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Full Length Article

Correlates of C-reactive protein with neural reward circuitry in adolescents with psychiatric symptoms

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ABSTRACT

Introduction: Increased inflammation has been implicated in many psychiatric conditions across ages. We previously reported relationships between blood cytokine levels and anhedonia, the decreased capacity to experience pleasure, as well as with reward-related brain activation in adolescents with psychiatric symptoms. Here, we sought to extend this work in a larger cohort of adolescents with psychiatric symptoms and assess the relationships of C-Reactive Protein (CRP, inflammation biomarker) with clinical symptoms and reward-related brain activation.

Methods: Subjects were 64 psychotropic-medication-free adolescents with psychiatric symptoms (ages: 15.17 ± 2.10, 44 female). All had psychiatric evaluations and dimensional assessments for anxiety, depression, anhedonia, and suicidality. Neuroimaging included the Reward Flanker fMRI Task examining brain activation during reward anticipation, attainment, and positive prediction error. Both whole-brain and ROI analyses focusing on reward circuitry were performed. All analyses were controlled for BMI, age, and sex at $p_{FWE} < 0.05$.

Results: No relationships were identified between CRP and clinical symptom severity.

CRP was positively associated with brain activation during reward attainment in regions of the visual and dorsal attention networks, as well as during positive prediction error in the cerebellum. In ROI analyses, CRP was negatively correlated with brain activation during reward anticipation in the dorsal anterior cingulate cortex. When one subject with high CRP was excluded, CRP was also positively correlated with positive predication error activation in the nucleus accumbens.

Conclusion: Despite the lack of association between CRP and clinical symptomatology, our fMRI findings suggest a relationship between inflammation and brain function early course of psychiatric conditions.

1. Introduction

Neuroimmunological processes have been hypothesized to play a key role in the pathogenesis of neuropsychiatric psychiatric conditions. While the mechanisms are not fully understood, it is well established that peripheral inflammation extends to the CNS and affects neurotransmission systems and neurocircuits. In acute inflammatory states, such reactions are called "sickness behavior," characterized by increased sleep, lethargy, irritability, concentration difficulties, and decrease hedonic capacity (Dantzer, 2001; Dantzer and Kelley, 2007; Dantzer et al., 2008; Miller et al., 2013). Immune system activation has been linked mainly to depression, though it has been documented in many psychiatric conditions, in both adult and adolescent populations (Bradley et al., 2015, 2019; Freed et al., 2018; Gabbay et al., 2010). The lack of diagnostic specificity of inflammation to one specific psychiatric disorder is most likely due to the complexity of neuroimmunological processes affecting multiple neural systems as well as the heterogeneity of psychiatric conditions, which are based on clusters of symptoms each with distinct etiology. Therefore, our group and others have increasingly utilized RDoC approach focusing on narrowly defined psychiatric symptoms and their underlying neural circuits rather than categorical psychiatric diagnoses alone. Relatedly, converging preclinical and clinical data suggest that inflammation interacts with the reward circuitry (Felger et al., 2016; Felger and Treadway, 2017; Swardfager et al., 2016).

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Clinically, anhedonia, the decreased capacity to experience pleasure, is one of the core symptoms of "sickness behavior". Preclinical data of studies in rhesus monkeys showed that chronic administration of interferon (IFN)-α resulted in decreased dopaminergic neurotransmission in association with anhedonia-like behavior (Felger et al., 2013). Neuroimaging work further documents the specific effects of inflammatory processes within the dopaminergic reward circuitry. Several positron emission tomography (PET) studies have demonstrated changes in glucose metabolism within the striatum subsequent to immunotherapy in adults (Capuron et al., 2007; Juengling et al., 2000). Functional MRI studies in patients undergoing therapy with IFN-α documented decreased striatal activation in response to rewarding stimuli (Capuron et al., 2012). Similarly, the administration of an endotoxin in healthy volunteers resulted in decreased ventral striatal activation during a reward task and in the anterior cingulate cortex (ACC) and insula when using a pain paradigm (Eisenberger et al., 2010; Karshikoff et al., 2016). In addition, typhoid vaccination in healthy volunteers has been shown to alter activity in the substantia nigra in relation to psychomotor slowing (Brydon et al., 2008). Findings from our laboratory provide additional support to the possible relationships between immune function and he reward circuitry. In a recent work examining a panel of 41 cytokines in relation to key psychiatric symptoms in 54 adolescents with diverse psychiatric symptoms, we documented that 19 cytokines were correlated with the severity of anhedonia, while there were no associations with any other clinical symptom (Freed et al., 2018). In a follow-up study, we examined relationships between the same 41-cytokine panel and brain function in 34 adolescents with psychiatric symptoms and 12 HC during the fMRI Reward Flanker Task (RFT), which assesses neural activity during reward anticipation and attainment. We found associations between the same set of anhedonia-related cytokines and activation in reward-related regions of the anterior/mid-cingulate cortex and basal ganglia, as well as posterior default mode areas (Bradley et al., 2019).

Extending this work, here we sought to examine relationships between C-Reactive Protein (CRP) levels and clinical symptom severity as well as brain function during the RFT in adolescents with diverse psychiatric symptoms. CRP is a non-specific biomarker produced in hepatocytes in response to inflammatory states or tissue injury. Increased CRP levels have been associated with a broad range of inflammatory conditions, including autoimmune disorders, cardiovascular disease, malignancies, and diabetes (Black et al., 2004; Du Clos, 2000; Pepys and Hirschfield, 2003). Relatedly, several studies have examined CRP in both adults and youths with current and past depressive episodes. While these studies have consistently suggested a relationship between CRP and depression in adults (Baumeister et al., 2016; Danese et al., 2008; Danner et al., 2003; Elovainio et al., 2009; Ford and Erlinger, 2004; Haroon et al., 2018), the majority of findings in adolescents have been negative (Baumeister et al., 2016; Flouri et al., 2020; Jha et al., 2020; Khandaker et al., 2014). In adolescents, one study documented a relationship between CRP and higher depression severity scores (Tabatabaeizadeh et al., 2018), but others have failed to document any such association. Similarly, we did not find an association between blood CRP levels and reward-related activation during our previous analyses of 46 adolescents (Bradley et al., 2019), although this negative finding might have been related to the modest sample size. The lack of data implicating CRP in youth raises the question of whether CRP elevation is a relevant biomarker for specific mood symptoms in youth, or reflects chronic inflammatory states with aging processes and illness as hypertension.

Our aims were to investigate associations between CRP levels and: a) clinical severity of anhedonia, depression, anxiety, and suicidality; and b) brain activation during reward anticipation, reward attainment, and positive prediction errors. As mood and anxiety symptoms as well as reward dysfunction are common across psychiatric disorders, we utilized an RDoC approach studying psychotropic-medication-free adolescents with diverse clinical symptoms, including comorbid and subthreshold diagnoses. As we expected to capture a wide range of symptom severity in our psychiatric cohort based on our previous work (Bradley et al., 2019; Freed et al., 2018; Gabbay et al., 2015), healthy controls were not included. As in our previous study (Bradley et al., 2019), brain activation during reward anticipation and attainment was measured by RFT fMRI and examined using both whole-brain and region-of-interest (ROI) analyses targeting reward-related areas of the basal ganglia (striatum) and prefrontal cortex (anterior cingulate). Additionally, we modeled brain activation during positive prediction errors (i.e. receiving a larger reward than expected). Positive prediction error is a critical component of reward learning, affecting both reward anticipation and attainment, and is mediated by dopaminergic neurotransmission throughout the frontal cortex and basal ganglia (Glimcher, 2011; Knutson and Cooper, 2005). The striatum and anterior cingulate cortex have been the major focus of our research over many studies, and their functional and neurochemical abnormalities have been consistently observed in youth with psychiatric conditions (Bradley et al., 2016, 2019; DeWitt et al., 2018; Gabbay et al., 2012, 2013, 2017). In addition to an expanded and clinically targeted sample, this study advances our earlier research by utilizing a suite of sophisticated preprocessing (Glasser et al., 2013), denoising (Griffanti et al., 2014; Salimi-Khorshidi et al., 2014), and alignment (Glasser et al., 2016; Robinson et al., 2014) techniques developed by the Human Connectome Project (HCP) to improve our power in detecting associations between inflammation and neural reward processes. Our approach included neuroanatomical accurate functional mapping to CIFTI grayordinates (i.e. 2D cortical surface + 3D subcortical volume), enabling us to define *a priori* ROIs similar to those used in our previous work (Bradley et al., 2019) but derived from the latest and most detailed brain parcellations available. Based on our prior findings, we hypothesized that blood CRP levels would be associated with: a) anhedonia severity, but not depression, anxiety, or suicidality severity; and b) brain activation during reward anticipation, reward attainment, and positive prediction error within the reward network.

2. Methods

2.1. Participants

Participants consisted of 64 adolescents (age, $M \pm SD$: 15.17 ± 2.10, range: 12–20 years; 44 female) with diverse psychiatric symptoms. At the time of the evaluation, 57 presented with mood and anxiety symptoms and 7 were without mood and anxiety symptoms but with other externalized behavior symptoms. All of the 64 adolescents had useable Reward Flanker Task (RFT) fMRI data. Another eight potential participants completed study procedures but were excluded because over 25% of RFT runs were unusable; excluded subjects had no differences in age (ranksum $Z = 1.10$, $p = 0.27$), sex ($\chi^2 = 0.13$, $p = 0.72$) or ethnicity ($\chi^2 = 4.39$, $p = 0.11$) from the final study sample. As a part of our ongoing research program, the current study included 30 adolescents (age, $M \pm SD$: 15.6 ± 2.25 range: 12–20 years; 18 female) previously reported in Bradley et al. (2019), as well as 27 adolescents (age, $M \pm SD$: 15.7 ± 2.34 range: 12–20 years; 18 female) previously reported in Freed et al. (2018). All of the overlapped subjects exhibited psychiatric symptoms, had CRP levels and adequate MRI quality for the new analyses we carried out.

Participants were recruited from the New York metropolitan area through affiliated Child and Adolescent Psychiatry Outpatient Clinics, physician referrals, and advertisements in the community. The study was approved by the Icahn School of Medicine at Mount Sinai Institutional Review Board (IRB), and written informed consent was obtained from participants age 18 and older. Those under the age of 18 provided signed assent, and a parent or legal guardian provided signed informed consent. Clinical data and demographics are compiled in Table 1.

2.2. Inclusion and exclusion criteria

Inclusion criteria: present with psychiatric symptoms, either above or sub-threshold, based on clinical diagnosis.

Exclusionary criteria: 1) any physical or neurological conditions; 2) a

Table 1
Demographic and clinical characteristics.

Demographics of whole sample			
Age (Years)	15.17 ± 2.10 (12–20)	Race (Caucasian/ African American/ Other)	31/19/14 (48.4/ 29.7/21.9%)
Sex (F/M)	44/20 (68.8/ 31.3%)		
Medication (Naïve/Free)	53/11 (82.8/ 17.2%)		
Psychiatric profile (Current/Past)			
MDD	28/0 (43.8/ 0%)	Anxiety	36/2 (56.3/3.1%)
Dysthymia	7/0 (10.9/ 0%)	ODD	7/1 (10.9/1.6%)
DD NOS	3/0 (4.7/0%)	ADHD	17/3 (26.6/4.7%)
Other Mood Disorders	4/1 (6.3/ 1.6%)	OCD	1/1 (1.6/1.6%)
		Other Disorders	2/1 (3.1/1.6%)
Symptom severity			
SHAPS	23.5 ± 6.5 (14–43)	BMI (kg/m^2)	24.6 ± 5.9 (15.9–43.6)
TEPS-AP [a]	45.7 ± 8.3 (20–60)	CDRS-R [b]	35.8 ± 14.4 (17–78)
TEPS-CP [a]	33.2 ± 7.2 (11–48)	BDI [b]	14.0 ± 12.5 (0–47)
BSSI	2.7 ± 5.7 (0–35)	MASC [b]	44.4 ± 16.6 (11–87)

Values reported as *M*±*SD* (Range) or *n* (%), as appropriate. Diagnoses and assessments were based on the DSM-IV to keep consistency across all participants over time. As participants could meet criteria for more than one disorder, totals not sum to 100%. *BMI:* Body mass index; *MDD:* major depressive disorder; *DD NOS:* depressive disorder not otherwise specified; *Anxiety:* includes generalized anxiety, social anxiety, phobia, post-traumatic stress, and panic disorders as well anxiety disorder not otherwise specified; *OCD*: obsessive-compulsive disorder; *ODD*: oppositional defiant disorder; *ADHD*: attention-deficit hyperactivity disorder. *SHAPS*: Snaith-Hamilton Pleasure Scale; *TEPS*: Temporal Experience of Pleasure Scale; *CDRS-R*: Children's Depression Rating Scale-Revised; *BDI*: Beck Depression Inventory; *BSSI*: Beck Scale for Suicide Ideation.

[a] Data missing from 12 participants.

[b] Data missing from 1 participant.

low IQ (<80), as assessed by the Kaufman Brief Intelligence Test (KBIT; Kaufman, 1990); 3) MRI contraindications; 4) a positive drug toxicology test; 5) a positive pregnancy test in females; 6) current psychosis, pervasive developmental disorder, and substance abuse disorders; 7) psychotropic-medication use in last 1–3 months before baseline visit, depending on drug half-life; 8) any inflammatory illnesses, including the common cold; and 9) taking anti-inflammatory medications, including over-the-counter remedies.

2.3. Clinical assessments

Clinical diagnostic procedures: All participants were assessed using the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (KSADS-PL; Kaufman et al., 1997), a semi-structured diagnostic interview. A board-certified child/-adolescent psychiatrist or a licensed clinical psychologist trained in administering the KSADS-PL carried out the diagnostic evaluation.

Anhedonia severity was assessed using the self-rated Snaith-Hamilton Pleasure Scale (SHAPS; Snaith et al., 1995), a 14-item scale with a total score range of 14–56 constructed to minimize age, sex, and cultural influences. The SHAPS is widely used and has been validated in children and adults (De Berardis et al., 2013; Farabaugh et al., 2015). In addition, temporal components of anhedonia severity were derived from Temporal Experience of Pleasure Scale (TEPS; Gard et al., 2006), a self-report questionnaire that quantifies both anticipatory (TEPS-AP, score range 10–60) and consummatory (TEPS-CP, score range 8–48) anhedonia. Unlike other scales used in this study, higher TEPS scores reflect lower levels of anhedonia.

Overall depression severity was measured by the clinician-rated Children's Depression Rating Scale–Revised (CDRS-R; Poznanski et al., 1985), which was administered to the participant and also a parent/guardian when the participant was under the age of 18. The CDRS-R has 17 items and a score range of 17–113. The self-rated Beck Depression Inventory–Second Edition (BDI; Beck et al., 1996), with 21 items and a score range of 0–63, was also administered.

Anxiety severity was assessed using the self-reported Multidimensional Anxiety Scale for Children (MASC; March et al., 1997), which has been validated in both clinical and non-clinical population. This scale contains 39 items and a score range of 0–117.

Suicidality severity was assessed by the 19-item self-rated Beck Scale for Suicide Ideation (BSSI; Beck et al., 1979) which evaluates suicidal thinking and has a total score range of 0–38.

2.4. C-Reactive Protein quantification

All participants had a fasting peripheral blood draw from the arm conducted by LabCorp (https://www.labcorp.com). CRP levels were analyzed by LabCorp via high-sensitivity C-Reactive Protein (hs-CRP) tests, which use immunochemiluminometric assays (ICMA). Since some samples with low CRP levels were only reported as below an upper bound (e.g., CRP < 0.1 mg/L), these were treated as equal to the bounding value (e.g., CRP = 0.1 mg/L) for group comparison and correlation analyses. Specifically, one CRP value reported as "< 0.1 mg/L", one reported as "< 0.2 mg/L", and 17 reported as "< 0.3 mg/L" were re-coded in this way. To avoid concerns about quantification accuracy, all statistical analyses were repeated excluding the subjects with re-coded CRP values, and similar results were found (see details in **Supplementary Results**).

2.5. Body mass index

Body mass index (BMI) is a standard index of obesity, which derived from the mass (kg) and height (m) of a person. BMI was calculated as mass/height^2.

2.6. Reward Flanker Task

During the RFT, participants were presented with a monetary cue, then made button presses and earned the cued reward amount if they correctly identified a target letter surrounded by four flanking letters during an allotted response interval. During each trial, the monetary cue was presented for 4–6 s. Four cues were used: high-reward (50¢), low-reward (10¢), no-reward (0¢), and uncertain-reward (?). Uncertain-reward cues led to high-, low-, or no-reward feedback with equal probability. After the cue, a flanker stimulus was presented for 300 ms, followed by a response interval that was calibrated for each participant based on performance during a pre-scan training session (maximum 1700 ms). Participants then received color-coded feedback for 2 s informing them of the value of the reward obtained or not obtained. A total of 120 trials were presented in a pseudo-random event-related design over four runs, with 30 trials per run. After each run, participants were told the exact money they had actually earned so far. Participants were informed of the performance-based bonus prior to starting the RFT in order to increase motivation. For additional details on the RFT, see Bradley et al. (2017).

2.7. Statistical analyses for clinical measurements

All statistical analyses for clinical measurements were performed in Matlab (2018b) (The MathWorks, Inc.). The CRP level was positively skewed (skewness = 5.62) and still not normally distributed after either ln or $\log_{10}$ transformation (Kolmogorov-Smirnov test, all KS > 0.26, all p

$< 1.5 \times 10^{-4}$). Therefore, we treated CRP level as a continuous variable and adopted nonparametric statistics (Spearman's rank correlation) in assessing relationships between CRP level and clinical symptom severity. Analyses were repeated excluding one subject with CRP higher than 10.5 mg/L in both clinical assessments analyses and fMRI analyses (see below). This subject remained with a high CRP level (10.9 mg/L) after three years as part of a follow-up study, suggesting a chronic inflammatory state. Therefore, we elected to retain this subject for our main analyses and reported results both including and excluding this subject. For all statistical analyses, age, sex, and BMI were included as confounds.

2.8. MRI data analyses

MRI analyses followed the Human Connectome Project (HCP) minimal preprocessing pipelines (Glasser et al., 2013), including gradient non-linearity and fieldmap-based EPI distortion correction, realignment, and normalization to standard Montreal Neurological Institute (MNI) space and CIFTI grayordinate (i.e., cortical surface, subcortical volume) templates. Then, structured noise components were identified and removed using an automated independent components analysis classifier, ICA-FIX (Griffanti et al., 2014; Salimi-Khorshidi et al., 2014). ICA-FIX was run on the concatenated RFT scans plus a 10 min (600 volumes) resting-state fMRI scan collected immediately prior to the RFT. All components identified as "unknown" and "signal" by ICA-FIX were reviewed and, where appropriate, reclassified as "noise". All final "noise" components were then regressed out of the concatenated timeseries, with all final "signal" and "unknown" components retained. Runs with excessive motion (both RFT and resting-state), defined as more than 3% of frames with relative motion greater than 1 mm, were excluded from ICA-FIX and further analyses. To improve inter-subject cortical alignment, we further performed multimodal surface matching (MSMAll), which uses cortical folding, myelination, and fMRI network features to robustly identify corresponding cortical areas even between subjects with divergent cortical folding patterns (Glasser et al., 2016; Robinson et al., 2014). Runs with empty response-dependent regressors (see below) were also eliminated from further analyses.

Subject-level analyses were performed in Statistical Parametric Mapping (SPM) version 12 (Wellcome Trust Center for Neuroimaging, London, UK) running on Matlab 2018b. Preprocessed fMRI data were spatially smoothed (4 mm FWHM) in CIFTI space and converted to SPM-supported NIFTI format via Connectome Workbench version 3.2.7 (Glasser et al., 2013). Eleven task-based regressors were specified: four for cues (high-, low-, no-, and uncertain-reward cues), six for feedback (high-, low-, and no-reward feedback on correct trials, separately for certain and uncertain cues), and one for error feedback (incorrect trials, if applicable). Each regressor was convolved with the hemodynamic response function using the general linear model (GLM). First-level contrasts examined: a) reward anticipation, defined as differential neural activation to reward (10¢ and 50¢) versus no-reward (0¢) cues; b) reward attainment, defined as differential neural activation to reward (10¢ and 50¢) versus no-reward (0¢) feedback, regardless of cues; and c) positive prediction error, defined as differential neural activation to reward feedback after uncertain (?) versus certain (10¢ and 50¢) cues. The resulting subject-level contrast maps were converted back to CIFTI space for group analyses.

For group-level analyses, the relationship between whole-brain activity and CRP levels was examined. Sex, age, and BMI were treated as covariates of no interest. All group-level analyses were performed in FSL PALM (Winkler et al., 2014) using Threshold-Free Cluster Enhancement (TFCE) and permutation-based non-parametric statistics to control the family-wise error (FWE) rate. Due to the spatial dependence of TFCE and the discrete representation of major brain structures in CIFTI space, analyses were performed separately for cortical surfaces and the subcortical volume, then merged. Results for main analyses were considered significant at the two-tailed $p_{TFCE\text{-}FWE} < 0.05$ level across the whole brain, adjusting for the two separate cortical and subcortical analyses. The information of significant clusters were reported using function *ciftify_statclust_report* implemented in Ciftify (Dickie et al., 2019). For subcortical clusters larger than 40 mm^3, we reported the activation volume, peak statistical value, and peak MNI coordinates. For cortical clusters larger than 40 mm^2, we reported the activation area, peak statistical value, and overlap with two widely used cortical atlases: a) the HCP multimodal parcellation (MMP; Glasser et al., 2016), and b) the 7-network intrinsic functional connectivity (iFC) atlas (Yeo et al., 2011). As there is currently no standard approach for reporting locations on the cortical surface, these atlases were used both to characterize cluster locations and to help interpret their possible functions.

2.9. ROI analyses

As secondary analyses, we also examined five anatomical *a priori* ROIs within bilateral ACC and striatum created in CIFTI space. Specifically, dorsal/caudal ACC (dACC) and rostral ACC (rACC) ROIs were based on Desikan-Killiany Atlas in cortical surface (Desikan et al., 2006). The nucleus accumbens, caudate and putamen ROIs were based on FreeSurfer subcortical segmentation (Fischl et al., 2002) in volume. Mean parameter estimates from each of these ROIs during reward anticipation, attainment and positive prediction error were extracted. Spearman's rank correlations between extracted parameter estimates in each of the ROIs and CRP levels were examined in the whole sample, controlling for age, sex, and BMI, with significance at two-tailed $p_{FWE} < 0.05$ across three contrasts. We also explored the relationship between CRP and neural reward activation in each single hemisphere ROIs.

3. Results

3.1. Demographic and clinical features

Demographic and clinical characteristics of the whole sample ($N = 64$) are presented in Table 1. As noted in the **Methods**, all participants were psychotropic-medication-free at recruitment.

3.2. Descriptive statistics

The concentration level of CRP in our sample ranged 0.1–26.2 mg/L ($M \pm SD = 1.80 \pm 3.66$). As this included one outlier participant with an extremely high CRP level (26.2 mg/L), all analyses were performed and reported both with and without this subject excluded. Without this subject, the concentration of CRP spanned a more typical range from 0.1–10.2 mg/L ($M \pm SD = 1.09 \pm 1.70$).

Consistent with our RDoC prediction, our sample exhibited a wide range of symptom severity on all clinical assessments including SHAPS, TEPS-AP, TEPS-CP, CDRS-R, BDI, MASC, and BSSI (Supplementary Figure 1). However, none of them followed normal distribution (one-sample Kolmogorov-Smirnov test, all $p < 9.2 \times 10^{-15}$).

Table 2
Correlations between CRP levels and clinical symptom severity.

	SHAPS	TEPS-AP	TEPS-CP	CDRS-R	BDI	MASC	BSSI
Whole sample							
N	64	52	52	63	63	63	64
rho	0.05	−0.04	−0.02	−0.07	−0.05	−0.04	0.08
p_{unc}	0.69	0.80	0.87	0.59	0.72	0.78	0.55
Subgroup with mood and anxiety symptoms							
n	57	49	49	56	56	57	57
rho	0.07	−0.07	−0.05	−0.08	−0.04	−0.06	0.06
p_{unc}	0.61	0.65	0.75	0.56	0.80	0.68	0.64

Analyses controlled for: age, sex, and BMI.

3.3. Correlations between blood CRP and clinical symptom severity

Correlation results are collected in Table 2 and Supplementary Table 1.

Anhedonia: Contrary to our hypotheses, there were no associations between anhedonia severity (measured by SHAPS, TEPS-AP, and TEPS-CP) and blood CRP levels in the whole sample (all $|rho| < 0.05$, all $p > 0.69$) or in the mood and anxiety subgroup alone when we excluded adolescents with only externalized behavior symptoms (all $|rho| < 0.07$, all $p > 0.65$). The results remained the same after excluding the high-CRP subject in both whole sample (all $|rho| < 0.04$, all $p > 0.80$) and mood and anxiety subgroup (all $|rho| < 0.07$, all $p > 0.65$).

Other mood and anxiety symptoms: Similarly, no significant correlations were identified between CRP levels with overall depression (CDRS-R and BDI), anxiety (MASC), or suicidality (BSSI) in the whole sample (all $|rho| < 0.08$, all $p > 0.55$) or the mood and anxiety subgroup alone (all $|rho| < 0.06$, all $p > 0.64$). The results remained the same after excluding the high-CRP subject in both whole sample (all $|rho| < 0.10$, all $p > 0.47$) and mood and anxiety subgroup (all $|rho| < 0.08$, all $p > 0.58$).

Additional *post hoc* analyses: To ensure that potential confounds did not contribute to Type II errors, we also repeated our analyses: a) within female-only subgroups to assess potential sex-specific effects, as a positive relationship between CRP levels and depression was previously documented only in adolescent girls (Tabatabaeizadeh et al., 2018); b) in unadjusted models to assess the impact of confound variables; and c) Finally, correlation analyses were repeated excluding subjects whose CRP concentrations were reported as bounded ranges rather than exact numerical values ($n = 25$; see **Methods**) to avoid concerns about quantification accuracy. As in the main analyses, no significant correlations were found between CRP levels and clinical symptoms in any of the *post hoc* analyses. See **Supplementary Results** for detailed findings.

3.4. Whole brain analyses assessing relationships between CRP levels and neural reward function

During reward anticipation, neural activation was not significantly (two-tailed $p_{TFCE\text{-}FWE} < 0.05$) associated with CRP levels in the whole sample. By contrast, neural activation during reward attainment was significantly correlated with CRP levels (Fig. 1, Table 3). Specifically, the CRP levels were positively correlated with activation in the left lateral occipital, posterior temporal, and superior parietal cortices; these clusters overlapped with parts of the visual and dorsal attention networks. Similarly, during positive prediction error, CRP was positively correlated with neural activation in lobule VI of the left cerebellum (Fig. 1, Table 3). However, after excluding the high-CRP subject, neural activation during all three stages, reward anticipation, reward attainment and positive prediction error were not significantly (two-tailed $p_{TFCE\text{-}FWE} < 0.05$) associated with CRP levels.

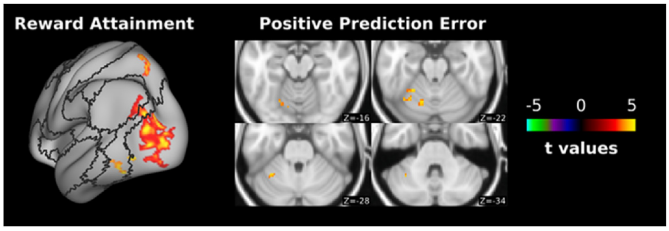

Fig. 1. Neural reward function correlations with CRP levels. Blood CRP levels significantly correlated with activation in left visual areas during reward attainment (left) and with activation in the left cerebellum during positive prediction error (right); no significant correlation with activation during reward anticipation was found. Black lines on the surface represent intrinsic functional connectivity (iFC) boundaries from the 7-network cortical parcellation (Yeo et al., 2011).

Table 3
Relationships between neural reward activation and CRP levels.

	Peak *T*	Area (mm^2)	Cluster Overlap: HCP MMP Atlas (Glasser et al., 2016)	Cluster Overlap: 7-Network iFC Atlas (Yeo et al., 2011)
		CRP & reward attainment (N = 64)[a]		
Left	5.33	1154.54	V4 (30.1%); PGp (19.0%); V3CD (18.5%); LO1 (10.1%)	Visual (86.0%)
Left	4.33	231.08	VIP (65.0%); MIP (33.7%)	Dorsal Attention (100%)
Left	5.02	172.28	PH (95.3%)	Dorsal Attention (100%)
Left	5.23	67.13	FST (74.4%); V4t (19.4%)	Visual (66.9%); Dorsal Attention (33.1%)
	Peak *T*	**Volume (mm^3)**	**Peak Coordinates (MNI X,Y,Z)**	**Brain Region**
		CRP & positive prediction error (N = 64)		
Left	4.78	742.19	(−18,−66,−18)	Cerebellum lobule VI
Left	5.26	559.68	(−30,−52,−24)	Cerebellum lobule VI

[a] Only parcellation labels with >10% overlap are listed here.

3.5. ROI analyses assessing relationships between CRP levels and neural reward function

Only neural activation in bilateral dACC during reward anticipation was negatively correlated with CRP levels after FWE correction (Table 4; $r = -0.35$; $p_{unc} = 0.006$). When examining ROIs in single hemisphere, the right dACC was the only ROI significantly correlated with CRP levels after FWE correction (Supplementary Table 5; $r = -0.32$; $p_{unc} = 0.01$).

Similarly, after excluding the one high-CRP subject (Supplementary Tables 6 and 7), the neural activation in bilateral dACC during reward anticipation remained to be negatively correlated with CRP levels ($r = -0.33$; $p_{unc} = 0.009$). In addition, CRP levels were also positively correlated with the bilateral accumbens nuclei activation during positive prediction error ($r = 0.31$; $p_{unc} = 0.016$). No significant association after FWE correction was found between CRP levels and single hemisphere ROI activation.

4. Discussion

This study sought to assess whether blood CRP levels in adolescents are associated with depression and anxiety symptom severity as well as with brain activation during an fMRI reward task. This study performed an exhaustive set of *a priori* and *post hoc* analyses to examine potential associations between CRP, mood and anxiety symptoms, and neural reward function in adolescents with diverse psychiatric profiles. Contrary to our hypotheses, we did not detect any significant relationships between CRP levels and the severity of anhedonia, overall depression, anxiety, or suicidality symptoms in our cohort. However, as hypothesized, CRP levels were related to brain activation during the reward fMRI task.

Our negative findings in relation to CRP and clinical symptomatology are in agreement with several similar studies in pediatric populations

Table 4
Correlations between region of interest activation and CRP levels.

		Striatum			ACC	
		Accumbens	Caudate	Putamen	dACC	rACC
Reward anticipation	*r*	0.12	−0.19	−0.14	−0.35	−0.28
	p_{unc}	0.34	0.14	0.30	0.006	0.03
Reward attainment	*r*	−0.07	−0.05	−0.23	0.02	−0.05
	p_{unc}	0.61	0.70	0.07	0.85	0.73
Positive prediction error	*r*	0.25	0.26	0.20	0.15	0.27
	p_{unc}	0.05	0.04	0.13	0.24	0.04

with mood and anxiety symptoms (Baumeister et al., 2016; Flouri et al., 2020; Jha et al., 2020; Khandaker et al., 2014). While one study identified relationships between CRP and depressive symptoms in a cohort of female adolescent alone (Tabatabaeizadeh et al., 2018), we did not observe such a relationship when males were excluded (see **Supplementary Results**). Since CRP is a fairly non-specific marker of immune activity, a plausible explanation is that inflammatory processes associated with depression in adolescents may not be as generalized as those in adults. Conversely, a recent study in adults suggested high CRP levels may represent a biological subtype of depression also characterized by high anhedonia severity and metabolic syndromes (Bekhbat et al., 2020); the latter is strongly associated with systemic inflammation and is less prevalent in younger populations.

Despite the apparent lack of association between CRP levels and clinical symptomatology in adolescents, we detected numerous significant relationships between CRP and neural activity during the RFT using both whole brain and ROI analyses. The whole brain analyses detected relationships within the visual and cognitive systems. Specifically, CRP was associated with brain activation during reward attainment in lateral occipital (LOC), posterior temporal, and superior parietal cortices, as well as during positive prediction error in the cerebellum. During reward attainment, CRP correlations were strongest in the left LOC centering around extrastriate visual area V4. Within the visual system, area V4 is noteworthy as one of the earliest regions where activity is modulated by attention (Grothe et al., 2018; Moran and Desimone, 1985), specifically including reward-related stimuli during the early processing stage (Apitz and Bunzeck, 2012). Clinically, increased activation of the LOC during both reward anticipation and attainment was documented in depressed adults following psychotherapy (Dichter et al., 2009). Additionally, hyper-activation in the LOC, as well as the superior parietal lobule (also found in the current study) and precuneus, was documented in male adolescents with cannabis use disorder while making risky reward decisions (De Bellis et al., 2013). Similarly, in the current study, activation during reward attainment in several regions corresponding to the dorsal attention network was also correlated with CRP levels. The convergence of CRP correlations on vision- and attention-processing regions is potentially significant given the need for tight functional coupling and sustained resource consumption by these systems during a perceptually demanding task like the RFT. Even at rest, however, superior parietal lobe iFC with the ventral caudate and posterior cingulate cortex (PCC) is reduced in depressive adults (Schilbach et al., 2016; Yang et al., 2017). These results supported a link between systemic inflammation and abnormal sensory and attention processing during reward. In addition, the whole-brain analyses also found that higher CRP levels were associated with stronger activation in lobule VI of the left cerebellum during positive prediction error. The cerebellum has been increasingly implicated in disorders entailing reward dysfunction, including depression, anxiety, and addiction (Miquel et al., 2009; Moulton et al., 2014; Phillips et al., 2015; Volkow et al., 2003). For example, cerebellar iFC with the PCC/precuneus was found to be reduced in adults with depression (Liu et al., 2012). The association between CRP and activation of lobule VI during positive prediction error in the current study is consistent with these dual roles and suggests the cerebellum as a possible site of inflammation-related reward dysfunction in adolescents.

Unlike the whole-brain analyses, the ROI analyses focused on reward circuitry yielded significant relationships with the dACC, a region consistently involved in reward anticipation (Bush et al., 2002; Cao et al., 2019; Liu et al., 2011). A recent study in 1,510 healthy adolescents showed dACC activation and increased striatum-dACC connectivity during reward anticipation (Cao et al., 2019). Altered dACC activity and connectivity is among the most consistently reported findings in fMRI studies of depression, both in adult and adolescent cohorts (Lichenstein et al., 2016; Nejad et al., 2013; Rive et al., 2013). The current findings support our prior data in youth documenting correlations between the inflammatory kynurenine pathway and resting state functional connectivity of the dACC (DeWitt et al., 2018). Similarly, we also documented relationships between cytokine (Eotaxin) levels and dACC activation during reward anticipation in a prior cytokine-fMRI study in a smaller sample (Bradley et al., 2019). Studies of neuroinflammatory states in adults have further implicated the dACC. For example, grey matter volume and thickness in the dACC have been repeatedly reported to correlate with peripheral inflammatory responses, indexed by CRP (Meier et al., 2016), kynurenine pathway activity (Meier et al., 2016), and IL-6 and other cytokines (Lin et al., 2020).

Notably, exclusion of the high-CRP subject had a differential effect on whole-brain and ROI analyses. After excluding this outlier subject, whole-brain findings no longer met significance, while findings in the dACC ROI remained intact and findings in the nucleus accumbens ROI passed the significance threshold. In line with our finding that nucleus accumbens activation during positive predication error was positively correlated with CRP levels, the nucleus accumbens has been consistently documented as a key region in representing reward prediction error (Hare et al., 2008; Peters and Büchel, 2010), and abnormalities in nucleus accumbens function are widely reported in adolescent depression (Keren et al., 2018). Although the outlier subject had unusually high CRP levels (26.2 mg/L), she did not present or report any recent illnesses or physical issues with the exception of a high BMI (30.2, in the obese range). However, analyses were controlled for BMI, and other subjects with higher BMI values had normal CRP levels. Additionally, blood work from the same subject collected three years later as part of a follow-up study also indicated unusually high CRP levels (10.9 mg/L), suggesting a chronic inflammatory state that may be related to the high BMI or the chronic depression state rather than an acute inflammatory response. As our goal was to assess associations between dimensional measures of psychiatric symptomatology and inflammatory tone, we elected to retain this subject for our main analyses. Given that sensitivity was reduced for whole-brain analyses but increased for ROI analyses with this subject excluded, further work with a denser sampling of high-CRP subjects is needed to resolve how best to treat such cases, which may represent a distinct biological phenotype with specific psychiatric manifestations.

Several limitations should be noted in this study. First, although we recruited a relatively large group of adolescents ($N = 64$), the majority had mood or anxiety symptoms, so the diversity of symptom profiles may be a limitation. Conversely, however, the wide severity range of symptoms in our clinical sample allowed for robust dimensional analyses, which were of primary interest in our study and address many of the methodological concerns with studying specific categorical diagnoses. We also need to point out that the healthy youth without psychiatric symptoms may exhibit varied distribution of symptom severity as well as different relationship with inflammation, although this is not the focus of current study. Our sample size for the fMRI analyses may have also contributed to Type II error particularly in our whole-brain analyses which require a larger sample size compared to the more focused ROI analyses. Another limitation is the wide age range across adolescence (12–20 years). However, all participants were Tanner stage ≥ 4 and thus had already achieved the later stages of puberty. Additionally, we did not take into account factors such as menstrual cycle stage, exercise, diet, stress, and sleep. Thus, while our study advances the understanding of inflammatory processes in adolescents with psychiatric disorders, replication in larger samples while examining other inflammation indices and controlling for additional health and lifestyle factors will be necessary to fully characterize the relationship between inflammation and reward processing in adolescents.

In conclusion, we found no relationship between blood CRP levels and anhedonia or other related mood and anxiety symptoms. However, CRP levels were significantly, correlated with neural activation in lateral occipital, posterior temporal, and superior parietal cortices during reward attainment, with additional activation in the cerebellum evident during positive prediction error. More focused ROI analyses further identified associations between increased CRP level and reduced dACC activation during reward anticipation, as well as elevated nucleus accumbens activation during positive predication error when the high-

CRP subject was excluded. Future studies should examine CRP in conjunction with other, more specific inflammatory indices such as cytokines. Further work is also needed to establish when and how the generalized inflammatory response seen in adults with depression first develops, and whether the transition into this higher-inflammation state serves as a longitudinal biomarker, or even a potential treatment target, for depression in adolescents.

Ethical statement

This study was approved by the Icahn School of Medicine at Mount Sinai Institutional Review Board. The written informed consent was obtained from participants age 18 and older. Those under the age of 18 provided signed assent, and a parent or legal guardian provided signed informed consent.

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Declaration of competing interest

The authors declare no conflict of interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2020.100153.

References

Apitz, T., Bunzeck, N., 2012. Reward modulates the neural dynamics of early visual category processing. Neuroimage 63, 1614–1622.
Baumeister, D., Akhtar, R., Ciufolini, S., Pariante, C.M., Mondelli, V., 2016. Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-α. Mol. Psychiatr. 21, 642–649.
Beck, A.T., Kovacs, M., Weissman, A., 1979. Assessment of suicidal intention: the scale for suicide ideation. J. Consult. Clin. Psychol. 47, 343.
Beck, A.T., Steer, R., Brown, G., 1996. Beck Depression Inventory, second ed. The Psychological Corporation, San Antonio, TX. Manual.
Bekhbat, M., Treadway, M.T., Goldsmith, D.R., Woolwine, B.J., Haroon, E., Miller, A.H., Felger, J.C., 2020. Gene Signatures in Peripheral Blood Immune Cells Related to Insulin Resistance and Low Tyrosine Metabolism Define a Sub-type of Depression with High CRP and Anhedonia. Brain, Behavior, and Immunity.
Black, S., Kushner, I., Samols, D., 2004. C-reactive protein. J. Biol. Chem. 279, 48487–48490.
Bradley, K.A., Case, J.A., Khan, O., Ricart, T., Hanna, A., Alonso, C.M., Gabbay, V., 2015. The role of the kynurenine pathway in suicidality in adolescent major depressive disorder. Psychiatr. Res. 227, 206–212.
Bradley, K.A., Case, J.A.C., Freed, R.D., Stern, E.R., Gabbay, V., 2017. Neural correlates of RDoC reward constructs in adolescents with diverse psychiatric symptoms: a Reward Flanker Task pilot study. J. Affect. Disord. 216, 36–45.
Bradley, K.A., Colcombe, S., Henderson, S.E., Alonso, C.M., Milham, M.P., Gabbay, V., 2016. Neural correlates of self-perceptions in adolescents with major depressive disorder. Developmental cognitive neuroscience 19, 87–97.
Bradley, K.A., Stern, E.R., Alonso, C.M., Xie, H., Kim-Schulze, S., Gabbay, V., 2019. Relationships between neural activation during a reward task and peripheral cytokine levels in youth with diverse psychiatric symptoms. Brain Behav. Immun. 80, 374–383.
Brydon, L., Harrison, N.A., Walker, C., Steptoe, A., Critchley, H.D., 2008. Peripheral inflammation is associated with altered substantia nigra activity and psychomotor slowing in humans. Biol. Psychiatr. 63, 1022–1029.
Bush, G., Vogt, B.A., Holmes, J., Dale, A.M., Greve, D., Jenike, M.A., Rosen, B.R., 2002. Dorsal anterior cingulate cortex: a role in reward-based decision making. Proc. Natl. Acad. Sci. Unit. States Am. 99, 523.
Cao, Z., Bennett, M., Orr, C., Icke, I., Banaschewski, T., Barker, G.J., Bokde, A.L.W., Bromberg, U., Büchel, C., Quinlan, E.B., Desrivières, S., Flor, H., Frouin, V., Garavan, H., Gowland, P., Heinz, A., Ittermann, B., Martinot, J.-L., Nees, F., Orfanos, D.P., Paus, T., Poustka, L., Hohmann, S., Fröhner, J.H., Smolka, M.N., Walter, H., Schumann, G., Whelan, R., Consortium, I., 2019. Mapping adolescent reward anticipation, receipt, and prediction error during the monetary incentive delay task. Hum. Brain Mapp. 40, 262–283.
Capuron, L., Pagnoni, G., Demetrashvili, M.F., Lawson, D.H., Fornwalt, F.B., Woolwine, B., Berns, G.S., Nemeroff, C.B., Miller, A.H., 2007. Basal ganglia hypermetabolism and symptoms of fatigue during interferon-alpha therapy. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology 32, 2384–2392.
Capuron, L., Pagnoni, G., Drake, D.F., Woolwine, B.J., Spivey, J.R., Crowe, R.J., Votaw, J.R., Goodman, M.M., Miller, A.H., 2012. Dopaminergic mechanisms of reduced basal ganglia responses to hedonic reward during interferon alfa administration. Arch. Gen. Psychiatr. 69, 1044–1053.
Danese, A., Moffitt, T.E., Pariante, C.M., Ambler, A., Poulton, R., Caspi, A., 2008. Elevated inflammation levels in depressed adults with a history of childhood maltreatment. Arch. Gen. Psychiatr. 65, 409–415.
Danner, M., Kasl, S.V., Abramson, J.L., Vaccarino, V., 2003. Association between depression and elevated C-reactive protein. Psychosom. Med. 65, 347–356.
Dantzer, R., 2001. Cytokine-induced sickness behavior: where do we stand? Brain Behav. Immun. 15, 7–24.
Dantzer, R., Kelley, K.W., 2007. Twenty years of research on cytokine-induced sickness behavior. Brain Behav. Immun. 21, 153–160.
Dantzer, R., O'Connor, J.C., Freund, G.G., Johnson, R.W., Kelley, K.W., 2008. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat. Rev. Neurosci. 9, 46–56.
De Bellis, M.D., Wang, L., Bergman, S.R., Yaxley, R.H., Hooper, S.R., Huettel, S.A., 2013. Neural mechanisms of risky decision-making and reward response in adolescent onset cannabis use disorder. Drug Alcohol Depend. 133, 134–145.
De Berardis, D., Marini, S., Fornaro, M., Srinivasan, V., Iasevoli, F., Tomasetti, C., Valchera, A., Perna, G., Quera-Salva, M.-A., Martinotti, G., di Giannantonio, M., 2013. The melatonergic system in mood and anxiety disorders and the role of agomelatine: implications for clinical practice. Int. J. Mol. Sci. 14, 12458–12483.
Desikan, R.S., Ségonne, F., Fischl, B., Quinn, B.T., Dickerson, B.C., Blacker, D., Buckner, R.L., Dale, A.M., Maguire, R.P., Hyman, B.T., Albert, M.S., Killiany, R.J., 2006. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage 31, 968–980.
DeWitt, S.J., Bradley, K.A., Lin, N., Yu, C., Gabbay, V., 2018. A pilot resting-state functional connectivity study of the kynurenine pathway in adolescents with depression and healthy controls. J. Affect. Disord. 227, 752–758.
Dichter, G.S., Felder, J.N., Petty, C., Bizzell, J., Ernst, M., Smoski, M.J., 2009. The effects of psychotherapy on neural responses to rewards in major depression. Biol. Psychiatr. 66, 886–897.
Dickie, E.W., Anticevic, A., Smith, D.E., Coalson, T.S., Manogaran, M., Calarco, N., Viviano, J.D., Glasser, M.F., Van Essen, D.C., Voineskos, A.N., 2019. Ciftify: a framework for surface-based analysis of legacy MR acquisitions. Neuroimage 197, 818–826.
Du Clos, T.W., 2000. Function of C-reactive protein. Ann. Med. 32, 274–278.
Eisenberger, N.I., Berkman, E.T., Inagaki, T.K., Rameson, L.T., Mashal, N.M., Irwin, M.R., 2010. Inflammation-induced anhedonia: endotoxin reduces ventral striatum responses to reward. Biol. Psychiatr. 68, 748–754.
Elovainio, M., Aalto, A.-M., Kivimäki, M., Pirkola, S., Sundvall, J., Lönnqvist, J., Reunanen, A., 2009. Depression and C-reactive protein: population-based health 2000 study. Psychosom. Med. 71, 423–430.
Farabaugh, A., Fisher, L., Nyer, M., Holt, D., Cohen, M., Baer, L., Shapero, B.G., Huz, I., Cardoos, A., Fava, M., Alpert, J.E., 2015. Similar changes in cognitions following cognitive-behavioral therapy or escitalopram for major depressive disorder: implications for mechanisms of change. Ann. Clin. Psychiatr. 27, 118–126.
Felger, J.C., Li, Z., Haroon, E., Woolwine, B.J., Jung, M.Y., Hu, X., Miller, A.H., 2016. Inflammation is associated with decreased functional connectivity within corticostriatal reward circuitry in depression. Mol. Psychiatr. 21, 1358–1365.
Felger, J.C., Mun, J., Kimmel, H.L., Nye, J.A., Drake, D.F., Hernandez, C.R., Freeman, A.A., Rye, D.B., Goodman, M.M., Howell, L.L., Miller, A.H., 2013. Chronic interferon-alpha decreases dopamine 2 receptor binding and striatal dopamine release in association with anhedonia-like behavior in nonhuman primates. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology 38, 2179–2187.
Felger, J.C., Treadway, M.T., 2017. Inflammation effects on motivation and motor activity: role of dopamine. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology 42, 216–241.
Fischl, B., Salat, D.H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., van der Kouwe, A., Killiany, R., Kennedy, D., Klaveness, S., Montillo, A., Makris, N., Rosen, B., Dale, A.M., 2002. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron 33, 341–355.
Flouri, E., Francesconi, M., Midouhas, E., Lewis, G., 2020. Prenatal and childhood adverse life events, inflammation and depressive symptoms across adolescence. J. Affect. Disord. 260, 577–582.
Ford, D.E., Erlinger, T.P., 2004. Depression and C-reactive protein in US adults: data from the third national health and nutrition examination survey. Arch. Intern. Med. 164, 1010–1014.
Freed, R.D., Mehra, L.M., Laor, D., Patel, M., Alonso, C.M., Kim-Schulze, S., Gabbay, V., 2018. Anhedonia as a clinical correlate of inflammation in adolescents across psychiatric conditions. World J. Biol. Psychiatr. : the official journal of the World Federation of Societies of Biological Psychiatry 1–11.

Gabbay, V., Bradley, K.A., Mao, X., Ostrover, R., Kang, G., Shungu, D.C., 2017. Anterior cingulate cortex gamma-aminobutyric acid deficits in youth with depression. Transl. Psychiatry 7, e1216.
Gabbay, V., Ely, B.A., Li, Q., Bangaru, S.D., Panzer, A.M., Alonso, C.M., Castellanos, F.X., Milham, M.P., 2013. Striatum-based circuitry of adolescent depression and anhedonia. J. Am. Acad. Child Adolesc. Psychiatr. 52, 628–641 e613.
Gabbay, V., Johnson, A.R., Alonso, C.M., Evans, L.K., Babb, J.S., Klein, R.G., 2015. Anhedonia, but not irritability, is associated with illness severity outcomes in adolescent major depression. Journal of Child and Adolescent Psychopharmacology 25, 194–200.
Gabbay, V., Liebes, L., Katz, Y., Liu, S., Mendoza, S., Babb, J.S., Klein, R.G., Gonen, O., 2010. The kynurenine pathway in adolescent depression: preliminary findings from a proton MR spectroscopy study. Progress in neuro-psychopharmacology & biological psychiatry 34, 37–44.
Gabbay, V., Mao, X., Klein, R.G., Ely, B.A., Babb, J.S., Panzer, A.M., Alonso, C.M., Shungu, D.C., 2012. Anterior cingulate cortex gamma-aminobutyric acid in depressed adolescents: relationship to anhedonia. Arch. Gen. Psychiatr. 69, 139–149.
Gard, D.E., Gard, M.G., Kring, A.M., John, O.P., 2006. Anticipatory and consummatory components of the experience of pleasure: a scale development study. J. Res. Pers. 40, 1086–1102.
Glasser, M.F., Coalson, T.S., Robinson, E.C., Hacker, C.D., Harwell, J., Yacoub, E., Ugurbil, K., Andersson, J., Beckmann, C.F., Jenkinson, M., Smith, S.M., Van Essen, D.C., 2016. A multi-modal parcellation of human cerebral cortex. Nature 536, 171–178.
Glasser, M.F., Sotiropoulos, S.N., Wilson, J.A., Coalson, T.S., Fischl, B., Andersson, J.L., Xu, J., Jbabdi, S., Webster, M., Polimeni, J.R., Van Essen, D.C., Jenkinson, M., 2013. The minimal preprocessing pipelines for the Human Connectome Project. Neuroimage 80, 105–124.
Glimcher, P.W., 2011. Understanding dopamine and reinforcement learning: the dopamine reward prediction error hypothesis. Proc. Natl. Acad. Sci. U. S. A. 108 (Suppl. 3), 15647–15654.
Griffanti, L., Salimi-Khorshidi, G., Beckmann, C.F., Auerbach, E.J., Douaud, G., Sexton, C.E., Zsoldos, E., Ebmeier, K.P., Filippini, N., Mackay, C.E., Moeller, S., Xu, J., Yacoub, E., Baselli, G., Ugurbil, K., Miller, K.L., Smith, S.M., 2014. ICA-based artefact removal and accelerated fMRI acquisition for improved resting state network imaging. Neuroimage 95, 232–247.
Grothe, I., Rotermund, D., Neitzel, S.D., Mandon, S., Ernst, U.A., Kreiter, A.K., Pawelzik, K.R., 2018. Attention selectively gates afferent signal transmission to area V4. J. Neurosci. 38, 3441–3452.
Hare, T.A., O'Doherty, J., Camerer, C.F., Schultz, W., Rangel, A., 2008. Dissociating the role of the orbitofrontal cortex and the striatum in the computation of goal values and prediction errors. J. Neurosci. 28, 5623–5630.
Haroon, E., Daguanno, A.W., Woolwine, B.J., Goldsmith, D.R., Baer, W.M., Wommack, E.C., Felger, J.C., Miller, A.H., 2018. Antidepressant treatment resistance is associated with increased inflammatory markers in patients with major depressive disorder. Psychoneuroendocrinology 95, 43–49.
Jha, M.K., Cai, L., Minhajuddin, A., Fatt, C.C., Furman, J.L., Gadad, B.S., Mason, B.L., Greer, T.L., Hughes, J.L., Xiao, G., Emslie, G., Kennard, B., Mayes, T., Trivedi, M.H., 2020. Dysfunctional adaptive immune response in adolescents and young adults with suicide behavior. Psychoneuroendocrinology 111, 104487.
Juengling, F.D., Ebert, D., Gut, O., Engelbrecht, M.A., Rasenack, J., Nitzsche, E.U., Bauer, J., Lieb, K., 2000. Prefrontal cortical hypometabolism during low-dose interferon alpha treatment. Psychopharmacology 152, 383–389.
Karshikoff, B., Jensen, K.B., Kosek, E., Kalpouzos, G., Soop, A., Ingvar, M., Olgart Hoglund, C., Lekander, M., Axelsson, J., 2016. Why Sickness Hurts: A Central Mechanism for Pain Induced by Peripheral Inflammation. Brain, Behavior, and Immunity.
Kaufman, A.S., 1990. Kaufman Brief Intelligence Test: KBIT. AGS, American Guidance Service Circle Pines, MN.
Kaufman, J., Birmaher, B., Brent, D., Rao, U.M.A., Flynn, C., Moreci, P., Williamson, D., Ryan, N., 1997. Schedule for affective disorders and schizophrenia for school-age children-present and Lifetime version (K-SADS-PL): initial reliability and validity data. J. Am. Acad. Child Adolesc. Psychiatr. 36, 980–988.
Keren, H., O'Callaghan, G., Vidal-Ribas, P., Buzzell, G.A., Brotman, M.A., Leibenluft, E., Pan, P.M., Meffert, L., Kaiser, A., Wolke, S., Pine, D.S., Stringaris, A., 2018. Reward processing in depression: a conceptual and meta-analytic review across fMRI and EEG studies. Am. J. Psychiatr. 175, 1111–1120.
Khandaker, G.M., Pearson, R.M., Zammit, S., Lewis, G., Jones, P.B., 2014. Association of serum interleukin 6 and C-reactive protein in childhood with depression and psychosis in young adult life: a population-based longitudinal study. JAMA Psychiatry 71, 1121–1128.
Knutson, B., Cooper, J.C., 2005. Functional magnetic resonance imaging of reward prediction. Curr. Opin. Neurol. 18, 411–417.
Lichenstein, S.D., Verstynen, T., Forbes, E.E., 2016. Adolescent brain development and depression: a case for the importance of connectivity of the anterior cingulate cortex. Neurosci. Biobehav. Rev. 70, 271–287.
Lin, K., Shao, R., Wang, R., Lu, W., Zou, W., Chen, K., Gao, Y., Brietzke, E., McIntyre, R.S., Mansur, R.B., Zhang, L., Yau, S.Y., Su, H., Xu, G., So, K.F., 2020. Inflammation, brain structure and cognition interrelations among individuals with differential risks for bipolar disorder. Brain Behav. Immun. 83, 192–199.
Liu, L., Zeng, L.L., Li, Y., Ma, Q., Li, B., Shen, H., Hu, D., 2012. Altered cerebellar functional connectivity with intrinsic connectivity networks in adults with major depressive disorder. PloS One 7, e39516.
Liu, X., Hairston, J., Schrier, M., Fan, J., 2011. Common and distinct networks underlying reward valence and processing stages: a meta-analysis of functional neuroimaging studies. Neurosci. Biobehav. Rev. 35, 1219–1236.
March, J.S., Parker, J.D., Sullivan, K., Stallings, P., Conners, C.K., 1997. The Multidimensional Anxiety Scale for Children (MASC): factor structure, reliability, and validity. J. Am. Acad. Child Adolesc. Psychiatr. 36, 554–565.
Meier, T.B., Drevets, W.C., Wurfel, B.E., Ford, B.N., Morris, H.M., Victor, T.A., Bodurka, J., Teague, T.K., Dantzer, R., Savitz, J., 2016. Relationship between neurotoxic kynurenine metabolites and reductions in right medial prefrontal cortical thickness in major depressive disorder. Brain Behav. Immun. 53, 39–48.
Miller, A.H., Haroon, E., Raison, C.L., Felger, J.C., 2013. Cytokine targets in the brain: impact on neurotransmitters and neurocircuits. Depress. Anxiety 30, 297–306.
Miquel, M., Toledo, R., Garcia, L.I., Coria-Avila, G.A., Manzo, J., 2009. Why should we keep the cerebellum in mind when thinking about addiction? Curr. Drug Abuse Rev. 2, 26–40.
Moran, J., Desimone, R., 1985. Selective attention gates visual processing in the extrastriate cortex. Science 229, 782–784.
Moulton, E.A., Elman, I., Becerra, L.R., Goldstein, R.Z., Borsook, D., 2014. The cerebellum and addiction: insights gained from neuroimaging research. Addiction Biol. 19, 317–331.
Nejad, A.B., Fossati, P., Lemogne, C., 2013. Self-referential processing, rumination, and cortical midline structures in major depression. Front. Hum. Neurosci. 7, 666-666.
Pepys, M.B., Hirschfield, G.M., 2003. C-reactive protein: a critical update. J. Clin. Invest. 111, 1805–1812.
Peters, J., Büchel, C., 2010. Neural representations of subjective reward value. Behav. Brain Res. 213, 135–141.
Phillips, J.R., Hewedi, D.H., Eissa, A.M., Moustafa, A.A., 2015. The cerebellum and psychiatric disorders. Front Public Health 3, 66-66.
Poznanski, E.O., Freeman, L.N., Mokros, H.B., 1985. Children's depression rating scale-revised Psychopharmacology. Bulletin 21, 979–989.
Rive, M.M., van Rooijen, G., Veltman, D.J., Phillips, M.L., Schene, A.H., Ruhé, H.G., 2013. Neural correlates of dysfunctional emotion regulation in major depressive disorder. A systematic review of neuroimaging studies. Neurosci. Biobehav. Rev. 37, 2529–2553.
Robinson, E.C., Jbabdi, S., Glasser, M.F., Andersson, J., Burgess, G.C., Harms, M.P., Smith, S.M., Van Essen, D.C., Jenkinson, M., 2014. MSM: a new flexible framework for Multimodal Surface Matching. Neuroimage 100, 414–426.
Salimi-Khorshidi, G., Douaud, G., Beckmann, C.F., Glasser, M.F., Griffanti, L., Smith, S.M., 2014. Automatic denoising of functional MRI data: combining independent component analysis and hierarchical fusion of classifiers. Neuroimage 90, 449–468.
Schilbach, L., Hoffstaedter, F., Müller, V., Cieslik, E.C., Goya-Maldonado, R., Trost, S., Sorg, C., Riedl, V., Jardri, R., Sommer, I., Kogler, L., Derntl, B., Gruber, O., Eickhoff, S.B., 2016. Transdiagnostic commonalities and differences in resting state functional connectivity of the default mode network in schizophrenia and major depression. Neuroimage: Clinica 10, 326–335.
Snaith, R., Hamilton, M., Morley, S., Humayan, A., Hargreaves, D., Trigwell, P., 1995. A scale for the assessment of hedonic tone the Snaith–Hamilton Pleasure Scale. Br. J. Psychiatr. 167, 99–103.
Swardfager, W., Rosenblat, J.D., Benlamri, M., McIntyre, R.S., 2016. Mapping inflammation onto mood: inflammatory mediators of anhedonia. Neurosci. Biobehav. Rev. 64, 148–166.
Tabatabaeizadeh, S.-A., Abdizadeh, M.F., Meshkat, Z., Khodashenas, E., Darroudi, S., Fazeli, M., Ferns, G.A., Avan, A., Ghayour-Mobarhan, M., 2018. There is an association between serum high-sensitivity C-reactive protein (hs-CRP) concentrations and depression score in adolescent girls. Psychoneuroendocrinology 88, 102–104.
Volkow, N.D., Wang, G.-J., Ma, Y., Fowler, J.S., Zhu, W., Maynard, L., Telang, F., Vaska, P., Ding, Y.-S., Wong, C., Swanson, J.M., 2003. Expectation enhances the regional brain metabolic and the reinforcing effects of stimulants in cocaine abusers. J. Neurosci. 23, 11461–11468.
Winkler, A.M., Ridgway, G.R., Webster, M.A., Smith, S.M., Nichols, T.E., 2014. Permutation inference for the general linear model. Neuroimage 92, 381–397.
Yang, X.H., Tian, K., Wang, D.F., Wang, Y., Cheung, E.F.C., Xie, G.R., Chan, R.C.K., 2017. Anhedonia correlates with abnormal functional connectivity of the superior temporal gyrus and the caudate nucleus in patients with first-episode drug-naive major depressive disorder. J. Affect. Disord. 218, 284–290.
Yeo, B.T., Krienen, F.M., Sepulcre, J., Sabuncu, M.R., Lashkari, D., Hollinshead, M., Roffman, J.L., Smoller, J.W., Zollei, L., Polimeni, J.R., Fischl, B., Liu, H., Buckner, R.L., 2011. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. J. Neurophysiol. 106, 1125–1165.