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Labile anger during interferon-alpha treatment is associated with a polymorphism in tumor necrosis factor-alpha

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Abstract

Objective—Inflammatory cytokines may influence both labile anger and depression. Both psychiatric conditions can occur during interferon-alpha (IFN–α) based treatments. Evidence also indicates a central nervous system role for TNF-α, whose expression may be increased by IFN-α. A polymorphism in the promoter region of TNF-α has been associated with various inflammatory illnesses. We therefore hypothesized that this TNF-α polymorphism would influence susceptibility to psychiatric symptoms during IFN-α therapy.

Methods—105 patients with hepatitis C, initially without active major depression (MDD), were treated with IFN-α and then prospectively monitored using the Structured Clinical Interview for DSM-IV, the Beck Depression Inventory-II (BDI), the Anger Irritability and Assault Questionnaire, and circulating TNF-α levels. The A-308G polymorphism (rs1800629) was determined using the 5′-nuclease assay. Repeated-measure mixed-effect analyses compared changes in symptoms over time.

Result—BDI increased during IFN-α therapy ($F = 6.2$; $p<0.001$), with 27% developing MDD. The TNF-α A allele was associated with worsened labile anger ($F = 2.5$; $p<0.05$) and fatigue ($F = 2.9$; $p<0.05$) during treatment, but not with major depression incidence ($X^2 = 0.0$; $p=0.99$) or increased BDI ($F = 1.2$; $p=0.31$). Labile anger was not predicted by the serotonin transporter polymorphism ($F = 0.8$; $p=0.59$).

Discussion—During treatment with an exogenous cytokine, vulnerability to worsening labile anger -- distinct from major depression -- is associated with genetic variability in TNF-α. This has implications both for patients being treated with IFN-α, as well as our understanding of genetic vulnerability for different subtypes of dysphoric and mood disorders.

Keywords

Cytokine; inflammation; genetic; polymorphism; anger

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Introduction

Inflammation may be involved in the etiology of mood disorders.[1] Genetic polymorphisms in the inflammatory system have been associated with major depressive disorder (MDD),[2] and twins concordant for MDD have elevated levels of inflammatory activity.[3] Additionally, inflammatory cytokines are implicated in the neurobiology of aggression,[4] and mice bred for high aggression have an elevated pro-inflammatory response.[5] Elevated production of tumor necrosis factor-α (TNF-α) has been associated with hostility in humans.[6-8] 'Anger attacks' have been described during MDD[9] and various other psychiatric diagnoses.[10] Abnormal regulation of anger, with both genetic and neurobiologic influences, can be related to significant violence.[11, 12] Labile anger can be measured by inquiring about having loss of control over switches in temper; sudden angry feelings with the urge to yell; or feeling so mad as to experience shaking, a pounding heart, and/or the urge to hit.

Consistent with a possible relationship between anger dysregulation and inflammatory cytokines, labile anger and hostility have been observed during exogenous interferon-alpha (IFN-α therapy.[13-20] During treatment with IFN-α, between 15-40% of patients also develop MDD.[21] However, worsened labile anger may be distinct from MDD.[22, 23] IFN-α based therapies are the primary recommendation for chronic hepatitis C,[20, 24] which affects over 170 million people and results in about 10,000 deaths per year in the U.S. [25, 26] Importantly, not everyone exposed to elevated inflammatory cytokines such as IFN-α develops worsened labile anger or MDD.

Genetic variation in the serotonergic system may be a source of resilience to developing MDD.[27-29] Less is know about resilience or vulnerability for developing worsened labile anger. However, genetic variation in tumor necrosis factor-alpha (TNF-α may be a plausible influence. TNF-α is biologically active in the brain and can influence synaptic strength,[30] ion channels,[31] synaptic scaling,[32] neurogenesis,[33] and serotonin transporter function.[34] It is produced throughout the limbic and hypothalamic regions, where it can be influenced by peripheral inflammatory cytokines.[35-39] TNF-α can mediate the induction of indolamine deoxygenase and depression-like behaviors following peripheral inflammation.[40] Peripherally administered TNF-α can affect both neurotransmitter and endocrine release.[41, 42] In humans, anti-TNF-α therapy may alleviate some mood related symptoms.[43-45] The 'A' allele in a promoter region of the TNF-α gene (A-308G) has been associated with higher TNF-α plasma levels,[46-48] arthritis,[49, 50] AIDS-associated dementia,[51] Parkinson's disease,[52] Alzheimer's,[53] asthma,[54-56] and metabolic syndrome.[57] In elderly patients, the A allele is associated with cognitive dysfunction.[58]

To date however, evidence for an association between the A allele and mood disorders is equivocal. Small studies suggest an association.[59-61] Conversely, other reports no association with MDD but a possible protective association with bipolar II disorder.[62] Several larger studies have found no association with childhood mood disorder[63-65] nor with post-partum mood disorder.[66] Whether it is associated with risk for labile anger has not been examined. Therefore, in subjects with elevated states of peripheral inflammation as a result of IFN-α administration, we prospectively examined the association of this candidate polymorphism with the development of either labile anger or depression.

Materials and methods

We followed subjects prescribed IFN-α as described previously,[28, 67] and as approved by the University of Pittsburgh Institutional Review Board. In brief, patients with chronic hepatitis C (n=105) who were initiating pegylated (PEG) IFN-α2 (PEG-IFN-α2a: 135 mg/

week or PEG-IFN-α2b: 120 or 150 mg/week) and oral ribavirin treatment were examined pre-treatment and then for 16 weeks during therapy.[68-72] Patients were excluded from these analyses if they had active mood, anxiety, psychotic, drug/alcohol use disorders within 6 months prior to starting IFN-α. As antidepressants can affect mood, labile anger,[73] and/or cytokine levels,[74] data from individuals on antidepressants were excluded.

MDD during IFN-α treatment was diagnosed using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I).[75] The 21 item Beck Depression Inventory-II (BDI) was used to assess depressive symptoms at week two and during monthly visits (but could be returned by mail if the participant was unable to attend the scheduled appointment).[76] The Anger Irritability and Assault Questionnaire (AIAQ), a 28 item self-report,[77] was similarly employed to prospectively assess labile anger. Items on this questionnaire are scored 0 to 3, with subscales that include labile anger (range 0-18), irritability, and assault.

Monthly plasma samples were used for enzyme linked immunosorbent assays to determine TNF-α levels (Alpco, Salem, NH; sensitivity = 1.56pg/mL), and were run in duplicate. Genomic DNA was isolated from lymphocytes using the PureGene kit (Gentra Systems, Minneapolis, MN), or from whole blood using the QuickGene-Mini-80 kit (Fujifilm Life Science; www.autogen.com). A-308G (rs1800629) was genotyped using the 5′-nuclease (Taqman) assay using the ABI 7900 DNA detection system, employing Assays-on-Demand and Assays-by-Design (Applied Biosystems, Inc., Foster City, CA). The uncommon A/A genotype was combined with the A/G heterozygotes for statistical analyses. The serotonin transporter promoter length polymorphism (5-HTTLPR) was assessed as previously described.[28]

All statistics employed SPSS 17.0. Skewed TNF-α levels were corrected using a square root transformation. Repeated-measure mixed-effect analyses with an ante-dependence covariance structure[78] were used to compare changes in either subjective symptoms over time (i.e., assessing an interaction between genotype and time). We confirmed the appropriate choice of covariance structure, as the ante-dependence model produced the smallest -2 log likelihood (data not shown). Kaplan-Meier survival analyses examining time until MDD development were compared using the Mantel-Cox log rank test. Results are presented as the mean +/- standard deviation, unless otherwise indicated.

Results

Participants were 67% male, 90% European-American, 47 +/-11 years (18-72), 87 +/- 17 Kg (46-144 Kg), 44% had any prior history of mood disorder, and 34% had any prior history of drug/alcohol use disorder. Demographics did not differ between those who developed MDD and those who did not (Table 1), nor did brand of IFN-α or dose of ribavirin. The TNF-α polymorphism was in Hardy-Weinberg Equilibrium with 4 A/A, 29 A/G, and 72 G/G. The A allele was more prevalent in African Americans ($t_{(103)} = 2.5$); but otherwise demographics did not differ between genotypes (Table 1). Because of racial differences in the prevalence of the A-308G polymorphism, we specifically examined Caucasian Americans; but we then repeated some analyses in all subjects regardless of self-reported race.

TNF-α polymorphism is associated with labile anger development

Among Caucasian subjects, labile anger increased more (Figure 1) in those with the A allele ($F_{(5,66.4)} = 2.5$; $p<0.05$) compared to those with the G/G genotype. There was no significant relationship between race and the development of labile anger ($F_{(5,79.4)} = 1.9$; $p=0.09$), and the genotype relationship with labile anger continued to be evident when including African-Americans in the analysis ($F_{(5,70.2)} = 3.1$; $p<0.05$).

TNF-α polymorphism is not associated with other mental health problems

Genotype was not associated with the development of irritability (p=0.45) or assault (p=0.72). Additionally, although sleep quality (as assessed with the Pittsburgh Sleep Quality Inventory) worsened over time ($F_{(5,70.3)} = 2.8$; $p<0.05$), there was no relationship between genotype and worsening sleep quality ($F_{(5,70.3)} = 1.4$; p=0.24). Time until development of MDD during IFN-α therapy, which occurred in 27 subjects, was also not associated with the TNF-α genotype in Caucasians ($X_{(1)}^2 = 0.4$; p=0.53) nor in all subjects combined ($X_{(1)}^2 = 0.0$; p=0.99). BDI increased over time during IFN-α therapy ($F_{(5,87.4)} = 6.2$; $p<0.001$), but this was not associated with genotype ($F_{(5,81.2)} = 1.2$; p=0.31). Nor was there any main effect of genotype on BDI ($F_{(1,87.2)} = 0.3$; p=0.63). When including African-Americans in the analysis of BDI, there was a trend for those with the A allele to develop more depression symptoms ($F_{(5,87.4)} = 2.1$; $p<0.08$), but this was not significant.

Exploratory analysis of TNF-α polymorphism and individual BDI items

Ten individual BDI items worsened during IFN-α treatment -- items #3,7,10,11,12,14,15,17,18, and 19 – past failure, self-dislike, crying, agitation, loss of interest, worthlessness, loss of energy, irritability, changes in appetite, and fatigue (results not shown). However, only two individual BDI measures worsened more in those with the A allele: loss of energy (question 15) ($F_{(5,76.3)} = 2.5$; $p<0.05$) and fatigue (question 20) ($F_{(5,86.5)} = 2.7$; $p<0.05$) (p values uncorrected for multiple testing).

A principal component factor analysis of the 21 BDI items extracted 3 components with an eigenvalue >1. The first component correlated (>0.4) with most questions except #10 (crying), #18 (changes in appetite) and # 21 (loss of interest in sex). The second correlated (>0.4) with #15 (loss of energy) and #20 (fatigue). The third correlated (>0.4) with #10 (crying), #11 (agitation), and #17 (irritability). Genotype was associated with a combined measure of fatigue and loss of energy ($F_{(5,78.0)} = 2.9$; $p<0.05$) (Figure 2a). An association between genotype and worsening of crying/agitation/irritability was not statistically significance ($F_{(5,86.8)} = 1.4$; p=0.22) (Figure 2b).

Association of TNF-α polymorphism and labile anger is not mediated by fatigue

The composite measure of fatigue/low energy was slightly correlated with labile anger (R=0.17; F=10.3; $p<0.001$), and both were associated with the TNF-α polymorphism. When including the composite fatigue/energy measure as a time-varying covariate in the repeated measure longitudinal mixed-effect analysis, the A allele continued to predict worsening of labile anger during IFN-α treatment ($F_{(5,70.4)} = 2.9$; $p<0.05$), arguing against mediation by fatigue.

Peripheral TNF-α levels and psychiatric symptoms

Monthly TNF-α levels (Figure 3) increased during IFN-α treatment ($F_{(4,54.9)} = 4.4$; $p<0.005$). But this was not associated with genotype ($F_{(4,45.8)} = 0.4$; p=0.78). Those who developed MDD trended towards greater TNF-α levels during treatment ($F_{(4.47.8)} = 2.3$; p=0.08). We next compared TNF-α levels in those with labile anger scores anytime during treatment > 5 (the median split point) with those scoring 5 or less (Figure 3). The difference in levels was not significant ($F_{(1,75.5)} = 1.1$; p=0.30).

Including peripheral TNF-α levels as a covariate, we repeated the repeated-measure mixed-effect analysis of genotype on labile anger. The association between the A allele and increased labile anger remained ($F_{(4,44.5)} = 15.7$; $p<0.001$). It is therefore unlikely that peripheral TNF-α levels mediate the relationship between the A-308G polymorphism and worsening labile anger.

5-HTTLPR is not associated with labile anger development

Because we have previously reported a relationship between the 5-HTTLPR genotype and MDD during IFN-α therapy in an overlapping set of these patients,[28] we assessed an association between 5-HTTLPR and the development of labile anger. No relationship was found ($F_{(10,52.3)} = 0.8$; p=0.59).

Discussion

The A allele in the -308 promoter region of TNF-α was specifically associated with worsening labile anger during IFN-α treatment. Labile anger was based on questions in the AIAQ about having minimal control over switches in temper; feeling normally "OK" but then suddenly feeling angry or furious with the urge to yell; or feeling so mad as to experience shaking, a pounding heart, and/or the urge to hit something.[77] Of note, the A allele was specifically associated labile anger and not with irritability or increases in assault behaviors (either verbal or physical). We also did not find any association between the TNF-α polymorphism and the development of categorical MDD or worsening BDI, consistent with most prior studies.[62-65]

Several groups have independently described increases in hostility-related complaints in patients receiving IFN-α treatment,[13-20] something very disruptive for patients.[17] This phenomenon occurs whether depression develops or not,[22] and is orthogonally distinct from increased depression on the symptom checklist-90.[23] Aggression and depression are under genetic influence in childhood twin studies, albeit via potentially distinct pathways.[79] Also, 5-HTTLPR was associated with risk for MDD during IFN-α treatment,[27, 28] but not risk for labile anger. There may be a relationship between elevated peripheral interleukin-6 (IL-6) levels and MDD during IFN-α therapy,[67, 80] despite no relationship between TNF-α levels and MDD. This is consistent with reports of elevated systemic IL-6 but not TNF-α in "idiopathic" MDD.[81]

It is entirely speculative as to what this labile-anger syndrome represents. 'Anger attacks' could be related to a depression subtype,[9] impulsive aggression,[10] mixed mood disorder,[70, 82] or an entirely distinct syndrome. Consistent with a 'mixed mood disorder' hypothesis, mood dysregulation may be related to risk for bipolar disorder;[83-89] bipolar disorder and elevated TNF-α levels both may predict worse response to classical antidepressants; [90, 91] and elevated TNF-α levels may occur in bipolar disorder.[92] Inconsistent with a 'mixed mood disorder' hypothesis, we very rarely observed grandiosity, decreased sleep requirements, or increased goal-directed activities during IFN-α treatment. Future work will be required to further delineate this labile anger 'syndrome'. An important limitation of this study is that our assessment of labile anger was limited to this single self-report questionnaire, and thus the findings should be considered preliminary.

Anger during depression has been previously examined in genetic association analyses, with possible associations with CREB1,[93] ABCG1 transporter,[94] tryptophan hydroxylase,[95] monoamine oxidase A,[11] and catecholamine-O-methyl transferase.[96] A limitation to this study is that we also did not examine these genes or several other polymorphisms that are upstream from the TNF-α transcription start site (e.g. positions -863, -376, -244, -238). Future work will be required to more fully examine the role of genetic variation across the TNF-α gene and other candidate genes in labile anger.

We did examine whether worsening fatigue mediates the increased labile anger. Fatigue and malaise are well-known symptoms of IFN-α treatment,[23, 97] and TNF-α has been associated with malaise in animal models.[98] Although TNF-α genotype was associated with increased

fatigue, no mediation was found. Thus, the A allele may increase sensitivity to both fatigue as well as labile anger, albeit independently.

Also, circulating levels of TNF-α were neither associated with psychiatric symptoms nor genotype. This is inconsistent with higher plasma TNF-α levels being associated with the A allele during inflammation[46-48] and increased depressive symptoms correlating with lymphocyte production of TNF-α.[99] Thus, our lack of associations with circulating TNF-α levels should be interpreted with caution. Nonetheless, the A-308G genotype has been associated with cognitive dysfunction in elderly subjects despite no association between genotype and peripheral TNF-α levels,[58] similar to our study. It is possible that central TNF-α may be of more relevance to psychiatric symptoms.

TNF-α levels in the brain can be influenced by stress or peripheral inflammation[35, 36, 38] as well as peripheral cytokines.[39] Similarly, IFN-α decreases cell proliferation in the hippocampus by induction of *local* cytokines.[100] Therefore, it is plausible that the A-308G polymorphism could particularly influence localized central nervous systems expression of TNF-α during IFN-α treatment. Consistent with this speculation, the A-308G polymorphism may affect the binding of some transcriptional regulators but not others.[101-105] Enhanced production of quinolinic acid may mediate some psychiatric effects of IFN-α[106] and elevated central TNF-α could be influential on this pathway.[40] Also, increased central nervous system TNF-α can increase norepinephrine and serotonin turnover,[107] possibly mediated by its effect on c-jun-N-terminal kinase.[108] As TNF-α can be induced in the limbic system, any of these central TNF-α influences could be a plausible mechanism leading to labile anger. Nonetheless, the pathway by which the A allele in the TNF-α promoter region specifically leads to enhanced labile anger requires future investigation.

In summary, the risk for inflammation-related labile anger may be enhanced in subjects with the A allele in the promoter region for TNF-α. However, it should be reiterated that this study was specifically performed in patients undergoing therapy with IFN-α. Whether TNF-α is associated with labile anger in other clinical situations requires examination. A strength of the IFN-α paradigm is the ability to prospectively assess the development of symptoms; however the limitation is the lack of generalization to other “stressful” or inflammatory scenarios. Also, although hypothesis driven, these analyses had no correction for multiple testing and require replication. Regardless, the results indicate that genetic variation upstream from TNF-α may influence labile anger during a state of heightened inflammation without concomitantly influencing risk for depression.

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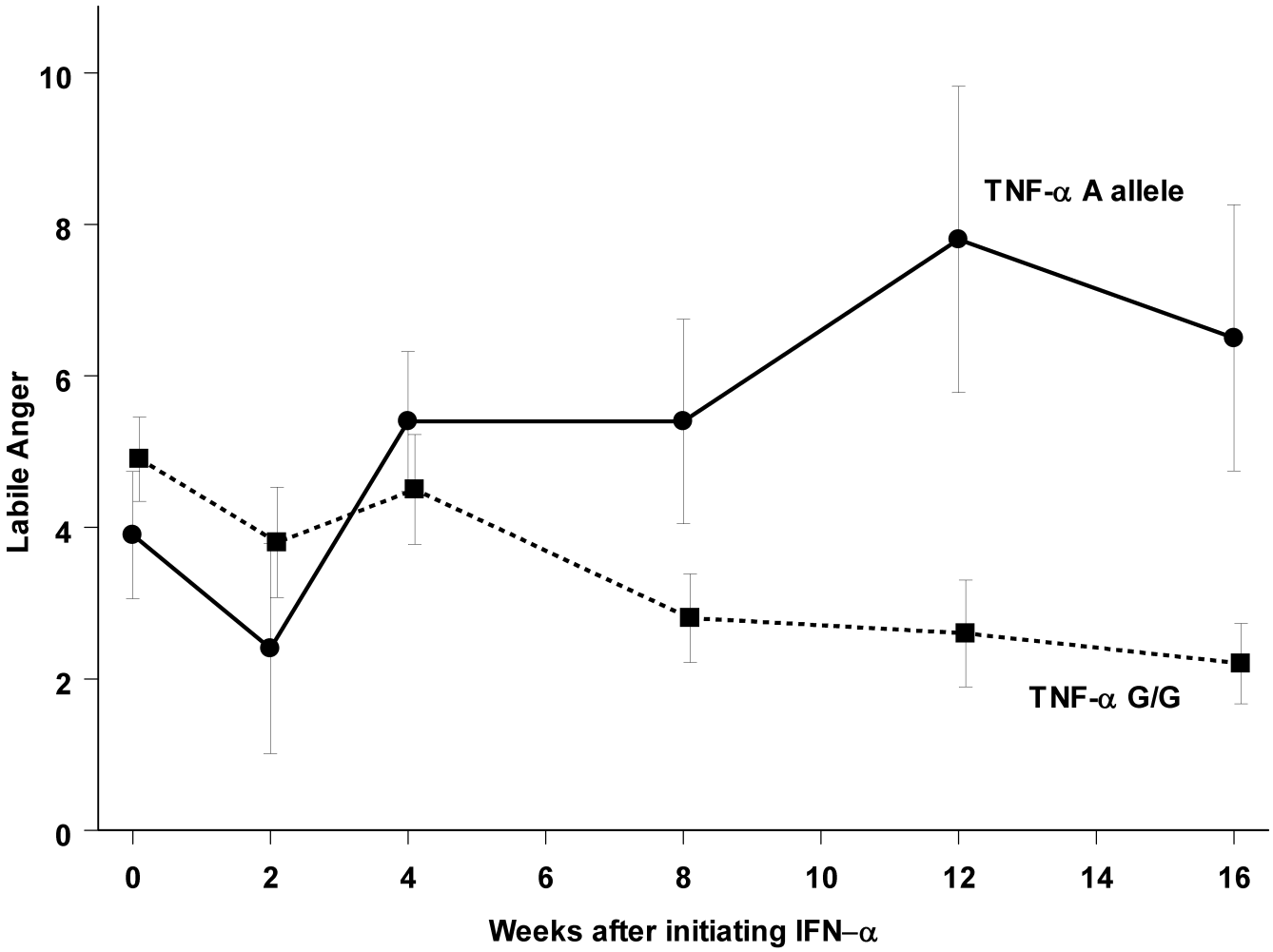

Figure 1.
Labile anger (mean +/- standard error the mean) increased more during IFN-α treatment in subjects with the A allele in the TNF-α upstream polymorphism.

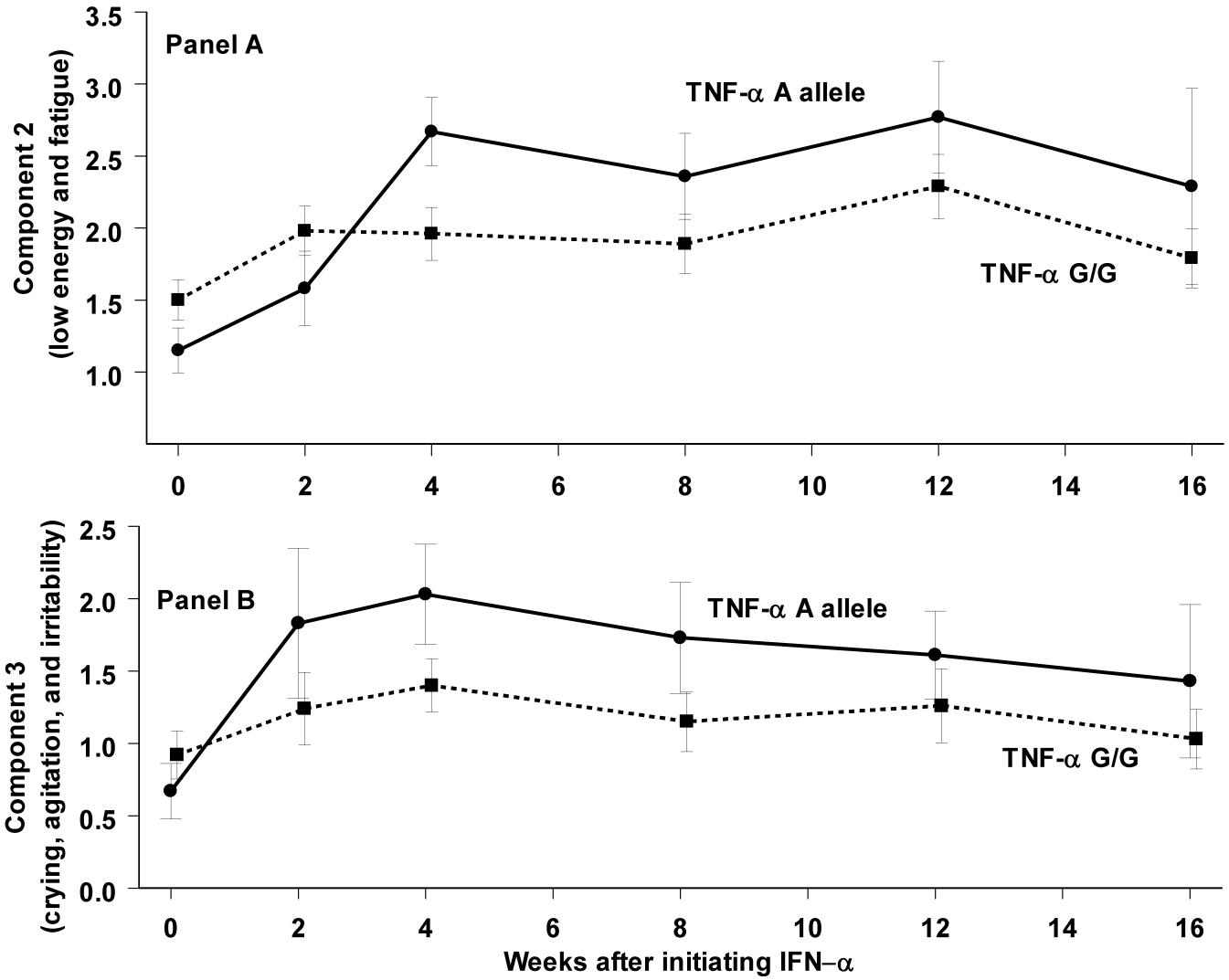

Figure 2.

A composite measure of low energy and fatigue (Panel A) from the BDI (mean +/- standard error the mean) increased more during IFN-α treatment in subjects with the A allele in the TNF-α upstream polymorphism; this trend was similar for a composite measure of crying, agitation, and irritability (Panel B) but was not significant.

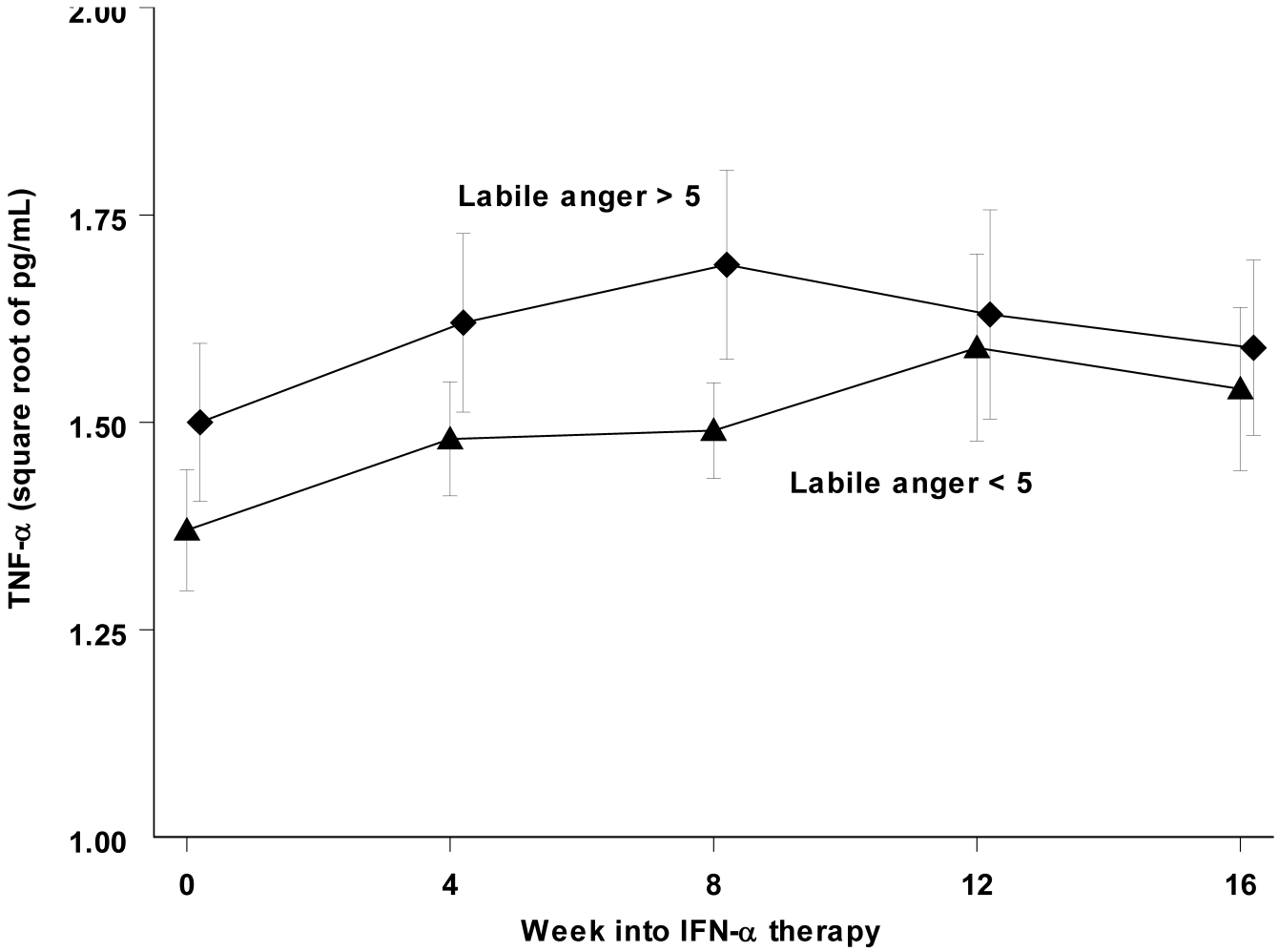

Figure 3.
Systemic TNF-α levels (mean +/- standard error the mean) increased during treatment. In subjects with labile anger scores greater than 5 at any time during treatment, this elevation was not significantly higher from those whose scores remained 5 or less.

Table 1

	MDD (n=27)	No MDD (n=78)		AA or AG (n=33)	GG (n=72)	
Gender (percent male)	66.7%	68.0%	ns	72.7%	65.3%	ns
Race (percent European-American)	85.2%	91.0%	ns	78.8%	94.4%	P=0.015
Age (years)	46.5 +/- 7.9	47.0 +/- 12.7	ns	45.7 +/- 10.6	47.4 +/- 12.2	ns
Weight (Kg)	87.0 +/- 13.7	86.5+/- 18.7	ns	85.4 +/- 15.3	87.2 +/- 18.4	ns
History of any mood disorder	48.2%	42.3%	ns	36.4%	47.2%	ns
History of drug or alcohol disorder	37.0%	33.3%	ns	30.3%	36.1%	ns

There were no statistically significant (ns) differences in demographics between subjects who developed major depressive disorder (MDD) and those who didn't. The A allele was more prevalent in self-identified African-Americans.