BIOGRAPHICAL SKETCH

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NAME: Andrew H. Miller, M.D.

POSITION TITLE: William P. Timmie Professor of Psychiatry and Behavioral Sciences

eRA COMMONS USER NAME (credential, e.g., agency login): amill02

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Hamilton College, Clinton, NY	BA	05/1977	Psychology
Medical College of Georgia, Augusta, GA	MD	07/1981	Medicine
Montefiore Medical Center, Bronx, NY		07/1982	Internship

A. Personal Statement

Our laboratory has published on the impact of inflammation on the brain in both medically healthy and medically ill individuals including patients with cancer. We have made multiple contributions to the understanding of the basic mechanisms involved in brain-immune interactions as well as translational contributions to novel treatments relative to the effects of inflammation on the brain. I have also had the opportunity to contribute to the education of young researchers, having served as the primary mentor for 8 NIH K awardees. In addition, I served as the PI on an NIH T32 postdoctoral training grant for 10 years and received an NIH R13 award for a mentoring program. I have also won 6 educational and mentorship awards including the 2017 Winship Faculty Mentor Award. Finally, I am currently PI on an NIH R25 Research Residency Training Program.

B. Positions and Honors

Professional Positions:

1981-1985 Psychiatric Resident, Department of Psychiatry, Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY
1985-1987 Research Fellow, Biological Psychiatry and Psychopharmacology, Department of Psychiatry, Albert Einstein College of Medicine, Bronx, NY
1986-1988 Assistant Professor, Department of Psychiatry, Albert Einstein College of Medicine, Bronx, NY
1988-1994 Assistant Professor, Department of Psychiatry, Mount Sinai School of Medicine, New York, NY
1994 Associate Professor, Department of Psychiatry, Mount Sinai School of Medicine, NY
1994-2000 Associate Professor, Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA
1994-2015 Director, Laboratory of Neuroendocrine-Immune Interactions, Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA
2000- Professor, Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA
2003- Director, Psychiatric Oncology, Winship Cancer Institute, Emory University, Atlanta, GA
2006- co-Leader, Cancer Prevention and Control Program, Winship Cancer Institute, Emory University, Atlanta, GA
2014-2016 Director, Division of Adult Outpatient Psychiatry, Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, Georgia
2015- Director, Emory Behavioral Immunology Program, Emory University, Atlanta, GA
2016- Vice Chair, Research, Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA

Selected Awards:

1989-2009	Recipient, Research Scientist Development Award, NIMH
1992-1996	Member, Initial Review Group, Mental Health Aspects of AIDS, NIMH
1996	Curt P. Richter Award, International Society of Psychoneuroendocrinology
1997	NARSAD Independent Investigator Award
1997-1998	Member, AIDS Biomedical and Clinical Research Subcommittee, National Institute of Drug Abuse
1997&2000	Outstanding Educator Award, Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, Georgia
2001-2004	Dean's Clinical Investigator Award, Emory University School of Medicine, Atlanta, Georgia
2006-	William P. Timmie Professor of Psychiatry and Behavioral Sciences
2006-2013	Associate (now Deputy) Editor of *Neuropsychopharmacology*
2008	Norman Cousin's Award for Research Distinction in Psychoneuroimmunology, Psychoneuroimmunology Research Society
2008-2009	President, Psychoneuroimmunology Research Society
2011-	Fellow, American College of Neuropsychopharmacology
2013-	Associate Editor, *Brain Behavior and Immunity*
2013-	Member, Interventions Committee for Adult Disorders, National Institute of Mental Health
2013	Faculty Mentor Award, Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, Georgia
2016-	Top Doctor (Psychiatry), Castle, Connolly Medical Ltd.
2016-	Field Editor, *Cancer*, journal of the American Cancer Society
2017	Faculty Mentor Award, Winship Cancer Institute
2018	Albert E. Levy Scientific Research Award, Emory University School of Medicine, Atlanta, GA

C. Contribution to Science

1) Conducted the first studies demonstrating that pretreatment with antidepressants could block the development of depression during cytokine therapy for cancer and hepatitis C.

Anecdotal reports indicated that cancer patients administered the inflammatory cytokine interferon (IFN)-alpha experienced significant depressed mood that often led to discontinuation of treatment and in some cases suicide. Based on laboratory animal studies that pretreatment with antidepressants could reduce depressive-like behavior following immune stimulation, we conducted randomized clinical trials of pretreatment with the selective serotonin reuptake inhibitor paroxetine to block the effects of IFN-alpha on behavior in patients with cancer and hepatitis C in separate studies. In both cases, paroxetine blocked the development of depression and reduced treatment discontinuation. Pretreatment with antidepressants in patients receiving IFN-alpha has now become standard practice in many hospitals and clinics.

1. Musselman, D.L., Lawson, D., Penna, S., Von Hohenleiten, C., Griener, K., Nemeroff, C.B., Miller, A.H. Paroxetine prevents depression and neurotoxicity induced by high dose interferon-alpha therapy. *N Engl J Med*, 344:961-966, 2001.
2. Capuron, L., Gumnick, J.F., Musselman, D.L., Lawson, D.H., Reemsnyder, A., Nemeroff, C.B., Miller, A.H. Neurobehavioral effects of interferon-alpha: phenomenology and antidepressant responsiveness of symptom dimensions. *Neuropsychopharmacology*, 26:643-652, 2002.
3. Raison, C.L., Capuron, C., Miller, A.H. Cytokines sing the blues: inflammation and the pathogenesis of depression. *Trends in Immunol*, 227:24-31, 2006. PMC3392963
4. Raison, C.L., Woolwine, B.J., Demetrashvili, M.F., Borisov, A.F., Weinreib, R., Staab, J.P., Zajecka, J.M., Bruno, C.J., Henderson, M.A., Reinus, J.F., Evans, D.L., Asnis, G.M., Miller, A.H. Paroxetine for prevention of depressive symptoms induced by interferon-alpha plus ribavirin for hepatitis C. *Alimentary Pharmacology and Therapeutics*, 25(10):1163-1174, 2007.

2) Identified cytokine targets in the brain including cytokine effects on dopamine and reward circuitry in the basal ganglia leading to anhedonia.

To determine the mechanisms by which inflammation affects the brain to change behavior, we studied patients undergoing treatment with IFN-alpha using a variety of neuroimaging strategies including positron emission

tomography and functional magnetic resonance imaging. Our data demonstrated that the basal ganglia are a primary target of cytokine effects on the brain, specifically through effects on dopamine-rich reward pathways. Human and non-human primate studies demonstrated that these effects of IFN-alpha on reward processing, motivation and ultimately anhedonia appear to be mediated by cytokine-induced inhibition of the synthesis and release of dopamine. We have recently extended these finding to patients with depression, demonstrating an association of increased inflammation as measured by c-reactive protein with decreased connectivity between the ventral striatum and the ventromedial prefrontal cortex which mediated the effects of inflammation on motivation (anhedonia).

5. Capuron L, Pagnoni G, Drake DF, Woolwine BJ, Spivey JR, Crowe RJ, Votaw JR, Goodman MM, Miller AH. Dopaminergic mechanisms of reduced basal ganglia responses to hedonic reward during interferon-alpha administration. *Arch Gen Psychiatry*, 69(10): 1044-53, 2012. PMC3640298.
6. Felger JC, Mun J, Kimmel HL, Nye JA, Drake DF, Hernandez CR, Freeman AA, Rye DB, Goodman MM, Howell LL, Miller AH: Chronic interferon-alpha decreases dopamine 2 receptor binding and striatal dopamine release in association with anhedonia-like behavior in non-human primates. *Neuropsychopharmacology*, 38(11): 2179-2187, 2013. PMC3773667
7. Felger, J.C., Hernandez, C.R., Miller, A.H. Levodopa reverses cytokine-induced reductions in striatal dopamine release. *Int J Neuropsychopharm,* 18(4), 2015. PMC4360218
8. Felger, J.C., Li, Z., Haroon, E., Woolwine, B.J., Jung, M.Y., Hu, X., Miller, A.H. Inflammation is associated with decreased functional connectivity within corticostriatal reward circuitry in depression. *Molecular Psychiatry*, 21:1358-1365, 2016. PMC4862934

3) Demonstrated the impact of inflammation on the kynurenine pathway in the peripheral blood and CNS of humans

Data in laboratory animals has demonstrated that activation of the kynurenine (KYN) pathway plays an important role in the development of depressive-like behaviors during immune activation. Our group has contributed to this effort by demonstrating that peripheral activation of the KYN pathway is also involved in symptoms of depression during immune stimulation with IFN-alpha in humans. More importantly, our group was the first to demonstrate that activation of the KYN pathway in the central nervous system is associated with depressive symptoms following immune stimulation in humans. We were also the first group to demonstrate that polymorphisms in the gene for indoleamine 2,3 dioxygenase (which catabolizes tryptophan to KYN) predicts the development of depressive symptoms during immune stimulation with IFN-alpha.

9. Capuron, L., Ravaud, A., Neveu, P.J., Miller, A.H., Maes, M., Dantzer, R. Association between decreased serum tryptophan concentrations and depressive symptoms in cancer patients undergoing cytokine therapy. *Molecular Psychiatry*, 7(5):468-473, 2002.
10. Capuron, L., Neurauter, G., Musselman, D.L., Lawson, D.H., Nemeroff, C.B., Fuchs, D., Miller, A.H. Interferon-Alpha-induced changes in tryptophan metabolism: relationship to depression and paroxetine treatment, *Biol Psychiatry,* 54:906-914, 2003.
11. Raison CL, Dantzer R, Kelley KW, Lawson MA, Woolwine BJ, Vogt G, Spivey JR, Saito K, Miller AH. CSF concentrations of brain tryptophan and kynurenines during immune stimulation with IFN-alpha: relationship to CNS immune responses and depression. *Mol Psychiatry*, 15(4): 393-403, 2010. PMC2844942.
12. Smith, A.K., Simon, J.S., Gustafson, E.L., Noviello, S., Cubells, J.F., Epstein, M.P., Devlin, D.J., Qiu, P., Albrecht, J.K., Brass, C.A., Sulkowski, M.S., McHutchinson, J.G., Miller, A.H. Association of a polymorphism in the indoleamine-2,3-dioxygenase gene and interferon-alpha-induced depression in patients with chronic hepatitis C. *Molecular Psychiatry*, 17(8):781-9, 2011. PMC3181969

4) Conducted the first study using a biologic cytokine antagonist to treat major depression in humans

The notion that cytokines may contribute to the development of major depression has emerged as a theoretical foundation for the use of anti-inflammatory therapies for the treatment of depression. Accordingly, our group was the first to test the relevance of cytokines to depression by using a highly selective and specific biologic antagonist of the inflammatory cytokine tumor necrosis factor (TNF) in patients with treatment resistant depression, a condition often associated with increased inflammation. Our study demonstrated that only

depressed patients with high inflammation responded to anti-TNF therapy. Moreover, gene expression patterns reflective of inhibition of TNF were predictive of treatment response to anti-TNF therapy within 6 hours of the first infusion of the TNF antagonist.

13. Raison CL, Rutherford RE, Woolwine BJ, Chen S, Schettler P, Drake DF, Haroon E, Miller AH. A randomized controlled trial of the tumor necrosis factor antagonist infliximab in treatment resistant depression: role of baseline inflammatory biomarkers. *JAMA Psychiatry*, 70:31-41, 2013. PMC4015348
14. Mehta D, Raison CL, Woolwine BJ, Haroon E, Binder EB, Miller AH, Felger JC. Transcriptional signatures related to glucose and lipid metabolism predict treatment response to the tumor necrosis factor antagonist infliximab in patients with treatment-resistant depression. *Brain Behav Immun*, 31:205-15, 2013. PMC3673885.
15. Weinberger, J.F., Raison, C.L., Rye, D.B., Montague, A.R., Woolwine, B.J., Felger, J.C., Haroon, E., Miller, A.H. Inhibition of tumor necrosis factor improves sleep continuity in patients with treatment resistant depression and high inflammation. *Brain Behav Immun,* 47:193-200, 2014. PMC4468009
16. Miller, A.H., Raison, C.L. Where the rubber meets the road: are anti-inflammatory therapies viable treatments for psychiatric disorders? *JAMA Psychiatry*, 72:527-8, 2015. PMC5542670

5) Demonstrated that cytokine administration increases CNS glutamate using magnetic resonance spectroscopy

Based on data that inflammatory cytokines can block the reuptake and stimulate the release of glutamate as well as activate the KYN pathway and quinolinic acid which can also stimulate glutamate release, we examined whether the inflammatory cytokine IFN-alpha could lead to increased glutamate in specific brain regions using magnetic resonance spectroscopy. IFN-alpha administration was associated with a significant increase in glutamate in the basal ganglia and dorsal anterior cingulate cortex. These data were the first to demonstrate that administration of an inflammatory stimulus could lead to increased glutamate in the brain, suggesting that increased inflammation in disorders like depression may also be associated with increases in glutamate and suggesting that inflammatory biomarkers might identify a subgroup of depressed patients who might be especially appropriate for treatments targeting glutamate.

17. Haroon, E., Raison, C.L., Miller, A.H. Psychoneuroimmunology meets neuropsychopharmacology: translational implications of the impact of inflammation on behavior. Neuropsychopharmacology, 37:137-162, 2012. PMC3238082
18. Miller AH: Conceptual confluence: the kynurenine pathway as a common target for ketamine and the convergence of the inflammation and glutamate hypothesis of depression. *Neuropsychopharmacology*, 38(9): 1607-1608, 2013. PMC371552
19. Haroon E, Woolwine BJ, Chen X, Pace TW, Parekh S, Spivey JR, Hu XP, Miller AH. IFN-alpha-induced cortical and subcortical glutamate changes assessed by magnetic resonance spectroscopy. *Neuropsychopharmacology*. 39(7): 1777-1785, 2014. PMID: 24481242. Epub. PMC4023151
20. Haroon, E., Fleischer, C., Felger, J.C., Chen, X., Woolwine, B.J., Patel, T., Hu, X., Miller, A.H. Conceptual convergence: increased inflammation is associated with increased basal ganglia glutamate in patients with major depression. *Molecular Psychiatry*, 21:1351-1357, 2016. PMC4940313

My Bibliography maintained by the US National Library of Medicine:
http://www.ncbi.nlm.nih.gov/sites/myncbi/andrew.miller.1/bibliograpahy/41139487/public/?sort=date&direction=ascending

D. Research Support

Active

1) R01MH112076 Miller (co-PI) 09/23/16-07/31/21
Inflammation-Induced CNS Glutamate Changes in Depression
This study will use the anti-inflammatory TNF antagonist infliximab as a pharmacologic probe to examine the cause and effect relationship between inflammation and increased CNS glutamate as well as the relationship among inflammation, increased glutamate, anhedonia and psychomotor retardation.

2) R25MH101079 Miller (co-PI) 07/01/14-06/31/19
Emory Psychiatry Clinical Scientist Training Program
The objective of this award is to develop a program of research for psychiatry residents that allows access to research educational activities for all psychiatry residents while also providing specialized research training and mentorship for residents who are interested in a career in research.

3) R21CA178603 Miller (site-PI) 09/01/2014-06/30/2018
Meriva for treatment-induced inflammation and fatigue in women with breast cancer
This study will use a randomized, double-blind clinical trial to determine the impact of curcumin (Meriva) for the inhibition of NF-kB DNA binding, inflammation and fatigue in breast cancer patients who have completed chemotherapy and radiation.

Relevant Completed

1) R21MH105897 Miller (PI) 12/01/14-11/30/17
Inflammation-Induced CNS Glutamate During Breast Cancer Treatment
The objective of this proposal is to examine effects of chemotherapy on CNS glutamate using magnetic resonance spectroscopy in breast cancer patients. Chemotherapy-associated changes in CNS glutamate will in turn be correlated with behavioral alterations including fatigue, depression and cognitive dysfunction.

2) R01 MH083746 Miller (PI) 07/01/09-02/28/14
Dopaminergic Mechanisms of Cytokine-Induced Behavioral Change
Using neuroimaging and in vivo microdialysis, this project will examine the impact of the innate immune cytokine, interferon-alpha, on basal ganglia dopamine function in rhesus monkeys.

3) R01MH087604 Miller (PI) 07/01/10-02/28/16
Phenotyping Major Depression with Increased Inflammation
Using repeated blood sampling, polysomnography, neurocognitive testing and cerebrospinal fluid assessments, this project will examine the relationship between depressed patients with high versus low inflammation in the domains of neuroendocrine function, sleep, neurocognition and neurotransmitter metabolism. The goal is so define relevant endophenotypes of patients with major depression and increased inflammation.

4) R03 MH100273 Miller (PI) 04/01/13-03/31/16
Predictors and Targets of Cytokine Antagonism in Depression
The proposed project will examine the pathophysiologic domains that predict and respond to successful therapy with the TNF-alpha antagonist infliximab in patients with treatment resistant depression. Measures of basal ganglia function, sleep, kynurenine pathway activation and hypothalamic-pituitary axis activity will be explored.