstrated reduced prefrontal cortex [medial (MPC), anterior and posterior cingulate cortex (ACC, PCC) and OFC] and increased insula and subcortical responses (amygdala, hippocampus, thalamus [34–38] on behavioral inhibitory control and emotional tasks; yet, little is known about the neural mechanisms underlying elevated trait anger.

One important element that may modulate the neural response by individuals with high trait anger is autonomic response characterized by overall low level of physiological arousal. We recently documented reduced blood pressure and reduced OFC response to violent video content in a reactive aggressive sample [11]. Cardiovascular hypoarousal is directly associated with neural activity within areas of the anterior cingulate cortex, OFC, medial prefrontal cortices, and the amygdala and often in interaction with activity in the insula, and relay regions of the thalamus and brainstem [22].

In this study we chose to explore the neuronal correlates of viewing images that are normatively considered unpleasant (i.e., of negative valence) in individuals with high trait anger in order to uncover the potential effects of increased attention or sensitivity to negatively valenced cues in this population. Our intent was to determine if individuals with elevated trait anger as compared to controls would demonstrate increased blood oxygenation level dependent (BOLD) activity in left-lateralized brain attention networks that are involved in processing of normatively considered ‘high arousal’ emotional visual stimuli. During fMRI, individuals with elevated trait anger and those with normative trait anger viewed affectively unpleasant and pleasant pictures, which varied on normative population values of subjective arousal (high vs. low). We hypothesized that, relative to controls, men with high trait anger (HTAs) would show left lateralized hyper-reactivity of networks involved in emotional processing and attention allocation, specifically in response to viewing high arousal unpleasant visual stimuli.

Because anger is often a precursor for violent behavior, there are clinically relevant implications to understanding psychiatric conditions that are marked by elevated levels of anger [i.e., IED, antisocial personality disorder (ASPD)]. As such, modulating neural reactivity to aversive

stimuli by individuals with high trait anger through biofeedback for example may be a candidate approach for therapeutic intervention.

Methods

Ethics statement

This research was approved by the Institutional Review Board (IRB) at Stony Brook University. All individuals provided written informed consent in accordance to the IRB prior to study participation.

Participants

Healthy individuals and those who felt their anger experiences were problematic were recruited from the general population, through newspaper advertisements and word-of-mouth. Inclusion criteria were for native English speaking and not currently taking any medication. Exclusion criteria were the following: 1) any neurological condition, history of seizures, and/or head trauma with loss of consciousness (>30 minutes); 2) use of any psychoactive medication within 6-months prior to the study; 3) history of cardiovascular (e.g., high blood pressure), endocrinological, metabolic, oncological, or autoimmune diseases; 4) contraindications to MRI; 5) history of major psychiatric disorder other than IED or ASPD; 6) current alcohol intoxication or positive urine screens for psychoactive drugs or their metabolites (amphetamine or methamphetamine, cocaine, phencyclidine, benzodiazepines, cannabis, opiates, barbiturates, or inhalants).

Thirty-seven male participants were grouped via median split using the State-Trait Anger Expression Inventory (STAXI-2) [3, 39, 40]. Specifically, the Trait Anger subscale divided subjects to the Trait Anger (HTAs) group [(N = 20, mean \pm standard deviation, 25.5 ± 1.8) and control group (N = 17, 11.8 ± 0.49)]. Using a one-sample t-test, the HTAs' mean score was significantly higher, and the controls' was significantly lower, than the normative Trait Anger score at the 50th percentile for men [40] (both $p < 0.001$), indicating that this split was a valid way of partitioning the groups. Participants underwent a comprehensive clinical interview consisting of the Structured Clinical Interview for DSM-IV Axis-I Disorders [41]; the Structured Clinical Interview for Axis-II personality disorders, specifically Cluster B (Antisocial Personality Disorder; ASPD) [42]; and an assessment for IED according to DSM-IV criteria (IED-IR) [43]. The psychiatric disorder IED is defined as the inability to resist aggressive impulses that result in repeated acts of verbal and/or physical aggression that are grossly out of proportion to the experienced provocation, affecting 7% of the US population (lifetime prevalence) [44, 45]. This disorder has been associated with affect dysregulation, clinically substantial features of increased levels of trait anger and deficits in social-emotional information processing [46, 47].

Based on this clinical interview, nine HTAs had a diagnosis related to anger/aggression, of which five met criteria for IED, and four met criteria for ASPD. No psychopathology was found in controls. Importantly, the groups were matched on age, race, handedness, education, and estimates of verbal and non-verbal intelligence (Table 1).

Task

Participants passively viewed a series of IAPS images [48], a normed image bank widely used in studies investigating the neural correlates of emotional processing [26]. This bank is comprised of emotion laden images selected with respect to ratings on the dimensions of valence and arousal. Using normative image values from male raters, and defining levels of arousal

Table 1. Demographics and estimates of intelligence for all study participants.

Participants (all male)	Test	p-value	HTAs (n = 20)	Controls (n = 17)
^a Age (years)	$t_{35} = 0.87$	0.38	34.9 ± 8.3	32.7 ± 6.5
^b Race (Black/Hispanic/Caucasian/Other)	$\chi^2 = 0.95$	0.82	12 / 4 / 3 / 1	10 / 4 / 3 / 0
Handedness (right/left)	$\chi^2 = 0.01$	0.91	19/1	16/1
Education (years)	$t_{35} = 0.50$	0.62	13.1 ± 1.5	13.3 ± 1.59
Verbal IQ: Wide Range Achievement Test III: Reading Scale	$t_{35} = 1.36$	0.18	10.6 ± 3.8	12.1 ± 2.3
Non-verbal IQ: WASI—Matrix Reasoning Subtest	$t_{35} = 0.98$	0.33	10.0 ± 2.7	10.9 ± 2.8

^a Values are frequencies or means ± standard deviation.

^b Race: Other (Asian / more than one race).

<https://doi.org/10.1371/journal.pone.0194444.t001>

based on one standard deviation above or below the mean, we selected an image subset of 100 images (25 per condition) for use in the construction of each unique block presented in the fMRI: unpleasant high-arousal (violence, bodily mutilation, and threat), unpleasant low-arousal (people in distress, accidents), pleasant high-arousal (nudity, erotica), and pleasant low-arousal (nature scenes, infants). Normative means and standard deviations for each image condition and tests comparing the conditions are presented in Table 2.

Each image was presented for 6.75 seconds in blocks of four images of the same type (e.g., unpleasant high-arousal) presented serially. Blocks were separated by a fixation cross (inter trial interval) of 20 seconds, presented before the first image block, but not after the last image block. This fixation cross served as the implicit baseline for our fMRI analyses. Participants completed two runs, each with eight unique blocks (32 images per block; total of 64 different images). Both the blocks and the presentation of the images within each block were pseudorandomized and counterbalanced within and across runs, such that blocks of the same condition were not repeated serially and block sequences of four were not repeated in a run (e.g., ABCD, CDBA). During the task, participants viewed the images through MR-compatible goggles; presentation of stimuli was controlled using an IBM-compatible computer running the E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA). Participants were instructed to keep their eyes open, not to move their head or body during the scan, and to press a button to confirm viewing each image. Prior to the first experimental run, participants were familiarized with the paradigm by completing a practice run of three blocks of neutral pictures.

After exiting the scanner, a subset of participants (HTAs, n = 12; controls, n = 12) completed ratings for a selection of the fMRI task images (12 images); nine unique sequences of 12

Table 2. Means and standard deviations for valence and arousal for the IPAS pictures in each condition and t-tests testing for significant differences between conditions.

	Mean ^a Valence	SD	Mean ^a Arousal	SD
Unpleasant-NA	2.88	.19559	4.58	.22630
Unpleasant-HA	2.7516	.35293	6.0491	.18666
Pleasant-NA	7.0133	.24203	4.4130	.20911
Pleasant-HA	7.2879	.27704	6.6293	.26090
Condition comparison	t-valence	p-value	t-arousal	p-value
Unpleasant-NA vs Unpleasant-HA	1.145	.258	-6.662	< 0.001
Pleasant-HA vs. Pleasant-NA	-1.436	.157	-8.125	< 0.001

^a Norm values are taken from Lang PB, MM; Cuthbert BN. International Affective Picture System (IAPS): Affective Ratings of Pictures and Instruction Manual. 2005.

<https://doi.org/10.1371/journal.pone.0194444.t002>

images were created. Each picture was accompanied by two questions, measuring arousal and valence, respectively: Arousal: “How *excited* or *calm* does this make you feel?” Valence: “How *pleasant* or *unpleasant* does this make you feel?” All responses were recorded using a visual analogue scale (1–9; where 1 designated no arousal or unpleasant and 9 designated high arousal or pleasant).

Functional MRI

Functional magnetic resonance imaging was performed on a 4T whole-body Varian/Siemens MRI scanner. The BOLD-fMRI responses were measured as a function of time using a T2*-weighted single-shot gradient-echo planar sequence (TE/TR = 20/1600 ms, 4 mm slice thickness, 1 mm gap, 33 coronal slices, 20 cm FOV, 64 × 64 matrix size, 90°-flip angle, 200 kHz bandwidth with ramp sampling, 470 time points, and 4 dummy scans to avoid non-equilibrium effects in the fMRI signal). Earplugs (28 dB sound attenuation; Aearo Ear TaperFit 2; Aearo Company) and headphones (30 dB sound attenuation; Commander XG MRI Audio System, Resonance Technology Inc.) were used to minimize scanner noise [49].

Image preprocessing and statistical analyses

Data were pre-processed and analysed using SPM8 (Wellcome Department of Cognitive Neurology, London UK) (<http://www.fil.ion.ucl.ac.uk/spm>) running on MATLAB 2007b (Mathworks Inc., Natick, MA). A six-parameter rigid-body transformation (3 rotations, 3 translations) was used for image realignment and to correct for head motion. Criteria for acceptable motion were <2 mm displacement and <2° rotation in any axis in any task run. The realigned datasets were spatially normalized to the standard stereotactic space of the Montreal Neurological Institute (MNI) using a 12-parameter affine transformation (3 translations, 3 rotations, 3 shears, 3 zooms), and a voxel size of 3-mm³. An 8-mm full-width-half-maximum Gaussian kernel spatially smoothed the data.

For first-level analysis, images were thresholded using the default masking threshold of 0.8. To calculate individual BOLD-fMRI maps for the task, which has a blocked design comprising 470 time points, a general linear model and a box-car design convolved with a canonical hemodynamic response function and high-pass filter (cutoff frequency 1/800s) was used. Four contrast images per participant were calculated for each of the image conditions (unpleasant low-arousal, unpleasant high-arousal, pleasant low-arousal, pleasant high-arousal). The second-level analysis was conducted to determine of the effects that are observed in the single-subject level differ as a function of group.

On the second—level, between-group differences and potential interactions were assessed with two separate valance-based flexible factorial models were estimated in SPM8 with a within-subjects factor of arousal (high, low) and a between-subjects factor of group (HTAs, control) using the contrast images mentioned above. Specifically, in the first design, we modeled the effects of brain response to arousing pictures during viewing of unpleasant images using a 2 (image type: unpleasant high-arousal, unpleasant low-arousal) × 2 (group: HTAs, controls) mixed design, and in the second, the effects of brain response to arousing pictures during viewing of pleasant images using a 2 (image type: pleasant high-arousal, pleasant low-arousal) × 2 (group: HTAs, controls) mixed design. Note that we did not perform a 2x2x2 (valance x arousal x group) because we did not have sufficient power to explore a 3-way interaction. To test for significance, a voxel-wise threshold of $p < 0.005$ was applied, combined with a minimum cluster-extent of 26 contiguous voxels (702 mm³), to yield a corrected cluster-level false positive rate of $p < 0.05$ as determined by Monte Carlo simulations (similar to AlphaSim) [50] (<http://www2.bc.edu/~slotnics/scripts.htm>). We examined any interaction

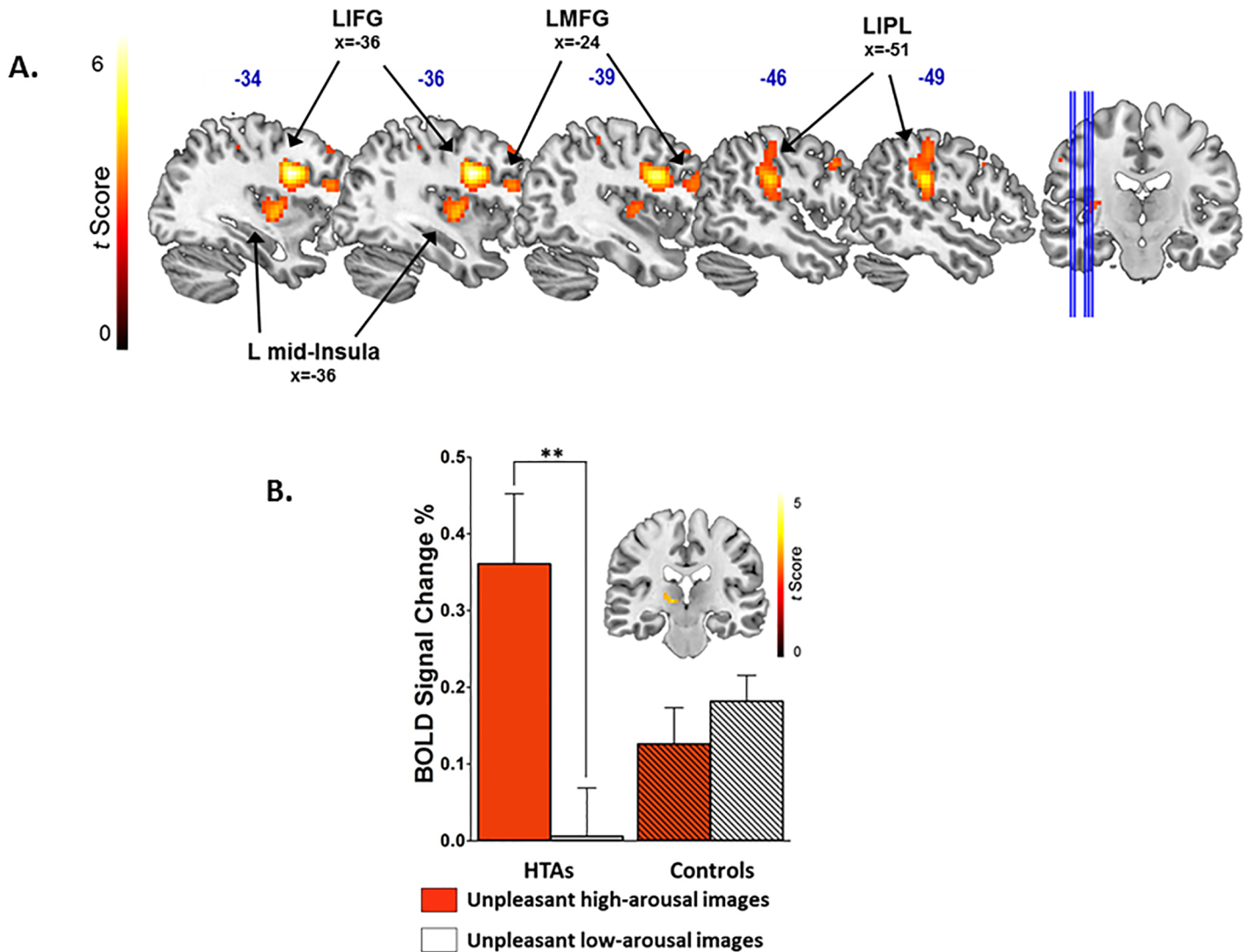


Fig 1. Brain response to unpleasant images. (A) Main effect of group (HTAs > controls) for unpleasant images across arousal conditions. The HTAs exhibited increased activations within the left IFG/precentral gyrus, MFG, insula, and IPL compared with the control group when viewing unpleasant images. (B) A significant group \times arousal interaction for unpleasant images emerged in the left thalamus (pulvinar) driven by the difference in brain response for arousal (high>low) within the HTAs [open bars; $t(19) = 3.20, p = 0.003$]. In the control group, no difference in the brain response to unpleasant images [diagonal filled bars; $t(16) = -0.62, p = 0.54$] emerged. Whole-brain significance threshold was set to $p < 0.005$, combined with a minimum cluster-extent of 26 contiguous voxels (702 mm^3), to yield a corrected cluster-level false positive rate of $p < 0.05$. IFG = inferior frontal gyrus, MFG = middle frontal gyrus, IPL = inferior parietal lobule. Red bars indicate unpleasant high-arousal images; white bars indicate unpleasant low-arousal images. ** $p < 0.01$.

<https://doi.org/10.1371/journal.pone.0194444.g001>

effects statistically in SPSS using the extracted cluster values from Marsbar (<http://marsbar.sourceforge.net/index.html>) in order to determine, through post-hoc comparisons, what BOLD response was driving the interaction.

The average percent signal change for all significant clusters were extracted with and were used to inspect for outliers (i.e., three standard deviations from the mean). No extracted fMRI-BOLD signals for any significant cluster were outside this range; therefore, no data were discarded from the analysis. Extracted data values were used to present the data in graphical form. T-maps were used to present significant clusters (Fig 1B).

Image ratings

To compare the subjective effects of arousal and group for the unpleasant images, we conducted a 2 x 2 repeated measures analysis of variance (ANOVA) with picture arousal (low vs. high) as the within subjects variable, and group (HTA vs. controls) as the between subjects variable. There was indeed a significant main effect for arousal [unpleasant: $F(1,22) = 12.51$, $p = 0.002$], validating the high and low-arousal distinction (high > low) in the task. Neither a main effect of group [unpleasant: $F(1,22) = 2.76$, $p = 0.11$], nor a group \times arousal interaction [unpleasant: $F(1,22) = 2.07$, $p = 0.16$] reached significance [26]. Identical analyses were used to compare subjective effects of arousal for pleasant images (See Supporting Information).

Finally, since nine participants within HTAs had anger and/or aggression diagnosis (i.e., IED or ASPD) we conducted additional analyses on brain response to the IAPS images comparing these diagnosed participants to those without a diagnosis related to anger/aggression within HTAs. Within the HTA group only, using SPSS, we compared the brain response between participants with an anger/aggression diagnosis (i.e., IED or ASPD, $n = 9$) to those participants in the HTA group that did not meet criteria for an anger/aggression diagnosis ($n = 11$). Here we used independent t-test to compare the extracted values obtained in MARS-BAR) for all significant clusters between the groups. No group differences were noted in brain response, or in demographic variables between participants ($p > .26$).

Results

Brain response to unpleasant images

There was a main effect of group for unpleasant images across arousal conditions such that HTAs showed higher left lateralized activations in the middle occipital gyrus (MGO), inferior frontal gyrus (IFG), middle frontal gyrus (MFG), mid-insula, and inferior parietal lobule (IPL) compared with controls (Fig 1A). Importantly, a group \times arousal interaction emerged in the left pulvinar/thalamus. Post-hoc analyses revealed that, as compared to controls, HTAs had increased responses for high > low arousal unpleasant images (Fig 1B). Table 3 provides these and additional results found during the whole-brain analyses of brain response to unpleasant images. Further analyses showed that diagnosis of IED and ASPD did not drive these results within HTAs. Imaging results for pleasant images are found in the supporting information, S1 Table.

For whole brain analysis, a voxel-wise threshold of $P < 0.005$ was applied, combined with a minimum cluster-extent of 26 contiguous voxels (702 mm^3), to yield a corrected cluster-level false positive rate of $p < 0.05$. This table includes the coordinates x, y, and z of the peak voxel given in Montreal Neurological Institute space and their statistical significance (t-values). BA, Brodmann area. ACC, anterior cingulate cortex; MOG, middle occipital gyrus; IFG, inferior frontal gyrus; MFG, middle frontal gyrus; IPL, inferior parietal lobule.

Discussion

In the current study, we investigated the influence of trait anger on the neural response to unpleasant and pleasant visual stimuli, selected based on high and low arousal. To the best of our knowledge, this is the first fMRI investigation that identifies distinct neural circuitry associated with the processing of unpleasant images as a function of elevated trait anger. We documented unique left lateralized activation in the IFG, MFG, and mid-posterior insula during viewing of unpleasant images in HTAs as compared to controls. We further found that HTAs had increased BOLD signal to high-arousing but not low-arousing unpleasant images relative to controls in the thalamus/pulvinar.

Table 3. Significant activations to unpleasant images revealed by whole brain analysis.

Contrast	aBrain Region	X	Y	Z	T	Cluster Size
Main Effect of Arousal						
High > Low	none					
Low > High						
	Left ACC (BA 32)	-15	38	16	3.75	54
	Right ACC (BA 32)	15	47	19	2.96	37
Main Effect of Group						
High Trait Anger > Control						
	Left MOG (BA 18)	-27	-97	4	3.69	44
	Left IFG (BA 6)	-36	2	31	5.81	163
	Left MFG (BA 46)	-42	35	28	3.35	73
	Left Insula (BA 48)	-36	-7	4	3.75	62
	Left IPL Supramarginal (BA 40, 3)	-51	-28	25	4.44	210
Control > High Trait Anger						
	Right Precuneus (BA 19)	27	-82	34	4.71	73
	Right Red Nucleus	0	-13	-8	4.69	260
	Right Precuneus (BA 7)	21	-58	58	3.97	62
	Right Postcentral (BA 5)	18	-55	70	3.97	54
	Right Lingual (BA18)	12	-70	4	3.53	32
Group × Arousal Interaction						
	Left Thalamus/pulvinar	-12	-22	1	3.01	30

<https://doi.org/10.1371/journal.pone.0194444.t003>

More specifically regarding the first result, we found increased engagement of the salience and the fronto-parietal attention networks (i.e., MFG/IFG, mid insula, and parietal regions) in HTAs relative to controls in response to viewing the unpleasant pictures [24]. The PFC and insula are part of a salience network that has extensive connectivity with the subcortical structures that underlie interoceptive autonomic processing [23]. Activation in this network, strongly influenced by motivational salience of the stimuli, was heightened while viewing negative images [51]. Prefrontal regions and insula are involved in the appraisal of emotional stimuli [52–54], emotion regulation, expression of emotion, explicit threat evaluation [55], and salience detection [23, 24]. The insula is commonly activated in tasks that are associated with the processing of negative emotion reactivity [56, 57] such as disgust, sadness [58–60], negative and visceral affective sensation and integration [53, 58, 60]. Although part of the salience network, the insula has also been found to coactivate with the ventral fronto-parietal attention network, with greater insular activity reflecting increased attentional bias to salient stimuli [61]. It has been postulated that increased activation of this region of the insula in emotion tasks involves initiation of attentional control, while engaging higher-order control processes [62] in tandem with salience discrimination and integration of sensory information [63]. Taken together, this pattern of neural activity may indicate emotional arousal through activation of the attentional and salience networks.

Increased activation levels in IFG and mid-posterior insula in HTAs was also associated with increased inferior parietal lobule activity, supporting an increased recruitment of the ventral fronto-parietal attention network in individuals with high anger [24, 64]. Within this network, the IFG, as part of the broader DLPFC, has been implicated in cognitive control and plays an important role in the processing of emotion mechanisms [65]. Activation of this region has been observed during various emotional processes such as emotion recognition and evaluation [66, 67] and emotional perspective taking [68] with the degree of activation

correlating with the degree of interpersonal involvement with the stimuli [68]. In this task, activation in the DLPFC potentially reflects an activation of the frontoparietal attention network, suggesting increased attention to the unpleasant images. Thus, one interpretation of the increased activation in the IFG in the HTA group in response to the unpleasant pictures is that the effect of increased activation relative to controls was due to a greater attentional bias towards threatening pictures in men who exhibit elevated levels of trait anger. This interpretation, however, must be tested more directly in future studies. Given the relatively modest effect sizes in these results it is probable that stronger effects can be attained through experimental paradigms that have a clear component of attentional effort.

There was no finding of self-report arousal differences between the groups. However, perhaps supporting a heightened arousal specific to HTAs in response to unpleasant images, we found a group \times arousal interaction in the left pulvinar. The pulvinar has an integrative function in bottom-up visual attention allocation functional loops, linking it to selective attention [69–74] to motivationally relevant features (saliency) of unpleasant visual stimuli [75]. Additionally, it plays an important role in coordinating and refining affective processing in dorsal and ventral (what and where) visual cortices involved in visual processing [76, 77]. Here it appears that unpleasant high-arousal images differentially activate the pulvinar, thereby highlighting its role in automatic, directed attention and the signaling of the saliency of the visual stimuli. It is important to note that a valid measure of attentional bias is needed to show a correlation with pulvinar signals in future studies to further validate our hypothesis. Likewise, a behavioral response directly measuring anger after each trial could increase the observed effects and would be better linked the fMRI findings.

Across conditions, consistent with our hypotheses, group differences observed in response to unpleasant images appeared lateralized, where HTAs showed activations on the left hemisphere and controls showed activations on the right hemisphere. This lateralization effect is in line with a motivational system theory that relate aspects of the experience and expression of emotions such as anger, sadness, and fear [31, 32, 78] to specific patterns of regional brain activity. Here, an approach system, involved in approaching/attending to rewarding or appetitive stimuli is associated with greater left than right frontal activity, and an avoidance system, associated withdrawal/avoidance from aversive stimuli, is associated with greater right than left frontal activity [1, 32, 79, 80]. Evidence suggests that individuals high in trait anger [30] exhibit increased levels of assertiveness and competitiveness which is a subcomponent of novelty seeking, that is itself associated with approach motivation [32] and left-dominant frontal neural activity [31]. Taken together, the increased left lateralized brain responses within the ventral fronto-parietal attention network suggest that individuals high in trait anger may have an attentional bias towards the unpleasant images which might be mediated by approach motivation. Further, right cortical activation seen in the control group may be involved in the modulation of arousal and threat response and avoidance-oriented attentional processes. These differences in activation patterns between groups may stem specifically from basic constitutional differences that underlie trait processes, since within HTAs those with psychiatric diagnosis did not differ from those without a diagnosis.

The present study focused on males. The question whether our results extend to female adults with high trait anger is a direction for future research. Although the amygdala is the structure most implicated in emotional processing [81, 82] we did not find amygdala activation in either HTAs or controls to the visual stimuli, and more specifically the unpleasant images. One potential reason for lack of amygdala activation could be the configuration of the stimuli presented in one block (pleasant or unpleasant—varied on arousal) may influence the participant's processing for subsequent stimuli. Moreover, activation of the amygdala might not have been detected by the block design of the fMRI paradigm given that the amygdala

habituates rapidly under aversive or fear stimulation [83, 84]. Additionally we examined the processing of emotional visual stimuli in a high trait anger group which included participants with heterogeneous disorders characterized by aggressive symptoms (ASPD and IED). In the future, the use of a larger sample would allow for direct comparison between these subgroups.

In conclusion, individuals high in trait anger demonstrate a unique pattern of neural activity distinguished by increased activation in the ventral fronto-parietal attention—salience networks during passive viewing of unpleasant images. Importantly, the activation in the pulvinar further supports our notion of automatic attentional bias to high-arousal unpleasant images in HTAs. In some cases, this increased activation may be associated with biased visual attention and increased engagement which were not observed in response to other types of highly arousing visual stimuli (e.g. pleasant, or pornographic images; supplement). Thus, this study is an important first step in exploring the neural correlates of emotion processing in angry individuals, a direction of research that is essential for uncovering potential effects of increased attention or sensitivity to negatively valenced cues. Insofar as anger is often a precursor to aggressive behavior, our results could also have important clinical implications and are relevant to understanding psychiatric conditions such as antisocial personality disorder, intermittent explosive disorder, and depression that are marked by increased negative emotions such as anger. Reducing the reactivity to salient aversive stimuli of these specific regions/systems through biofeedback and/or pharmacological interventions may be a candidate approach for novel therapeutics.

Supporting information

S1 Table. Results and discussion. Functional MRI activations to pleasant IAPS conditions of high and low arousal, inclusive of results and discussion on response to pleasant images. (DOCX)

Acknowledgments

This work was supported by a grant from the National Institute of Health (nih.gov; R01MH090134 to N.A.K.) and grants from the National Institute on Drug Abuse (drugabuse.gov; 5T32DA007135-32 to R.P.-C., K01DA037452 to S.J.M., F32DA033088 to M.A.P., and T32-DA007135-31 to K.B.).

Author Contributions

Conceptualization: Nelly Alia-Klein, Scott J. Moeller, Anna B. Konova, Rita Z. Goldstein.

Formal analysis: Rebecca N. Preston-Campbell, Scott J. Moeller, Muhammad A. Parvaz, Keren Bachi, Gabriela Gan, Anna Zilverstand, Anna B. Konova.

Funding acquisition: Nelly Alia-Klein, Rita Z. Goldstein.

Methodology: Rebecca N. Preston-Campbell, Scott J. Moeller, Muhammad A. Parvaz, Anna Zilverstand.

Project administration: Nelly Alia-Klein, Muhammad A. Parvaz.

Resources: Nelly Alia-Klein, Rita Z. Goldstein.

Supervision: Nelly Alia-Klein, Scott J. Moeller, Muhammad A. Parvaz.

Writing – original draft: Nelly Alia-Klein, Rebecca N. Preston-Campbell, Scott J. Moeller, Muhammad A. Parvaz, Gabriela Gan, Anna Zilverstand, Anna B. Konova, Rita Z. Goldstein.

Writing – review & editing: Nelly Alia-Klein, Rebecca N. Preston-Campbell, Keren Bachi, Anna Zilverstand.

References

1. Carver CS, Harmon-Jones E. Anger is an approach-related affect: evidence and implications. *Psychological bulletin*. 2009; 135:183–204. <https://doi.org/10.1037/a0013965> PMID: 19254075
2. Harmon-Jones E, Allen JJ. Anger and frontal brain activity: EEG asymmetry consistent with approach motivation despite negative affective valence. *J Pers Soc Psychol*. 1998; 74:1310–6. PMID: 9599445
3. Spielberger CD, Gorsuch R.L., Lushene R.E. STAI Manual for the State-Trait Anxiety Inventory ("Self-Evaluation Questionnaire"). Palo Alto, CA: Consulting Psychologists Press, Inc.; 1970.
4. Alia-Klein N, Goldstein RZ, Tomasi D, Woicik PA, Moeller SJ, Williams B, et al. Neural mechanisms of anger regulation as a function of genetic risk for violence. *Emotion*. 2009; 9:385–96. <https://doi.org/10.1037/a0015904> PMID: 19485616
5. Harmon-Jones E. Contributions from research on anger and cognitive dissonance to understanding the motivational functions of asymmetrical frontal brain activity. *Biological psychology*. 2004; 67:51–76. <https://doi.org/10.1016/j.biopsycho.2004.03.003> PMID: 15130525
6. Wilkowski BM, Robinson MD. The anatomy of anger: an integrative cognitive model of trait anger and reactive aggression. *Journal of personality*. 2010; 78:9–38. <https://doi.org/10.1111/j.1467-6494.2009.00607.x> PMID: 20433611
7. Hewig J, Hagemann D, Seifert J, Naumann E, Bartussek D. On the selective relation of frontal cortical asymmetry and anger-out versus anger-control. *J Pers Soc Psychol*. 2004; 87:926–39. <https://doi.org/10.1037/0022-3514.87.6.926> PMID: 15598115
8. Rybak M, Crayton JW, Young IJ, Herba E, Konopka LM. Frontal alpha power asymmetry in aggressive children and adolescents with mood and disruptive behavior disorders. *Clinical EEG and neuroscience*. 2006; 37:16–24. <https://doi.org/10.1177/155005940603700105> PMID: 16475480
9. Wilkowski BM, Robinson MD. The cognitive basis of trait anger and reactive aggression: an integrative analysis. *Personality and social psychology review: an official journal of the Society for Personality and Social Psychology, Inc.* 2008; 12:3–21.
10. Robinson MD, Wilkowski BM. Personality processes in anger and reactive aggression: an introduction. *Journal of personality*. 2010; 78:1–8. <https://doi.org/10.1111/j.1467-6494.2009.00606.x> PMID: 20433610
11. Alia-Klein N, Wang GJ, Preston-Campbell RN, Moeller SJ, Parvaz MA, Zhu W, et al. Reactions to media violence: it's in the brain of the beholder. *PloS one*. 2014; 9:e107260. <https://doi.org/10.1371/journal.pone.0107260> PMID: 25208327
12. Eckhardt CI, Cohen DJ. Attention to anger-relevant and irrelevant stimuli following naturalistic insult. *Personality and Individual Differences*. 1997; 23:619–29.
13. Smith P, Waterman M. Processing bias for aggression words in forensic and nonforensic samples. *Cognition and Emotion*. 2003; 17:681–701.
14. Stewart JL, Silton RL, Sass SM, Fisher JE, Edgar JC, Heller W, et al. Attentional bias to negative emotion as a function of approach and withdrawal anger styles: an ERP investigation. *International journal of psychophysiology: official journal of the International Organization of Psychophysiology*. 2010; 76:9–18.
15. Britton JC, Taylor SF, Berridge KC, Mikels JA, Liberzon I. Differential subjective and psychophysiological responses to socially and nonsocially generated emotional stimuli. *Emotion*. 2006; 6:150–5. <https://doi.org/10.1037/1528-3542.6.1.150> PMID: 16637758
16. Gerdes AB, Wieser MJ, Muhlberger A, Weyers P, Alpers GW, Plichta MM, et al. Brain Activations to Emotional Pictures are Differentially Associated with Valence and Arousal Ratings. *Frontiers in human neuroscience*. 2010; 4:175. <https://doi.org/10.3389/fnhum.2010.00175> PMID: 21088708
17. Lang PJ, Bradley MM, Cuthbert BN. Emotion, motivation, and anxiety: brain mechanisms and psychophysiology. *Biological psychiatry*. 1998; 44:1248–63. PMID: 9861468
18. Garavan H, Pendergrass JC, Ross TJ, Stein EA, Risinger RC. Amygdala response to both positively and negatively valenced stimuli. *Neuroreport*. 2001; 12:2779–83. PMID: 11522965

19. Pessoa L, Ungerleider LG. Neuroimaging studies of attention and the processing of emotion-laden stimuli. *Progress in brain research*. 2004; 144:171–82. [https://doi.org/10.1016/S0079-6123\(03\)14412-3](https://doi.org/10.1016/S0079-6123(03)14412-3) PMID: 14650848
20. Wright P, He G, Shapira NA, Goodman WK, Liu Y. Disgust and the insula: fMRI responses to pictures of mutilation and contamination. *Neuroreport*. 2004; 15:2347–51. PMID: 15640753
21. Aldhafeeri FM, Mackenzie I, Kay T, Alghamdi J, Sluming V. Regional brain responses to pleasant and unpleasant IAPS pictures: different networks. *Neuroscience letters*. 2012; 512:94–8. PMID: 22326384
22. Laird AR, Fox PM, Eickhoff SB, Turner JA, Ray KL, McKay DR, et al. Behavioral interpretations of intrinsic connectivity networks. *J Cogn Neurosci*. 2011; 23:4022–37. https://doi.org/10.1162/jocn_a_00077 PMID: 21671731
23. Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, et al. Dissociable intrinsic connectivity networks for salience processing and executive control. *The Journal of neuroscience: the official journal of the Society for Neuroscience*. 2007; 27:2349–56.
24. Corbetta M, Shulman GL. Control of goal-directed and stimulus-driven attention in the brain. *Nature reviews Neuroscience*. 2002; 3:201–15. <https://doi.org/10.1038/nrn755> PMID: 11994752
25. Lang PJ, Greenwald MK, Bradley MM, Hamm AO. Looking at pictures: affective, facial, visceral, and behavioral reactions. *Psychophysiology*. 1993; 30:261–73. PMID: 8497555
26. Lang PJ B M, Cuthbert BN. *International affective picture system (IAPS): technical manual and affective ratings*. Gainesville: University of Florida, Center for Research in Psychophysiology; 1999.
27. Russell JA. A Circumplex Model of Affect. *Journal of Personality and Social Psychology*. 1980; 39:1161–78.
28. Anders S, Lotze M, Erb M, Grodd W, Birbaumer N. Brain activity underlying emotional valence and arousal: a response-related fMRI study. *Human brain mapping*. 2004; 23:200–9. <https://doi.org/10.1002/hbm.20048> PMID: 15449355
29. Lang PJ, Bradley MM, Cuthbert BN. Emotion and motivation: measuring affective perception. *Journal of clinical neurophysiology: official publication of the American Electroencephalographic Society*. 1998; 15:397–408.
30. Engels AS, Heller W, Mohanty A, Herrington JD, Banich MT, Webb AG, et al. Specificity of regional brain activity in anxiety types during emotion processing. *Psychophysiology*. 2007; 44:352–63. <https://doi.org/10.1111/j.1469-8986.2007.00518.x> PMID: 17433094
31. Wacker J, Heldmann M, Stemmler G. Separating emotion and motivational direction in fear and anger: effects on frontal asymmetry. *Emotion*. 2003; 3:167–93. PMID: 12899417
32. Stewart JL, Levin-Silton R, Sass SM, Heller W, Miller GA. Anger style, psychopathology, and regional brain activity. *Emotion*. 2008; 8:701–13. <https://doi.org/10.1037/a0013447> PMID: 18837620
33. Moeller SJ, Frobose MI, Konova AB, Misyrlis M, Parvaz MA, Goldstein RZ, et al. Common and distinct neural correlates of inhibitory dysregulation: stroop fMRI study of cocaine addiction and intermittent explosive disorder. *Journal of psychiatric research*. 2014; 58:55–62. <https://doi.org/10.1016/j.jpsychires.2014.07.016> PMID: 25106072
34. Denson TF, Pedersen WC, Ronquillo J, Nandy AS. The angry brain: neural correlates of anger, angry rumination, and aggressive personality. *J Cogn Neurosci*. 2009; 21:734–44. <https://doi.org/10.1162/jocn.2009.21051> PMID: 18578600
35. Carter CS, Macdonald AM, Botvinick M, Ross LL, Stenger VA, Noll D, et al. Parsing executive processes: strategic vs. evaluative functions of the anterior cingulate cortex. *Proc Natl Acad Sci U S A*. 2000; 97:1944–8. PMID: 10677559
36. Milham MP, Banich MT, Barad V. Competition for priority in processing increases prefrontal cortex's involvement in top-down control: an event-related fMRI study of the stroop task. *Brain research Cognitive brain research*. 2003; 17:212–22. PMID: 12880892
37. Mohanty A, Herrington JD, Koven NS, Fisher JE, Wenzel EA, Webb AG, et al. Neural mechanisms of affective interference in schizotypy. *Journal of abnormal psychology*. 2005; 114:16–27. <https://doi.org/10.1037/0021-843X.114.1.16> PMID: 15709808
38. Meyer-Lindenberg A, Buckholtz JW, Kolachana B, A RH, Pezawas L, Blasi G, et al. Neural mechanisms of genetic risk for impulsivity and violence in humans. *Proc Natl Acad Sci U S A*. 2006; 103:6269–74. <https://doi.org/10.1073/pnas.0511311103> PMID: 16569698
39. Forgays DG, Forgays DK, Spielberger CD. Factor structure of the State-Trait Anger Expression Inventory. *Journal of personality assessment*. 1997; 69:497–507. https://doi.org/10.1207/s15327752jpa6903_5 PMID: 9501480
40. Spielberger CD. *State-Trait-Anger-Expression-Inventory*. Palo Alto, CA: Consulting Psychologist Press; 1988.

41. First MB, Spitzer R.L., Gibbon M., Williams J. Williams J. Structured Clinical Interview for DSM-IV Axis I disorders—Patient Edition (SCID-I/P, Version 2.0). Biometrics Research Department, New York State Psychiatric Institute: New York. 1996.
42. First M, Gibbon M, Spitzer RL, Williams JBW, Benjamin LS. Structured Clinical Interview for DSM-IV Axis II Personality Disorders, (SCID-II). Washington, D.C.: American Psychiatric Press, Inc.; 1997.
43. Coccaro EF S C, Samuels JF, & Nestadt G. Lifetime and 1-month prevalence rates of intermittent explosive disorder in a community sample. *Journal of Clinical Psychiatry* 2004; 65:820–4. PMID: [15291659](#)
44. Kessler RC, Coccaro EF, Fava M, Jaeger S, Jin R, Walters E. The prevalence and correlates of DSM-IV intermittent explosive disorder in the National Comorbidity Survey Replication. *Archives of general psychiatry*. 2006; 63:669–78. <https://doi.org/10.1001/archpsyc.63.6.669> PMID: [16754840](#)
45. Coccaro EF, Lee R, McCloskey MS. Validity of the new A1 and A2 criteria for DSM-5 intermittent explosive disorder. *Comprehensive psychiatry*. 2014; 55:260–7. <https://doi.org/10.1016/j.comppsy.2013.09.007> PMID: [24321204](#)
46. Coccaro EF, Lee R, McCloskey MS. Relationship between psychopathy, aggression, anger, impulsivity, and intermittent explosive disorder. *Aggressive behavior*. 2014; 40:526–36. <https://doi.org/10.1002/ab.21536> PMID: [24760575](#)
47. Look AE, McCloskey MS, Coccaro EF. Verbal versus physical aggression in Intermittent Explosive Disorder. *Psychiatry research*. 2015; 225:531–9. <https://doi.org/10.1016/j.psychres.2014.11.052> PMID: [25534757](#)
48. Lang PB, MM; Cuthbert BN. International Affective Picture System (IAPS): Affective Ratings of Pictures and Instruction Manual. 2005.
49. Tomasi D, Caparelli EC, Chang L, Ernst T. fMRI-acoustic noise alters brain activation during working memory tasks. *NeuroImage*. 2005; 27:377–86. PMID: [15893942](#)
50. Slotnick SD, Moo LR, Segal JB, Hart J Jr. Distinct prefrontal cortex activity associated with item memory and source memory for visual shapes. *Brain research Cognitive brain research*. 2003; 17:75–82. PMID: [12763194](#)
51. Ochsner KN, Bunge SA, Gross JJ, Gabrieli JD. Rethinking feelings: an FMRI study of the cognitive regulation of emotion. *J Cogn Neurosci*. 2002; 14:1215–29. <https://doi.org/10.1162/089892902760807212> PMID: [12495527](#)
52. Davidson RJ, Abercrombie H, Nitschke JB, Putnam K. Regional brain function, emotion and disorders of emotion. *Current opinion in neurobiology*. 1999; 9:228–34. PMID: [10322186](#)
53. Davidson RJ, Irwin W. The functional neuroanatomy of emotion and affective style. *Trends in cognitive sciences*. 1999; 3:11–21. PMID: [10234222](#)
54. Hariri AR, Bookheimer SY, Mazziotta JC. Modulating emotional responses: effects of a neocortical network on the limbic system. *Neuroreport*. 2000; 11:43–8. PMID: [10683827](#)
55. Etkin A, Egner T, Kalisch R. Emotional processing in anterior cingulate and medial prefrontal cortex. *Trends in cognitive sciences*. 2011; 15:85–93. <https://doi.org/10.1016/j.tics.2010.11.004> PMID: [21167765](#)
56. Ochsner KN, Gross JJ. Cognitive Emotion Regulation: Insights from Social Cognitive and Affective Neuroscience. *Current directions in psychological science*. 2008; 17:153–8. <https://doi.org/10.1111/j.1467-8721.2008.00566.x> PMID: [25425765](#)
57. Anand A, Li Y, Wang Y, Wu J, Gao S, Bukhari L, et al. Activity and connectivity of brain mood regulating circuit in depression: a functional magnetic resonance study. *Biological psychiatry*. 2005; 57:1079–88. <https://doi.org/10.1016/j.biopsych.2005.02.021> PMID: [15866546](#)
58. Phan KL, Wager T, Taylor SF, Liberzon I. Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. *NeuroImage*. 2002; 16:331–48. PMID: [12030820](#)
59. Schienle A, Stark R, Walter B, Blecker C, Ott U, Kirsch P, et al. The insula is not specifically involved in disgust processing: an fMRI study. *Neuroreport*. 2002; 13:2023–6. PMID: [12438918](#)
60. Augustine JR. Circuitry and functional aspects of the insular lobe in primates including humans. *Brain research Brain research reviews*. 1996; 22:229–44. PMID: [8957561](#)
61. Kilts CD, Kennedy A, Elton AL, Tripathi SP, Young J, Cisler JM, et al. Individual differences in attentional bias associated with cocaine dependence are related to varying engagement of neural processing networks. *Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology*. 2014; 39:1135–47.
62. Menon V, Uddin LQ. Saliency, switching, attention and control: a network model of insula function. *Brain structure & function*. 2010; 214:655–67.

63. Denny BT, Fan J, Liu X, Guerrerri S, Mayson SJ, Rimsky L, et al. Insula-amygdala functional connectivity is correlated with habituation to repeated negative images. *Social cognitive and affective neuroscience*. 2014; 9:1660–7. <https://doi.org/10.1093/scan/nst160> PMID: 24170933
64. Corbetta M, Patel G, Shulman GL. The reorienting system of the human brain: from environment to the theory of mind. *Neuron*. 2008; 58:306–24. <https://doi.org/10.1016/j.neuron.2008.04.017> PMID: 18466742
65. Ochsner KN, Gross JJ. The cognitive control of emotion. *Trends in cognitive sciences*. 2005; 9:242–9. <https://doi.org/10.1016/j.tics.2005.03.010> PMID: 15866151
66. Carr L, Iacoboni M, Dubeau MC, Mazziotta JC, Lenzi GL. Neural mechanisms of empathy in humans: a relay from neural systems for imitation to limbic areas. *Proc Natl Acad Sci U S A*. 2003; 100:5497–502. <https://doi.org/10.1073/pnas.0935845100> PMID: 12682281
67. Seitz RJ, Schafer R, Scherfeld D, Friederichs S, Popp K, Wittsack HJ, et al. Valuating other people's emotional face expression: a combined functional magnetic resonance imaging and electroencephalography study. *Neuroscience*. 2008; 152:713–22. <https://doi.org/10.1016/j.neuroscience.2007.10.066> PMID: 18313858
68. Derntl B, Finkelmeyer A, Eickhoff S, Kellermann T, Falkenberg DI, Schneider F, et al. Multidimensional assessment of empathic abilities: neural correlates and gender differences. *Psychoneuroendocrinology*. 2010; 35:67–82. <https://doi.org/10.1016/j.psyneuen.2009.10.006> PMID: 19914001
69. Grieve KL, Acuna C, Cudeiro J. The primate pulvinar nuclei: vision and action. *Trends in neurosciences*. 2000; 23:35–9. PMID: 10631787
70. Robinson DL. Functional contributions of the primate pulvinar. *Progress in brain research*. 1993; 95:371–80. PMID: 8493346
71. Wester K, Irvine DR, Hugdahl K. Auditory laterality and attentional deficits after thalamic haemorrhage. *Journal of neurology*. 2001; 248:676–83. PMID: 11569896
72. Fischer J, Whitney D. Attention gates visual coding in the human pulvinar. *Nature communications*. 2012; 3:1051. <https://doi.org/10.1038/ncomms2054> PMID: 22968697
73. Pessoa L, Adolphs R. Emotion processing and the amygdala: from a 'low road' to 'many roads' of evaluating biological significance. *Nature reviews Neuroscience*. 2010; 11:773–83. <https://doi.org/10.1038/nrn2920> PMID: 20959860
74. Frank DW, Sabatinelli D. Human thalamic and amygdala modulation in emotional scene perception. *Brain research*. 2014; 1587:69–76. <https://doi.org/10.1016/j.brainres.2014.08.061> PMID: 25173075
75. Kanai R, Komura Y, Shipp S, Friston K. Cerebral hierarchies: predictive processing, precision and the pulvinar. *Philosophical transactions of the Royal Society of London Series B, Biological sciences*. 2015; 370.
76. Ungerleider LG, Haxby JV. 'What' and 'where' in the human brain. *Current opinion in neurobiology*. 1994; 4:157–65. PMID: 8038571
77. Goodale MA, Milner AD. Separate visual pathways for perception and action. *Trends in neurosciences*. 1992; 15:20–5. PMID: 1374953
78. Lang PJ, Bradley MM, Cuthbert BN. Emotion, attention, and the startle reflex. *Psychological review*. 1990; 97:377–95. PMID: 2200076
79. Davidson RJ. EEG measures of cerebral asymmetry: conceptual and methodological issues. *The International journal of neuroscience*. 1988; 39:71–89. PMID: 3290140
80. Nielen MM, Heslenfeld DJ, Heinen K, Van Strien JW, Witter MP, Jonker C, et al. Distinct brain systems underlie the processing of valence and arousal of affective pictures. *Brain and cognition*. 2009; 71:387–96. <https://doi.org/10.1016/j.bandc.2009.05.007> PMID: 19665830
81. Liberzon I, Phan KL, Decker LR, Taylor SF. Extended amygdala and emotional salience: a PET activation study of positive and negative affect. *Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology*. 2003; 28:726–33.
82. Cohen BM, Cherkerzian S, Ma J, Ye N, Wager C, Lange N. Cells in midline thalamus, central amygdala, and nucleus accumbens responding specifically to antipsychotic drugs. *Psychopharmacology*. 2003; 167:403–10. <https://doi.org/10.1007/s00213-003-1423-0> PMID: 12709776
83. Sprengelmeyer R, Rausch M, Eysel UT, Przuntek H. Neural structures associated with recognition of facial expressions of basic emotions. *Proceedings Biological sciences / The Royal Society*. 1998; 265:1927–31.
84. Guyer AE, Monk CS, McClure-Tone EB, Nelson EE, Roberson-Nay R, Adler AD, et al. A developmental examination of amygdala response to facial expressions. *J Cogn Neurosci*. 2008; 20:1565–82. <https://doi.org/10.1162/jocn.2008.20114> PMID: 18345988