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Anhedonia as a Clinical Correlate of Inflammation in Adolescents across Psychiatric Conditions

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Abstract

Objectives—Peripheral inflammation has been associated with multiple psychiatric disorders, particularly with depression. However, findings remain inconsistent and unreproducible, most likely due to the disorder's heterogeneity in phenotypic presentation. Therefore, in the present study, in an effort to account for inter-individual differences in symptom severity, we utilised a dimensional approach to assess the relationships between a broad panel of inflammatory cytokines and key psychiatric symptoms (i.e., depression, anhedonia, anxiety, fatigue, and suicidality) in adolescents across psychiatric disorders. We hypothesised that only anhedonia—reflecting deficits of reward function—will be associated with inflammation.

Methods—Participants were 54 psychotropic medication-free adolescents with diverse psychiatric conditions and 22 healthy control (HC) adolescents, ages 12–20. We measured 41 cytokines after in-vitro lipopolysaccharide stimulation. Mann-Whitney U and Spearman correlation tests examined group comparison and associations, respectively, while accounting for multiple comparisons and confounds, including depression severity.

Results—There were no group differences in cytokine levels. However, as hypothesised, within the psychiatric group, only anhedonia was associated with 19 cytokines, including hematopoietic growth factors, chemokines, and pro-inflammatory cytokines.

Conclusions—Our findings suggest that general inflammation may induce reward dysfunction, which plays a salient role across psychiatric conditions, rather than be specific to one categorical psychiatric disorder.

Keywords

inflammation; cytokines; anhedonia; adolescent; reward

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Statement of Interest

The authors declare no conflict of interest.

Introduction

Adolescence is a developmental period notable for its increased prevalence of psychiatric conditions (Merikangas et al. 2010). Although the underlying mechanisms are not fully understood, inflammatory processes have been implicated, particularly in depression (Felger and Lotrich 2013; Gabbay et al. 2009b; Irwin and Miller 2007), but also across psychiatric conditions both in paediatric and adult populations (Furtado and Katzman 2015; Gabbay et al. 2009a; Gabbay et al. 2009c; Michopoulos et al. 2017; Mitchell and Goldstein 2014; Munkholm et al. 2013). Hence, inflammation does not seem to have diagnostic specificity, which may be due to high diagnostic comorbidity, shared etiological pathways, and/or overlapping symptoms across disorders. The non-specific association between inflammation and psychiatric conditions might be even more prominent in adolescents in light of the rapid brain changes in certain regions (e.g., frontal-striatal) (Brenhouse and Schwarz 2016).

Addressing the above phenomena, several studies have examined the relationships between inflammation, brain functions, and associated neuropsychiatric symptoms, as opposed to categorical psychiatric diagnoses (e.g., Capuron and Castanon 2017; Miller et al. 2013). Converging data suggest that inflammation may target the brain's reward circuitry, which is known to be impaired across psychiatric conditions (Whitton et al. 2015). It has been hypothesised that inhibition of reward function by inflammation occurs in order to conserve energy needed to facilitate the healing process (Aubert 1999; De La Garza 2005; Felger and Miller 2012). Supporting this theory, immunotherapy with interferon alpha (IFN-α) in humans induces anhedonia—the decreased capacity to experience pleasure, known to reflect deficits of reward function—along with other "flu-like'" symptoms (Capuron and Miller 2004). Further, a randomised trial with the immune activator lipopolysaccharide (LPS) and a placebo (saline) in healthy individuals found that exposure to LPS induced motivational changes, as measured by a behavioural task (Lasselin et al. 2017). Neuroimaging work, using PET and fMRI modalities, adds to this literature by documenting the specific effects of inflammatory processes within the dopaminergic reward circuitry (Capuron et al. 2007; Capuron et al. 2012; Eisenberger et al. 2010; Juengling et al. 2000). A similar phenomenon has also been reported in non-human primates; for example, a study in rhesus monkeys demonstrated that chronic administration of IFN-α resulted in decreased dopaminergic neurotransmission in association with anhedonia-like behaviour (Felger et al. 2013). Similarly, cross-sectional studies have shown that patients with the melancholic subtype of major depressive disorder, characterised by high anhedonia, have elevated levels of certain pro-inflammatory cytokines (interleukin [IL]-6, IL-1β, and IL-1 receptor antagonist [ra]), compared to both healthy controls and patients with non-melancholic major depressive disorder (Dunjic-Kostic et al. 2013; Kaestner et al. 2005; Rush et al. 2016). Consistent with this, a recent fMRI study documented a negative correlation between C-reactive protein—a marker of overall inflammation—and connectivity within reward-related brain regions in adults with depression; this study further showed that this relationship was, in turn, related to higher levels of anhedonia (Felger et al. 2016). Taken together, these data suggest that inflammation may affect the reward circuitry rather than be specific to one psychiatric condition. However, no studies have examined relationships between peripheral

inflammation and clinical manifestations reflecting reward function, such as anhedonia severity, in adolescents.

Therefore, in the current study, we sought to assess relationships between a broad profile of inflammatory cytokines and anhedonia in adolescents. Our sample included psychotropic medication-free adolescents with diverse psychiatric symptoms and healthy control (HC) adolescents. We elected not to focus on one specific categorical diagnosis since anhedonia and other behavioural dimensions are salient across psychiatric conditions and therefore may share the same aetiology. To better quantify the immune system, peripheral blood mononuclear cells (PBMCs) were stimulated with LPS, a bacterial endotoxin and an immune activator. Building upon findings to date, hypotheses were that: a) adolescents with psychiatric symptoms would exhibit higher levels of inflammatory cytokines compared to HCs; and b) in light of specific relationships between immune reactivity and reward processes, levels of cytokines would be associated with anhedonia severity, but not depression, suicidality, anxiety, or fatigue severity, all of which are symptoms often associated with anhedonia but do not reflect specific deficits of reward. We limited this latter hypothesis to the psychiatric group, as the HC group was not expected to exhibit a range of severity on the studied clinical measures.

Methods

Participants and Clinical Procedure

Adolescents, ages 12–20, were recruited in the greater New York City area. Participants under age 18 provided written assent, and a parent or guardian gave written informed consent; participants 18 years and older provided written informed consent. The study was approved by the Institutional Review Board at the Icahn School of Medicine at Mount Sinai.

Adolescents were evaluated for lifetime history of Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) psychiatric disorders to assess study eligibility. On a separate visit, occurring within two weeks of the diagnostic evaluation, participants underwent a fasting blood draw and completed clinical questionnaires. A urine toxicology test and pregnancy test (in females) were also administered, and vitals (i.e., blood pressure, pulse, weight, and height) were taken. Adolescents with a current or past DSM-IV diagnosis of schizophrenia, pervasive developmental disorder, or substance use disorder were excluded. Additional exclusion criteria for HC adolescents were any current or past DSM-IV diagnosis and/or psychiatric treatment. Participants were also excluded if they had taken any psychotropic medication in the thirty days prior to the blood draw, had taken any immune-affecting medications or herbal supplements (e.g., steroids, non-steroidal anti-inflammatory drugs, and omega-3 fatty acids) in the two weeks prior to the blood draw, or if they had a positive urine toxicology or pregnancy test. Finally, we excluded all participants with a history of any chronic inflammatory conditions or who had had an inflammatory illness (e.g., cold, flu) in the two weeks prior to the blood draw.

Clinical Measures

Diagnoses.—DSM-IV symptoms and diagnoses (at a clinical and sub-clinical level) were obtained by a trained licensed psychiatrist or clinical psychologist using the Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version for School Aged Children (K-SADS-PL) (Kaufman et al. 1997). The interview was administered to adolescent participants, as well as to a parent or guardian when the participant was under age 18. To enhance diagnostic reliability, evaluations were discussed between the interviewing clinician and the Principal Investigator (a board-certified child and adolescent psychiatrist).

Depression severity.—Participants self-reported on their depression severity using the Beck Depression Inventory-II (BDI-II) (Beck et al. 1996). The BDI-II is a 21-item self-report scale that assesses symptoms and features of depression over the previous two weeks. The BDI-II has been validated for its high internal consistency in clinical (Krefetz et al. 2002) and non-clinical (Osman et al. 2008) adolescent populations. Reliability was excellent in the present sample (α = .94).

Anhedonia.—Participants completed the Snaith-Hamilton Pleasure Scale (SHAPS) (Snaith et al. 1995), a self-report measure of anhedonia severity. The SHAPS is a measure of consummatory reward across four positive valence subcategories: hobbies, social interactions, sensory experiences, and food. Higher total scores reveal greater difficulty experiencing pleasure in these areas. The SHAPS has been validated in clinical and non-clinical populations of adolescents and adults (Franken et al. 2007; Leventhal et al. 2015) and is currently considered the “gold standard” for measuring anhedonia in depression (Leventhal et al. 2015; Rizvi et al. 2016). Reliability was good in the present sample (α = .89).

Anxiety.—The Multidimensional Anxiety Scale for Children (MASC) (March et al. 1997) was used as a measure of anxiety severity. The MASC is a 39-item, self-report scale that assesses anxiety across four main symptom areas: 1) Physical Symptoms; 2) Social Anxiety; 3) Harm Avoidance; and 4) Separation Anxiety. Higher scores indicate greater anxiety severity. Deemed reliable and validated in both clinical and non-clinical populations (March et al. 1997), the MASC is able to discriminate between anxiety and depression in participants (Rynn et al. 2006). The full MASC score was utilised for the present analyses. Reliability was excellent in the present sample (α = .92).

Suicidality.—Participants were administered the Beck Scale for Suicidal Ideation (BSS) (Beck et al. 1988), a 21-item self-report measure used to evaluate suicidality. The first 19 items assess for suicidal ideation in the past two weeks, and items 20 and 21 assess for lifetime suicidality. The BSS has been validated for use with adolescent populations (Steer et al. 1993). Reliability was excellent in the present sample (α = .98).

Fatigue.—Fatigue was assessed using the 18-item self-report *PedsQL™ Multidimensional Fatigue Scale* (MFS) (Varni and Limbers 2008). The MFS is designed to measure fatigue over the past month in paediatric and young adult populations across three domains: general

fatigue, sleep/rest fatigue, and cognitive fatigue. The total score was used in the present analyses with lower scores indicating greater fatigue. The MFS has demonstrated good to excellent validity and reliability, spanning age and sex groups in paediatric and young adult populations with a variety of conditions (Panepinto et al. 2014; Tomlinson et al. 2013; Varni and Limbers 2008). Reliability was excellent in the present sample (α = .92).

Multiplex analysis

All blood samples were collected between 9:00 and 10:00 AM after an overnight fast (≥ 12 hours). Samples were processed within 20 minutes of collection and stored at −80º C. Detailed sera cytokine profile was measured using a Luminex-200 system and the XMap Platform (Luminex Corporation). Acquired fluorescence data were analysed by the xPONENT software. Levels of inflammatory cytokines were determined in duplicate 25 μL volumes of plasma or serum using the multiplex cytokine panels (Multiplex High Sensitivity Human Cytokine Panel, Millipore Corp.). Assays were performed by laboratory staff at Mount Sinai's Human Immune Monitoring Center (HIMC) who were blind to participants' clinical status. The assays included 41 cytokines (listed in Supplementary Tables 1 and 2). To assess participants' functional immune responses, whole blood was stimulated for 6 hours with toll-like receptor 4 (TLR4) agonist LPS, a well-established and potent immune activator (Lu et al. 2008). Following the 6-hour exposure, supernatants were harvested and analysed by Luminex for the panel of cytokines. The potency of LPS was authenticated on a quarterly basis using the in-house reference PBMCs collected from a healthy donor in the Multiplex cytokine assay.

Median fluorescence intensity (MFI) values were not transformed into absolute concentration values for the current analyses. The use of MFI values provides direct comparison of the data without introducing any bias for the samples with very low or high values in relation to the provided standard curves (Breen et al. 2015; Breen et al. 2016).

Statistical procedures

All statistical analyses were performed in SPSS, version 22. According to Shapiro-Wilk tests, all inflammatory cytokines were found to have a non-normal distribution in our sample, necessitating the use of non-parametric analyses. Prior to our main analyses, we examined group differences in demographic variables (i.e., age, sex, and ethnicity), as well as in the relationships between demographic and clinical variables, to detect any potential confounds. We also examined body mass index (BMI) as a potential confound, in light of findings that adiposity increases inflammatory responses to stress (McInnis et al. 2014) and may mediate the relationship between depression and inflammation (Miller et al. 2003).

We first ran Mann-Whitney U tests comparing adolescents with psychiatric symptoms and HC adolescents on MFI values for each of the 41 inflammatory cytokines following LPS stimulation (post-LPS). Given the large number of comparisons, a False Discovery Rate (FDR) adjustment (Benjamini and Hochberg 1995), corrected to $p < .05$, was applied.

Next, for the psychiatric group, we conducted Spearman correlations to examine the associations between clinical measures (BDI, SHAPS, MASC, BSS, MFS) and post-LPS MFI values. For these analyses, BMI, age, and sex were included as covariates, given the

wide age range of participants in our study and the compelling literature linking BMI to inflammation (Miller et al. 2003) and sex differences in immune response (Oertelt-Prigione 2012; Roved et al. 2017). For each set of correlations, an FDR adjustment, corrected to $p < .05$, was applied. To control for the potential confounding role of overall depression severity, for correlations with the SHAPS, MASC, BSS, and MFS, the total BDI score was included as a covariate (i.e., partial correlation). Importantly, in order to limit shared variance between the clinical measures and the items on the BDI that correspond to these constructs, we removed these items prior to controlling for the BDI total score. Specifically, for the partial correlations between SHAPS and post-LPS MFI values, we removed BDI Item 2, assessing anhedonia ("difficulty having fun"), from the total BDI score. Similarly, for the partial correlations between BSS and post-LPS MFI values, we removed BDI Item 13 ("suicidal ideation") from the total BDI score. Finally, for the partial correlations between the MFS and post-LPS MFI values, we removed BDI Item 6 ("excessive fatigue") from the total BDI score. There is no item assessing anxiety on the BDI, so for the partial correlations between the MASC and post-LPS MFI values, we controlled for the total BDI score with no items removed.

Results

Participant characteristics

The sample consisted of 76 adolescents, ages 12–20 (56.6% female), including 54 adolescents with DSM-IV psychiatric symptoms and 22 HC adolescents. The adolescents with psychiatric symptoms met criteria for one or more DSM-IV diagnoses on a clinical or sub-clinical level. The majority of participants (92% of the full sample, and 97% of the psychiatric group) were in an advanced puberty (i.e., Tanner stages 4 and 5; as assessed by self-report based on sex-specific drawings). Table 1 provides demographic and clinical characteristics for the sample. Adolescents with psychiatric symptoms had significantly higher scores on all clinical measures. The groups did not differ on any demographic variables or in BMI.

In adolescents with psychiatric disorders, BDI, BSS, SHAPS, and MFS scores were moderately intercorrelated, but MASC scores were only associated with the BDI. No demographic variables were associated with these clinical measures. Despite this, as noted above, we took a conservative approach and controlled for age, sex, and BMI in analyses examining correlations between clinical measures and post-LPS MFI values.

One participant in the psychiatric group was removed from the cytokine analyses given extreme levels (i.e., greater than 2 standard deviations above the mean) of a number of the 41 cytokines measured.

Group differences in inflammatory cytokines

HC adolescents and adolescents with psychiatric symptoms did not differ on post-LPS MFI values for any of the examined inflammatory cytokines at the FDR corrected threshold (see Supplementary Table 1).

Correlations between inflammatory cytokines and clinical measures

The SHAPS was the only clinical measure associated with inflammatory cytokines in the psychiatric group at the FDR corrected thresholds. As presented in Table 2, controlling for BMI, age, sex, and depression severity (as described above), SHAPS scores were significantly positively correlated with post-LPS values of the following 19 cytokines at the FDR corrected threshold: FGF-2, Flt3-L, Fractalkine, G-CSF, GM-CSF, IL-1α, IL-2, IL-3, IL-4, IL-7, IL-9, IL-10, IL-12p40, IL-12p70, IL-15, IL-17α, MCP-3, TNF-β, VEGF.

Discussion

This is the first study to our knowledge to examine peripheral inflammatory cytokines and anhedonia severity as well as other related behavioural dimensions in adolescents with diverse psychiatric conditions. Contrary to our first hypothesis, our findings did not suggest that psychotropic medication-free adolescents with psychiatric conditions exhibit overall increased inflammation when compared to healthy adolescents. However, in line with our second hypothesis, across clinical measures, only anhedonia severity showed associations with multiple cytokines, lending support to the idea that inflammation is associated specifically with reward system deficits. We discuss our findings below.

In contrast to a number of studies in individuals with depression and other psychiatric conditions, (Dowlati et al. 2010; Furtado and Katzman 2015; Miller et al. 2009; Munkholm et al. 2013; Young et al. 2014) including from our laboratory (Gabbay et al. 2009a; Gabbay et al. 2009b; Gabbay et al. 2009c), the current study failed to detect any compelling group differences in levels of inflammatory cytokines between adolescents with psychiatric conditions and healthy control adolescents. Similarly, a number of other studies in both adult and youth populations did not find significant group differences (Byrne et al. 2013; Cilan et al. 2012; Einvik et al. 2012; Kim et al. 2014; Marques-Deak et al. 2007), including a recent large-scale study examining peripheral inflammation in psychotropic medication-free adults with major depressive disorder and healthy controls (Cassano et al. 2017). The latter study also failed to detect relationships with depression illness severity (Cassano et al. 2017). Such inconsistencies across studies can be attributed to the high inter-individual variability of clinical presentation, even in a homogenous clinical diagnostic category such as major depressive disorder (Gabbay et al. 2015). Indeed, as mentioned above, in our prior published paper (Gabbay et al. 2009b), we did report increased levels of pro-inflammatory cytokines and a pro-inflammatory state in adolescents with major depressive disorder compared to healthy controls. However, this prior sample of major depressive disorder had high illness severity, which may have reflected higher anhedonia. This is in contrast to the current sample that consisted of participants with diverse psychiatric conditions with high variability of anhedonia severity (as presented in Table 1). The lack of detected group differences in the current study supports our overall approach that a dimensional investigative method may be preferred to better detect neurobiological underpinnings of behavioural constructs (Insel 2014).

As hypothesised, our data demonstrated that only anhedonia was associated with levels of inflammatory cytokines, and all correlations were positive. This finding is consistent with past research demonstrating associations between inflammation and deficits in reward-

related neural correlates in adult populations (Capuron et al. 2012; Eisenberger et al. 2010; Felger et al. 2016). Our finding is also supported by a recent randomised trial with LPS and placebo (saline) in healthy adult individuals, which showed that LPS induces motivational changes as measured by a behavioural task (Lasselin et al. 2017).

Although no other studies have examined relationships between peripheral inflammatory markers and anhedonia in adolescent populations, our research group and others have found associations between the inflammatory kynurenine pathway (KP) and anhedonia (Gabbay et al. 2012; Gabbay et al. 2010a; Gabbay et al. 2010b; Savitz et al. 2015). The KP metabolises tryptophan into several neurotoxins hypothesised to induce central nervous system (CNS) alterations seen in depression and is induced by pro-inflammatory cytokines. Our findings include increased KP activation in adolescents with the melancholic subtype of depression (Gabbay et al. 2010a), characterised by high levels of anhedonia, as well as relationships between KP metabolites and dimensional measures of anhedonia severity (Gabbay et al. 2012). More recently, in an fMRI study, we documented associations between KP metabolite blood levels and connectivity within the reward and salience networks in adolescents with depression (DeWitt et al. 2017). Therefore, our present finding of relationships among a wide variety of cytokine levels and anhedonia severity adds additional evidence that inflammation may have a specific role in the reward circuitry in youth.

Despite a conservative statistical approach with a correction for multiple comparisons while controlling for several potential covariates (i.e., depression severity, age, sex, BMI), 19 cytokines were found to be associated with anhedonia. This result suggests that generalised and complex immunological reactions may play a role in the induction of reward dysfunction. Our detected associations include several classes of cytokines that are involved in multiple stages of an immune reaction including: a) hematopoietic growth factors (IL-2, IL-3, IL-7, IL-9, IL-12p40, IL-12p70, IL-15, IL-17α, FGF-2, Flt3-L, VEGF, G-CSF, GM-CSF, TNF-β), which induce proliferation and maturation of blood cells including the initiation of an immune reaction by stimulating the production of immune cells from the bone marrow (e.g., G-CSF, GM-CSF) b) chemokines (Fractalkine, MCP-3), which induce immune cell migration, c) pro-inflammatory cytokines (IL-1α, IL-2, IL-3, IL-7, IL-9, IL-12p40, IL-12p70, IL-15, IL-17α, FGF-2, Flt3-L, VEGF, G-CSF, GM-CSF, TNF-β), which are part of complex inflammatory pathways, and d) anti-inflammatory cytokines (IL-4, IL-10), which regulate the inflammatory immune response, interacting with cytokine inhibitors and receptors. Importantly, some cytokines have overlapping immune functions (see Figure 1 illustrating the function of these cytokines within the immune system). Due to technological advances, our approach of assessing multiple cytokines simultaneously has only been recently utilised, and very few papers have examined them in relation to behavioural domains in clinical populations. However, converging evidence has associated these cytokines with the CNS as well as with depression symptomatology (Clark-Raymond and Halaris 2013; Dahl et al. 2014; Gaughran et al. 2006; Shelton et al. 2011; Simon et al. 2008; Zhao et al. 2015).

Within the hematopoietic growth factor family, both FGF-2 and VEGF have a role in promoting neuronal survival within the fronto-striatal region (Reuss and von Bohlen und Halbach 2003; Sharma et al. 2016). While we would have expected a negative correlation

between these neurotrophic factors and anhedonia, the positive relationship may represent a compensatory mechanism to the overall heightened immune system activation. Within the chemokine family, fractalkine is found throughout the brain with preclinical studies implicating it with anhedonia. Specifically, fractalkine receptor knockout mice did not exhibit any anhedonic like symptoms post stress, suggesting that fractalkine may impact the reward circuitry (Winkler et al. 2017).

Although others have found relationships between cytokine levels and overall depression and anxiety severity (Vogelzangs et al. 2016), such a relationship was not present among our sample of youth with diverse psychiatric conditions. However, both anxiety and depression severity are associated with disturbances of reward processes, and these prior studies did not assess such relationships with anhedonia severity (Morris et al. 2015).

Our results must be interpreted in light of several limitations. First, the combination of a relatively small sample size with a stringent threshold for determining statistical significance (given multiple comparisons) may have meant that smaller effects of inflammation on psychiatric symptomatology were not detected. However, at both $p = .05$ and at the FDR-corrected threshold, anhedonia was the only clinical characteristic that showed relationships with multiple cytokines. Regardless, further studies are needed using larger samples of youth with psychiatric symptoms to confirm the present findings. As a second limitation, in an effort to examine relationships with adolescent reward function, we utilised self-report measures of anhedonia. Although the SHAPS and other clinical measures of anhedonia have been shown to be associated with reward system neurocircuitry (Felger et al. 2016), the measures may not completely map onto decreased reward-related brain function. Future studies should utilise neuroimaging approaches to more accurately capture the neural underpinnings of reward anticipation and attainment (Bradley et al. 2017). Finally, our analyses did not account for other biological triggers (e.g., physical exercise, menstrual cycle stage) which may impact cytokine levels (Allen et al. 2015; Whitcomb et al. 2014). Importantly, our approach of *in vitro* LPS stimulation minimizes the effect of these factors as it assesses the immune system subsequent to a biological stressor.

In summary, this study supports the notion that peripheral inflammation may be associated with disturbances in reward function in adolescents rather than underlie a specific psychiatric category. Since psychiatric manifestation in youth can evolve into different psychiatric conditions at adulthood, there is a critical need to develop biomarkers that would predict course of illness and progression. Our finding of associations between cytokine levels and anhedonia is an important development in this direction. This study underscores the importance of incorporating dimensional analyses to address the heterogeneous nature of psychiatric conditions and overlapping symptomatology among disorders. Future studies should utilise longitudinal analyses to assess whether such relationships predict illness progression while assessing reward function objectively with neuroimaging or reward tasks.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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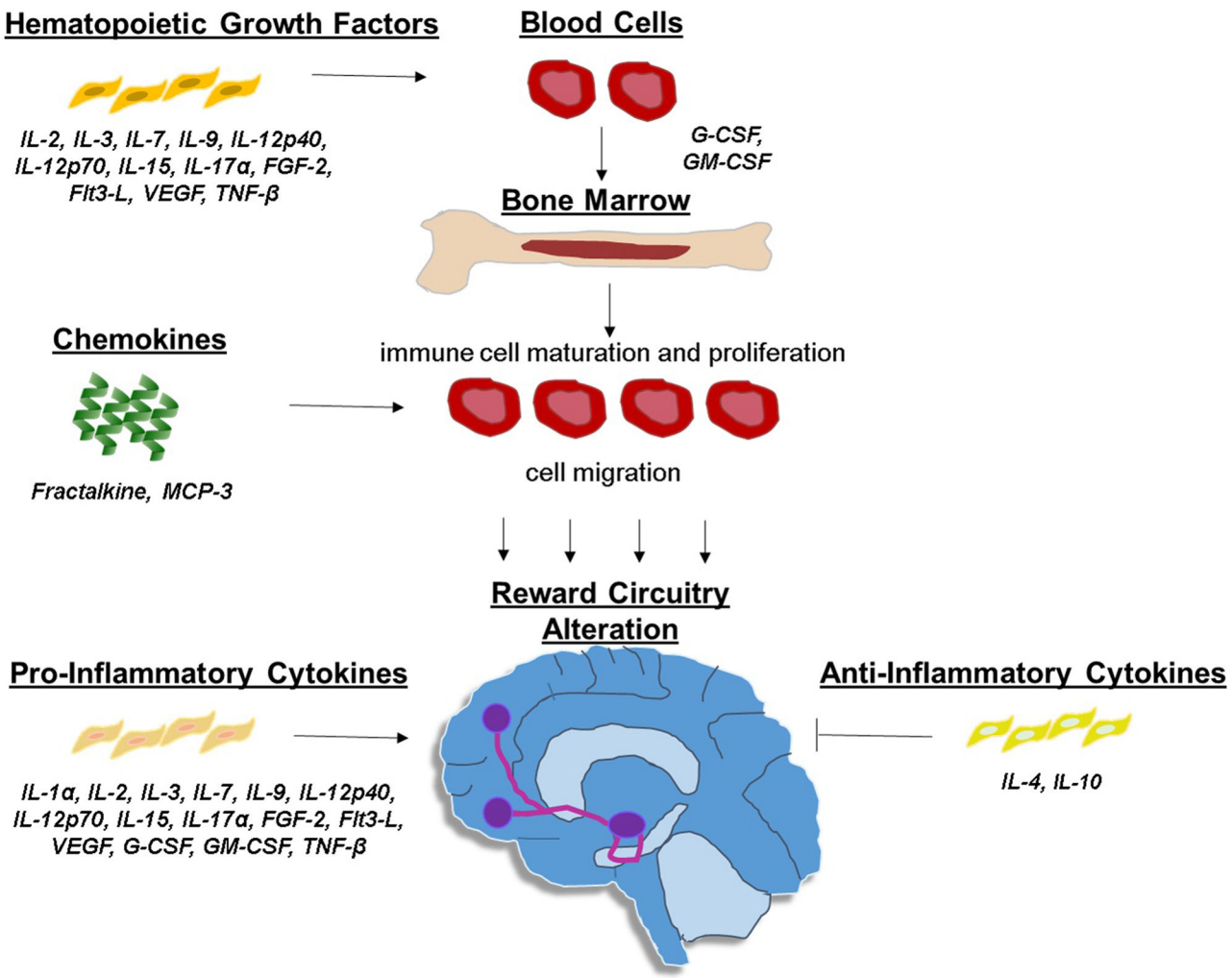

Figure 1. Function of our detected cytokines within the immune system.

Flt3-L = fms-like tyrosine kinase 3-ligand; G-CSF = granulocyte colony-stimulating factor; GM-CSF = granulocyte-macrophage colony-stimulating factor; IL = interleukin; MCP = monocyte chemotactic protein; TNF = tumour necrosis factor; VEGF = vascular endothelial growth factor.

Table 1.

Demographic and diagnostic data

	Psychiatric Group (*n* = 54)	Healthy Control Group (*n* = 22)
Age in years [Mean ± SD]	15.37 ± 2.23	15.45 ± 2.77
Sex female [%]	55.6%	59.1%
Race [%]		
White	44.4%	50.0%
Black	35.2%	36.4%
Asian	3.7%	0.0%
More than one race/other	16.7%	13.6%
Ethnicity [%]		
Hispanic	46.3%	27.3%
Non-Hispanic	53.7%	72.7%
Body mass index [Mean ± SD]	26.16 ± 7.68	23.12 ± 5.47
Clinical measures [Mean ± SD]		
BDI	14.27 ± 11.41	1.18 ± 1.74***
SHAPS	24.22 ± 6.06	17.10 ± 3.63***
MASC	41.90 ± 19.34	24.05 ± 10.98***
BSS	2.51 ± 4.66	0.00 ± 0.00***
MFS	31.91 ± 13.13	13.63 ± 9.63***
DSM-IV lifetime diagnoses [%] [a,b]		
Depressive disorder [c]	59.3%	
Bipolar spectrum disorder [d]	7.4%	
Anxiety disorder [e]	51.9%	
Attention deficit hyperactivity disorder	42.6%	
Behavioural disorder [f]	20.4%	
Other disorder [g]	9.3%	
Number of lifetime diagnoses [%]		
One	31.5%	
Two	33.3%	
Three or more	35.2%	

BDI = Beck Depression Inventory; SHAPS = Snaith-Hamilton Pleasure Scale; MASC = Multidimensional Anxiety Scale for Children; BSS = Beck Scale for Suicidal Ideation; MFS = PedsQL™ Multidimensional Fatigue Scale.

[a] includes subthreshold presentations;

[b] some participants have more than one disorder;

[c] major depressive disorder (*n* = 28), dysthymic disorder (*n* = 5), depressive disorder not otherwise specified (NOS; *n* = 3);

[d] bipolar II disorder (*n* = 1), bipolar disorder NOS (*n* = 2), mood disorder NOS (*n* = 1);

[e] social anxiety disorder (n = 11), generalised anxiety disorder (n = 13), panic disorder (n = 1), separation anxiety disorder (n = 2), specific phobia (n = 3), obsessive-compulsive disorder (n = 2), posttraumatic stress disorder (n = 6), anxiety disorder NOS (n = 1);

[f] oppositional defiant disorder (n = 5), behavioural disorder NOS (n = 1);

[g] eating disorder NOS (n = 1), adjustment disorder (n = 1), enuresis (n = 1), Tourette's disorder (n = 1).

*** Significant group differences at $p < .001$

Table 2.

Significant relationships[a] between inflammatory cytokines following LPS stimulation and clinical measures within the psychiatric group

	SHAPS[b]	
Cytokine	**Correlation (ρ)**	**p-value**
FGF-2	.421	.004
Flt3-L	.513	.000
Fractalkine	.572	.000
G-CSF	.570	.000
GM-CSF	.488	.001
IL-1α	.436	.002
IL-2	.349	.018
IL-3	.387	.008
IL-4	.379	.009
IL-7	.479	.001
IL-9	.419	.004
IL-10	.334	.023
IL-12p40	.372	.011
IL-12p70	.542	.000
IL-15	.548	.000
IL-17α	.370	.011
MCP-3	.350	.017
TNF-β	.371	.011
VEGF	.506	.000

SHAPS = Snaith-Hamilton Pleasure Scale; FGF = fibroblast growth factor; Flt3-L = fms-like tyrosine kinase-3 ligand; G-CSF = granulocyte colony-stimulating factor; GM-CSF = granulocyte-macrophage colony-stimulating factor; IL = interleukin; MCP = monocyte chemotactic protein; TNF = tumour necrosis factor; VEGF = vascular endothelial growth factor.

[a] at the FDR correction threshold;

[b] controlling for BDI with anhedonia item removed, body mass index, age, and sex.