Published in final edited form as:

J Affect Disord. 2009 May ; 115(1-2): 177–182. doi:10.1016/j.jad.2008.07.022.

Immune system dysregulation in adolescent major depressive disorder

Vilma Gabbay^{a,*}, Rachel G. Klein^a, Carmen M. Alonso^a, James S. Babb^b, Melissa Nishawala^a, Georgette De Jesus^a, Glenn S. Hirsch^a, Pauline M.Z. Hottinger-Blanc^a, and Charles J. Gonzalez^c

^aNew York University School of Medicine, NYU Child Study Center, United States

^bNew York University School of Medicine, Department of Radiology, Research, United States

^cNew York State Department of Health, AIDS Institute, United States

Abstract

Background—A large body of evidence suggests that immune system dysregulation is associated with Major Depressive Disorder (MDD) in adults. This study extends this work to adolescent MDD to examine the hypotheses of immune system dysregulation in adolescents with MDD, as manifested by significantly: (i) elevated plasma levels of cytokines (interferon [IFN]- γ , tumor necrosis factor- α , interleukin [IL]-6, IL-1 β , and IL-4); and (ii) Th1/Th2 cytokine imbalance shifted toward Th1 as indexed by increased IFN- γ /IL-4.

Method—Thirty adolescents with MDD (19 females; 13 medication-free/naïve; ages 12–19) of at least 6 weeks duration and a minimum severity score of 40 on the Children's Depression Rating Scale—Revised, and 15 healthy comparisons (8 females), group-matched for age, were enrolled. Plasma cytokines were examined using enzyme-linked immunosorbent assay. Mann–Whitney test was used to compare subjects with MDD and controls.

Results—Adolescents with MDD had significantly elevated plasma IFN- γ levels (3.38 ± 11.8 pg/ml versus 0.37 ± 0.64 pg/ml; $p < 0.003$), and IFN- γ /IL-4 ratio (16.6 ± 56.5 versus 1.76 ± 2.28 ; $p = 0.007$). A trend for IL-6 to be elevated in the MDD group was also observed (1.52 ± 2.88 pg/ml versus 0.49 ± 0.90 pg/ml; $p = 0.09$). Importantly, findings remained evident when medicated subjects were excluded.

Conclusions—Findings suggest that immune system dysregulation may be associated with adolescent MDD, with an imbalance of Th1/Th2 shifted toward Th1, as documented in adult MDD. Larger studies with medication-free adolescents should follow.

Keywords

Major depressive disorder; Adolescent depression; Cytokines; Interferon- γ ; Interleukin-6; Th1/Th2

© 2008 Elsevier B.V. All rights reserved.

*Corresponding author. Department of Child and Adolescent Psychiatry, New York University School of Medicine, 577 First Avenue, New York, NY 10016, United States. Tel.: +1 212 263 2731; fax: +1 212 263 8662. vilma.gabbay@nyumc.org (V. Gabbay).

Conflict of interest

Drs. Vilma Gabbay, Rachel G. Klein, Carmen M. Alonso, James S. Babb, Melissa Nishawala, Georgette De Jesus, Glenn S. Hirsch, Pauline M.Z. Hottinger-Blanc, and Charles J. Gonzalez report no conflicts of interest.

1. Introduction

Adolescent major depressive disorder (MDD) is a major public health concern. It is associated with severe consequences, including academic and social impairment, increased risk for substance use, and most critically suicide, the third leading cause of death in adolescence (Birmaher et al., 1996). Furthermore, adolescent MDD is a strong predictor of MDD in adulthood, which carries its own burden of disadvantage (Weissman et al., 1999). Findings highlight the need for specific biological research in adolescent MDD. However, to date, such research has been scarce.

Accumulating evidence suggests that MDD in adults is associated with immune system dysregulation (Irwin and Miller, 2007). Cytokines, signaling molecules that mediate key steps in cellular and humoral immunity, have been increasingly implicated in adult MDD (Irwin and Miller, 2007). Cytokines are divided into two broad subsets: T-helper (Th)1 cytokines induce cellular mediated immunity and include interleukin (IL)-12, and interferon (IFN)- γ , and Th2 cytokines promote humoral immunity and include IL-4 and IL-10. Cytokines are also characterized as pro-inflammatory (e.g. IFN- γ) or anti-inflammatory (e.g. IL-4). Multiple studies have reported increased levels of cytokines, including IFN- γ , tumor necrosis factor (TNF)- α , IL-6, IL-1 β , and IL-12 in adult MDD (Irwin and Miller, 2007; Pavon et al., 2006; Simon et al., 2008), suggesting a generalized inflammatory state in adult MDD. Several studies documented an imbalance between Th1 and Th2, or pro-inflammatory and anti-inflammatory cytokines, as manifested by increased Th1/Th2 ratio (e.g. IFN- γ /IL-4, IFN- γ /IL-10), (Irwin and Miller, 2007; Kim et al., 2007; Myint et al., 2005). Clinically, a high proportion of patients treated with IFN- α or IL-2 develop depressive symptoms (Bonaccorso et al., 2002; Van Gool et al., 2003) that may be amenable to treatment with antidepressants (Musselman et al., 2001).

Different mechanisms are speculated to link systemic cytokines to MDD, including effects on central monoamines, activation of the hypothalamic-pituitary-adrenal (HPA) axis, up-regulation of the serotonin transporter gene, and increased tryptophan metabolism—all pathways relevant to MDD (Yirmiya et al., 2000). Further, peripheral cytokines can cross the blood-brain barrier and influence complex brain functions (Pollmacher et al., 2002).

Studies of the immune system in adolescent MDD remain sparse. Studies of natural killer (NK) cell activity in adolescent MDD have yielded contradictory findings (Bartlett et al., 1995; Birmaher et al., 1994; Schleifer et al., 2002; Shain et al., 1991). Only one study of cytokines in pediatric MDD has been reported, detecting no differences in IL-1 β and TNF- α plasma levels in a group of children and adolescents with MDD compared to healthy controls (Brambilla et al., 2004). To date, no study has examined cytokines in a homogenous group of adolescents with MDD. Investigating biological markers early in the course of the disease provides the advantage of minimizing the confounding effects of chronicity. Our aims were to test the hypotheses that compared to non-ill controls, medically healthy adolescents with MDD would have significantly: (i) elevated plasma levels of IFN- γ , TNF- α , IL-6, IL-1 β , and IL-4; and (ii) Th1/Th2 cytokine imbalance shifted toward Th1 as indexed by IFN- γ /IL-4 ratio. Relationships between clinical features of MDD and the above measures were also examined.

2. Materials and methods

2.1. Subjects

The MDD sample consisted of thirty adolescents (nineteen females), thirteen of whom were psychotropic-free (ten medication-naïve), ages 12–19, who met DSM-IV criteria for MDD, with a minimum duration of 6 weeks and of at least moderate severity, defined as a score of ≥ 40 on the Children's Depression Rating Scale—Revised (CDRS-R). They were recruited

from the New York University (NYU) Child Study Center, the Department of Psychiatry at Bellevue Hospital, and the inpatient psychiatric unit at NYU Tisch Hospital. Fifteen healthy comparison subjects (eight females) were recruited from families of NYU staff.

For participants age 18 and over, signed informed consent was obtained; those under age 18 provided assent, and a parent or guardian provided signed consent.

A child psychiatrist interviewed all participants and parents, using the Schedule for Affective Disorders and Schizophrenia—Present and Lifetime Version for Children (Kaufman et al., 1997), a semi-structured psychiatric interview. Based on the interview, the psychiatrist rated severity of depression on the CDRS-R, and overall adjustment on the Children's Global Assessment Scale. Participants completed the Beck Depression Inventory, 2nd edition (BDI-II) and the Beck Scale for Suicidal Ideation (BSS). Baseline medical assessments included medical history and laboratory tests (complete blood count, metabolic panel, liver function, thyroid function tests, and a urine toxicology test and pregnancy test).

Exclusion criteria for all subjects were: immune-affecting medications taken in the past 6 months, any immunological or hematological disorder, chronic fatigue syndrome, any infectious disease in the month prior to enrollment (including common cold), significant medical or neurological disorders, and, in females, a positive urine pregnancy test.

Exclusionary psychiatric disorders for subjects with MDD were: (i) bipolar disorder, (ii) schizophrenia, (iii) pervasive developmental disorder, (iv) post-traumatic stress disorder, (v) obsessive-compulsive disorder, (vi) Tourette's disorder, (vii) eating disorder, and (viii) a substance-related disorder in the past 12 months (based on history and urine toxicology test). Control subjects could not meet criteria for any major current or past DSM-IV diagnosis.

2.2. Cytokine measurements

Blood samples (10 ml) were drawn between 08:00 and 09:00 AM after an overnight fast; the EDTA blood was processed within 20 min of collection. Aliquots of the plasma samples were stored at -80°C for appropriate serial immuno-assay analysis.

The quantitative determination of the plasma levels of IFN- γ , TNF- α , IL-6, IL-1 β , and IL-4 were performed in duplicate for each of the serial aliquots by commercial enzyme-linked immunosorbent assays (ELISA) in accordance with the manufacturers' instructions. All thawed samples for the respective cytokines were run simultaneously. The intra-assay variability was less than 10%. The mean of the available duplicate sample values was used. All assays were performed by CG, who was blind to the subjects' clinical status.

2.3. Statistical analysis

As data were not normally distributed, the nonparametric Mann-Whitney test was used to compare subjects with MDD and controls. Spearman rank correlation coefficients were used to characterize the association of cytokine levels with the number of past suicide attempts, CDRS-R, BDI-II, BSS scores, and duration of depressive illness. All reported p-values are exact two-sided significance levels. Statistical significance was defined as $p < 0.05$. SAS version 9.0 (SAS Institute, Cary, NC) was used for all statistical computations.

3. Results

3.1. Participants

Ten (10/30, 33%) MDD patients were medication-naïve, three (3/30, 10%) had been psychotropic-free for at least one year, and seventeen (17/30, 57%) were on medication and

had been treated for periods ranging from one month to two-and-a-half years. All patients on medications had failed to respond to their treatment regimen at the time of their blood draw. Many of the medicated patients were taking multiple medications, including selective serotonin reuptake inhibitors (ten on fluoxetine, three on sertraline, and one on citalopram), atypical antidepressants (one on bupropion), mood stabilizers (three patients each on lamotrigine and lithium), and atypical antipsychotics (two on risperidone). Demographics, diagnoses, and treatment profiles are compiled in Table 1.

3.2. Cytokines findings

Means and standard deviations of plasma cytokine levels are summarized in Table 2.

3.2.1. MDD adolescents versus controls—As hypothesized, adolescents with MDD had significantly higher levels of plasma IFN- γ compared to healthy controls (3.38 ± 11.8 pg/ml versus 0.37 ± 0.64 pg/ml, rank static = 219.5; $p < 0.003$, Bonferroni corrected $p < 0.02$). There was also a trend for IL-6 to be elevated in the MDD group compared to the control group (1.52 ± 2.88 pg/ml versus 0.49 ± 0.90 pg/ml, rank static = 274.0; $p = 0.09$). Other cytokines did not differ between the two groups (Table 2).

Our second hypothesis was also supported, suggesting a Th1/Th2 cytokine imbalance shifted toward Th1, as we found increased IFN- γ /IL-4 ratio in adolescents with MDD compared to controls (16.6 ± 56.5 versus 1.76 ± 2.28 , rank static = 235.0; $p = 0.007$, Bonferroni corrected $p < 0.05$).

3.2.2. Medication-free MDD adolescents versus controls—Since psychotropic treatment may affect cytokines, we compared cytokine levels between the thirteen non-medicated adolescents with MDD (free and naïve) and controls. IFN- γ was still significantly increased in the unmedicated MDD group compared to the control group (5.66 ± 17.0 pg/ml versus 0.37 ± 0.64 pg/ml; rank static = 240.0; $p < 0.02$). In spite of the small sample size, there was still a trend for IL-6 to be elevated in the unmedicated adolescent MDD group compared to the controls (1.72 ± 3.63 pg/ml versus 0.49 ± 0.90 pg/ml, rank static = 227.0; $p = 0.07$). Other cytokines did not differ between the groups (Table 2).

With respect to our second hypothesis, IFN- γ /IL-4 was also significantly elevated in the unmedicated MDD group compared to the control group (24.9 ± 78.0 versus 1.76 ± 2.28 , rank static = 233.0; $p < 0.04$).

3.3. Correlations of MDD features and cytokine plasma levels

No significant correlations were found between MDD features and cytokine plasma levels.

4. Discussion

This is the first study that examines cytokines in adolescent MDD. Findings support our hypothesis that immune system dysregulation may accompany MDD in adolescence as has been documented in adult MDD. The major finding is of significantly increased plasma levels of IFN- γ and IFN- γ /IL-4 ratio in adolescents with MDD compared to controls. Importantly, these findings remained significant when medicated patients were excluded. We also found a trend for increased IL-6 in adolescents with MDD compared to controls. However, our hypotheses that other cytokines would also be elevated were not substantiated.

Our finding of increased plasma IFN- γ in adolescent MDD is consistent with some (Maes et al., 1994; Myint et al., 2005; Seidel et al., 1995; Simon et al., 2008), but not all (Kim et al., 2007) studies in adult MDD. Discrepancies among adult studies may be due to differences in

subtypes of depression, severity, medication status, sample sizes, and immunological assays. Tsao et al. (2006) recently reported a study of messenger RNA expression of several cytokines and found increased expression of IFN- γ , as well as of IL-6, IL-1 β , and TNF- α in adults with MDD. Additional evidence linking IFN- γ to MDD is derived from reports that antidepressants have a common, negative immuno-regulatory effect, suppressing IFN- γ , IFN- γ /IL-10 production ratio, and IFN- γ gene expression (Kubera et al., 2001; Maes et al., 1999; Tsao et al., 2006). One possible link between IFN- γ and MDD is the enzyme indoleamine 2,3-dioxygenase (IDO), which is the rate-limiting enzyme in the tryptophan-kynurenine pathway that converts tryptophan (TRP) to kynurenine (KYN), and is mainly induced by IFN- γ (Fujigaki et al., 2001). In cases of over-stimulation, induction of this pathway may lead to lower TRP concentrations (serotonin substrate), which have been implicated in MDD (Wirleitner et al., 2003). KYN itself is further metabolized to quinolinic acid or kynurenic acid, a potent *N*-methyl-D-aspartate (NMDA) receptor agonist and antagonist, respectively (Stone and Darlington, 2002). Another possible link between IFN- γ and MDD is the serotonin transporter (5-HTT), which removes serotonin from the synaptic cleft, and thus determines the magnitude and duration of serotonergic responses. An in-vitro study documented that IFN- α and IFN- γ increase the gene expression of the 5-HTT (Morikawa et al., 1998), suggesting another pathway linking IFN- γ to MDD.

Our second finding of increased IFN- γ /IL-4 in adolescents with MDD compared to controls is also in agreement with several adult MDD studies (but not all (Pavon et al., 2006)) and further supports the notion of immune system dysregulation in adolescent MDD with a Th1/Th2 cytokine imbalance shifted to Th1 (Huang and Lee, 2007; Irwin and Miller, 2007; Kim et al., 2007; Myint et al., 2005). Relatedly, one of the therapeutic properties contributing to the efficacy of antidepressants could be the suppression of Th1/Th2 ratios (e.g. IFN- γ /IL-10) (Kubera et al., 2001; Maes et al., 1999).

While not significant, we did detect a trend toward increased IL-6 plasma levels in adolescents with MDD compared to controls. Multiple studies in adult MDD found IL-6 to be increased (Frommberger et al., 1997; Maes et al., 1997; Maes and Meltzer, 1995; Sluzewska et al., 1995; Song et al., 1998). Of relevance to MDD, animal studies document that peripheral administration of IL-6 affects central monoamines (Connor and Leonard, 1998). Additionally, IL-6 is known to stimulate the HPA axis and play a key role in the stress response (Dentino et al., 1999), pathways hypothesized to be relevant to MDD.

Our finding of immune system dysregulation in adolescent MDD may also represent unrecognized risk factors for other medical illnesses that are not simply the direct consequence of the underlying mood disorder (Kapczinski et al., 2008; Kupfer, 2005). Indeed, adolescent MDD was shown to increase the risk of obesity (Goodman and Whitaker, 2002). As such, our findings further emphasize the need for early identification and treatment of youth with mood disorders.

Our findings should be considered preliminary in light of several limiting factors: First, the cohort size was relatively modest. Further, many patients (57%) were treated with psychotropics, which have been reported to have negative immuno-regulatory effects in adults with MDD. This possible confound may have limited our ability to discern other group differences of cytokines and contributed to a type II error.

In summary, our findings support the notion that adolescent MDD may entail immune system dysregulation as documented in adult MDD. Our findings suggest a possible role of IFN- γ , IL-6, and a Th1/Th2 imbalance in adolescent MDD. These findings should be replicated in a larger sample of medication-free adolescents, with additional focus on other immunological

markers, including T cell subtypes, natural killer, and the utilization of molecular biology techniques.

Acknowledgments

This study was supported by grants from NIH (AT002395, MH077072), the American Foundation for Suicide Prevention, the NYU School of Medicine General Clinical Research Center grant (M01-RR00096), and generous gifts from the Anita Saltz Foundation, and from Bruce and Claude Wasserstein. The authors thank Dr. F. Xavier Castellanos for his helpful comments on this manuscript.

Role of funding source

This study was supported by grants from NIH (AT002395, MH077072), the American Foundation for Suicide Prevention, the NYU School of Medicine General Clinical Research Center grant (M01-RR00096), and generous gifts from the Anita Saltz Foundation, and from Bruce and Claude Wasserstein. These sources of funding had no further role in the study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

References

- Bartlett JA, Schleifer SJ, Demetrikopoulos MK, Keller SE. Immune differences in children with and without depression. *Biol. Psychiatry* 1995;38:771–774. [PubMed: 8580234]
- Birmaher B, Rabin BS, Garcia MR, Jain U, Whiteside TL, Williamson DE, al Shabbout M, Nelson BC, Dahl RE, Ryan ND. Cellular immunity in depressed, conduct disorder, and normal adolescents: role of adverse life events. *J. Am. Acad. Child Adolesc. Psych* 1994;33:671–678.
- Birmaher B, Ryan ND, Williamson DE, Brent DA, Kaufman J. Childhood and adolescent depression: a review of the past 10 years. Part II. *J. Am. Acad. Child Adolesc. Psych* 1996;35:1575–1583.
- Bonaccorso S, Marino V, Biondi M, Grimaldi F, Ippoliti F, Maes M. Depression induced by treatment with interferon-alpha in patients affected by hepatitis C virus. *J. Affect. Disord* 2002;72:237–241. [PubMed: 12450640]
- Brambilla F, Monteleone P, Maj M. Interleukin-1beta and tumor necrosis factor-alpha in children with major depressive disorder or dysthymia. *J. Affect. Disord* 2004;78:273–277. [PubMed: 15013254]
- Connor TJ, Leonard BE. Depression, stress and immunological activation: the role of cytokines in depressive disorders. *Life Sci* 1998;62:583–606. [PubMed: 9472719]
- Dentino AN, Pieper CF, Rao MK, Currie MS, Harris T, Blazer DG, Cohen HJ. Association of interleukin-6 and other biologic variables with depression in older people living in the community. *J. Am. Geriatr. Soc* 1999;47:6–11. [PubMed: 9920223]
- Frommberger UH, Bauer J, Haselbauer P, Fraulin A, Riemann D, Berger M. Interleukin-6-(IL-6) plasma levels in depression and schizophrenia: comparison between the acute state and after remission. *Eur. Arch. Psychiatry Clin. Neurosci* 1997;247:228–233. [PubMed: 9332905]
- Fujigaki S, Saito K, Sekikawa K, Tone S, Takikawa O, Fujii H, Wada H, Noma A, Seishima M. Lipopolysaccharide induction of indoleamine 2,3-dioxygenase is mediated dominantly by an IFN-gamma-independent mechanism. *Eur. J. Immunol* 2001;31:2313–2318. [PubMed: 11477543]
- Goodman E, Whitaker RC. A prospective study of the role of depression in the development and persistence of adolescent obesity. *Pediatrics* 2002;110:497–504. [PubMed: 12205250]
- Huang TL, Lee CT. T-helper 1/T-helper 2 cytokine imbalance and clinical phenotypes of acute-phase major depression. *Psychiatry Clin. Neurosci* 2007;61:415–420. [PubMed: 17610667]
- Irwin MR, Miller AH. Depressive disorders and immunity: 20 years of progress and discovery. *Brain Behav. Immun* 2007;21:374–383. [PubMed: 17360153]
- Kapczynski F, Vieta E, Andreazza AC, Frey BN, Gomes FA, Tramontina J, Kauer-Sant’anna M, Grassi-Oliveira R, Post RM. Allostatic load in bipolar disorder: implications for pathophysiology and treatment. *Neurosci. Biobehav. Rev* 2008;32:675–692. [PubMed: 18199480]
- Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, Williamson D, Ryan N. 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. Psych* 1997;36:980–988.

- Kim YK, Na KS, Shin KH, Jung HY, Choi SH, Kim JB. Cytokine imbalance in the pathophysiology of major depressive disorder. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* 2007;31:1044–1053.
- Kubera M, Lin AH, Kenis G, Bosmans E, van Bockstaele D, Maes M. Anti-Inflammatory effects of antidepressants through suppression of the interferon-gamma/interleukin-10 production ratio. *J. Clin. Psychopharmacol* 2001;21:199–206. [PubMed: 11270917]
- Kupfer DJ. The increasing medical burden in bipolar disorder. *Jama* 2005;293:2528–2530. [PubMed: 15914754]
- Maes M, Meltzer H. The serotonin hypothesis of major depression. In: Bloom, F.; Kupfer, D., editors. *Psychopharmacology: The Fourth Generation of Progress*. New York: Raven Press; 1995. p. 933–944.
- Maes M, Scharpe S, Meltzer HY, Okayli G, Bosmans E, D'Hondt P, Vanden Bossche BV, Cosyns P. Increased neopterin and interferon-gamma secretion and lower availability of l-tryptophan in major depression: further evidence for an immune response. *Psychiatry Res* 1994;54:143–160. [PubMed: 7761549]
- Maes M, Bosmans E, De Jongh R, Kenis G, Vandoolaeghe E, Neels H. Increased serum IL-6 and IL-1 receptor antagonist concentrations in major depression and treatment resistant depression. *Cytokine* 1997;9:853–858. [PubMed: 9367546]
- Maes M, Song C, Lin AH, Bonaccorso S, Kenis G, De Jongh R, Bosmans E, Scharpe S. Negative immunoregulatory effects of antidepressants: inhibition of interferon-gamma and stimulation of interleukin-10 secretion. *Neuropsychopharmacology* 1999;20:370–379. [PubMed: 10088138]
- Morikawa O, Sakai N, Obara H, Saito N. Effects of interferon-alpha, interferon-gamma and cAMP on the transcriptional regulation of the serotonin transporter. *Eur. J. Pharmacol* 1998;349:317–324. [PubMed: 9671113]
- Musselman DL, Lawson DH, Gumnick JF, Manatunga AK, Penna S, Goodkin RS, Greiner K, Nemeroff CB, Miller AH. Paroxetine for the prevention of depression induced by high-dose interferon alfa. *N. Engl. J. Med* 2001;344:961–966. [PubMed: 11274622]
- Myint AM, Leonard BE, Steinbusch HW, Kim YK. Th1, Th2, and Th3 cytokine alterations in major depression. *J. Affect. Disord* 2005;88:167–173. [PubMed: 16126278]
- Pavon L, Sandoval-Lopez G, Eugenia Hernandez M, Loria F, Estrada I, Perez M, Moreno J, Avila U, Leff P, Anton B, Heinze G. Th2 cytokine response in Major Depressive Disorder patients before treatment. *J. Neuroimmunol* 2006;172:156–165. [PubMed: 16457895]
- Pollmacher T, Haack M, Schuld A, Reichenberg A, Yirmiya R. Low levels of circulating inflammatory cytokines—do they affect human brain functions? *Brain Behav. Immun* 2002;16:525–532. [PubMed: 12401466]
- Schleifer SJ, Bartlett JA, Keller SE, Eckholdt HM, Shiflett SC, Delaney BR. Immunity in adolescents with major depression. *J. Am. Acad. Child Adolesc. Psych* 2002;41:1054–1060.
- Seidel A, Arolt V, Hunstiger M, Rink L, Behnisch A, Kirchner H. Cytokine production and serum proteins in depression. *Scand. J. Immunol* 1995;41:534–538. [PubMed: 7539545]
- Shain BN, Kronfol Z, Naylor M, Goel K, Evans T, Schaefer S. Natural killer cell activity in adolescents with major depression. *Biol. Psychiatry* 1991;29:481–484. [PubMed: 2018821]
- Simon NM, McNamara K, Chow CW, Maser RS, Papakostas GI, Pollack MH, Nierenberg AA, Fava M, Wong KK. A detailed examination of cytokine abnormalities in Major Depressive Disorder. *Eur. Neuropsychopharmacol* 2008;18:230–233. [PubMed: 17681762]
- Sluzewska A, Rybakowski JK, Laciak M, Mackiewicz A, Sobieska M, Wiktorowicz K. Interleukin-6 serum levels in depressed patients before and after treatment with fluoxetine. *Ann. N. Y. Acad. Sci* 1995;762:474–476. [PubMed: 7668562]
- Song C, Lin A, Bonaccorso S, Heide C, Verkerk R, Kenis G, Bosmans E, Scharpe S, Whelan A, Cosyns P, De Jongh R, Maes M. The inflammatory response system and the availability of plasma tryptophan in patients with primary sleep disorders and major depression. *J. Affect. Disord* 1998;49:211–219. [PubMed: 9629951]
- Stone TW, Darlington LG. Endogenous kynurenes as targets for drug discovery and development. *Nat. Rev. Drug Discov* 2002;1:609–620. [PubMed: 12402501]
- Tsao CW, Lin YS, Chen CC, Bai CH, Wu SR. Cytokines and serotonin transporter in patients with major depression. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* 2006;30:899–905.

- Van Gool AR, Fekkes D, Kruit WH, Mulder PG, Ten Hagen TL, Bannink M, Maes M, Eggermont AM. Serum amino acids, biopterin and neopterin during long-term immunotherapy with interferon-alpha in high-risk melanoma patients. *Psychiatry Res* 2003;119:125–132. [PubMed: 12860366]
- Weissman MM, Wolk S, Goldstein RB, Moreau D, Adams P, Greenwald S, Klier CM, Ryan ND, Dahl RE, Wickramaratne P. Depressed adolescents grown up. *J. Am. Med. Assoc* 1999;281:1707–1713.
- Wirleitner B, Neutrauer G, Schrocksnadel K, Frick B, Fuchs D. Interferon-gamma-induced conversion of tryptophan: immunologic and neuropsychiatric aspects. *Curr. Med. Chem* 2003;10:1581–1591. [PubMed: 12871129]
- Yirmiya R, Pollak Y, Morag M, Reichenberg A, Barak O, Avitsur R, Shavit Y, Ovadia H, Weidenfeld J, Morag A, Newman ME, Pollmacher T. Illness, cytokines, and depression. *Ann. N. Y. Acad. Sci* 2000;917:478–487. [PubMed: 11268375]

Table 1

Demographic and clinical characteristics of adolescents with major depressive disorder (MDD) and healthy control subjects.

Characteristic	MDD subjects <i>n</i> = 30	Controls <i>n</i> = 15
Age (years)	16.3 ± 2.0	15.6 ± 3.0
Gender (male/female)	11/19 ^a (37/63%)	7/8 ^a (47/53%)
<i>Illness history</i>		
Duration of illness (months)	18.7 ± 16.5 ^b (1.5–84)	0
Number of suicide attempts	1.0 ± 1.0 ^b (0–3)	0
Medication-naïve/medication-free/medicated	10/3/17 ^a (33/10/57%)	15/0/0 ^a (100/0/0%)
CDRS-R ^c	61.8 ± 15.9 ^b (40–97)	17.9 ± 1.7 ^b (17–23)
BDI-II ^d	25.0 ± 12.6 ^b (4–53)	2.5 ± 3.2 ^b (0–11)
BSS ^e	10.8 ± 9.9 ^b (0–33)	0.1 ± 0.4 ^b (0–1)
<i>Current comorbidity</i>		
ADHD ^f	4 ^a (13%)	0
ODD ^g	2 ^a (7%)	0
Any anxiety disorder	11 ^a (37%)	0
Any comorbidity	16 ^a (53%)	0

^aRespective percentages (may not add up to 100% due to rounding).

^bRange.

^cChildren's Depression Rating Scale—Revised.

^dBeck Depression Inventory-II.

^eBeck Scale for Suicidal Ideation.

^fAttention Deficit Hyperactivity Disorder.

^gOppositional Defiant Disorder.

Table 2

Mean (SD) levels of plasma cytokines in controls and MDD subjects.

Cytokine measure	Controls (n=15)	MDD subjects	
		All patients (n = 30)	Non-medicated (n = 13)
Interferon (IFN)- γ	0.37 (0.64)	3.38 (11.8) **	5.66 (17.0) *
Tumor necrosis factor (TNF)- α /TNFSF1A	4.13 (13.4)	19.1 (86.2)	7.06 (20.2)
Interleukin (IL)-6	0.49 (0.90)	1.52 (2.88)	1.72 (3.63)
IL-1 β	0.16 (0.05)	0.16 (0.08)	0.13 (0.05)
IL-4	0.28 (0.35)	0.21 (0.09)	0.24 (0.11)
IFN- γ /IL-4	1.76 (2.28)	16.6 (56.5) **	24.9 (78.0) *

*
 $p < 0.05$.**
 $p < 0.05$, Bonferroni corrected.