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Research report

Positive and negative acute phase proteins in affective subtypes

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Abstract

Background: Patients with affective disorders show evidence of increased positive acute phase proteins (e.g., C-reactive protein [CRP], α-1-acid glycoprotein, haptoglobin) and decreased negative acute phase proteins (e.g., albumin, transferrin [TFN]). CRP reductions have been reported to be greater in patients who later respond to lithium augmentation, and these patients also demonstrate higher CRP levels on the failed antidepressant, prior to the addition of lithium. However, association of such systemic immune changes with affective subtypes, mood state, psychotropic medications, age and gender has not been extensively explored. *Methods:* The present study assessed levels of CRP and TFN in 79 bipolar I, 24 bipolar II, and 46 unipolar depressed outpatients in comparison to 22 healthy controls. *Results:* Patients on lithium monotherapy were significantly less likely to demonstrate elevated CRP, and a similar trend was noted in those patients taking lithium in combination with an antidepressant. The frequency of elevated CRP levels did not significantly vary for different psychotropic medications, affective subgroups, or mood states. TFN levels were not influenced by diagnosis, affective state or psychotropic medications. *Limitations:* Due to the retrospective nature of this analysis, the affective subgroups were heterogenous with regard to medications and affective state, and differed significantly in age. Due to limitations in subgroup sample size, significant effects of clinical variables may have been masked by interactions of medications, age, affective subtype, and mood state. *Conclusions:* The results imply that lithium may play a role in normalizing systemic immune activation associated with depression. Whether such immune changes may be restricted to lithium-responsive subgroups deserves further evaluation. © 1998 Elsevier Science B.V.

Keywords: Affective disorders; Acute phase proteins; C-reactive protein; Transferrin

1. Introduction

Major depression has been associated not only with reductions in certain parameters of cellular immunity such as natural killer cell activity (Kronfol et al., 1989; Irwin and Gillian, 1987; Irwin et al., 1990) and mitogen responses of peripheral blood monocytes (Schleifer et al., 1984; Maes et al., 1989), but there have also been reports of chronic, systemic immune activation (Maes, 1995; Maes et al., 1992a,b, 1995a; Joyce et al., 1992; Hornig-Rohan et al., 1995, 1996; Sluzewska et al., 1995a, 1996). Such persistent immune activation is often noted in acute and chronic autoimmune and inflammatory condi-

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tions such as rheumatoid arthritis, and is marked by increases in autoantibody production and acute phase responses. The acute phase response is characterized by increases in certain plasma proteins of hepatic origin, the so-called positive acute phase proteins (APP) such as C-reactive protein (CRP), haptoglobin, and α-1-acid glycoprotein (AGP), and a corresponding reduction in negative APPs such as transferrin (TFN) and α-2-macroglobulin (De Jong et al., 1990; Kushner, 1982).

As is seen in acute or chronic inflammation, several researchers have observed a robust inflammatory response in patients with major depression, with increases in positive APP such as haptoglobin (Maes et al., 1992b,c, 1993a; Joyce et al., 1992; Song et al., 1994; Seidel et al., 1995), AGP (Nemeroff et al., 1990; Healy et al., 1991; Kehoe et al., 1991; Sluzewska and Rybakowski, 1993; Sluzewska et al., 1993, 1995; Maes et al., 1992b, 1993), α_1-antichymotrypsin (Joyce et al., 1992), α_1-antitrypsin (Song et al., 1994), and CRP (Maes et al., 1992c; Sluzewska and Rybakowski, 1993; Sluzewska et al., 1994, 1995a; Seidel et al., 1995) and decreases in negative APP such as albumin (Maes et al., 1995b; Song et al., 1994) and TFN (Maes et al., 1992c; Maes, 1993).

We previously reported differences in acute phase and immunomodulatory proteins in bipolar type I (BPI) as compared to unipolar depressives (MDD; Hornig-Rohan et al., 1995), although only certain immune parameters differed significantly from the control group. In addition, this analysis was limited by a lack of controls for such variables as affective state at the time of blood draw, medication status, and length of illness. Overall, potential differences in immune aberrations amongst depressive subtypes have not been clearly elucidated. Thus, it is unclear whether immune disturbances relate to the state of depression, and thus would be predicted to resolve along with clinical remission from the major depressive episode, or whether such changes in immune status may serve as a trait marker that varies as a function of clinical diagnosis. We hypothesized that both affective state and diagnostic subtype are related to immune status. However, as there have been numerous reports of immunopotentiation with lithium both in vitro (Hart, 1979a,b; Wilson et al., 1989; Shenkman et al., 1978; Wu and Yang, 1991; Weetman et al., 1982) and in vivo (Fernandez and Fox, 1980; Senger et al., 1982; Wahlin et al., 1984; Wilson et al., 1991; Rybakowski et al., 1993a,b, 1995) the possibility that patients on lithium would show a normalizing effect on the acute phase response, with a lower rate of CRP positivity and of hypotransferrinemia, was considered. Additionally, an intriguing report by Rybakowski et al. (1995) found evidence of immune activation, including increased CRP, in depressed patients on a variety of antidepressants who went on to respond to lithium augmentation; the lithium responders also showed normalization of their APP levels, while lithium nonresponders did not show any change in APPs either before or after addition of lithium to their failed antidepressant trial. Thus, it was predicted that patients of any affective subtype who were in the midst of a depressive episode would show evidence of an acute phase response (i.e., increased positive APP such as CRP and decreased negative APP such as TFN), but that this effect would be reduced in patients on lithium, independent of diagnostic subtype. This investigation thus focused on the evaluation of the acute phase response in patients with bipolar and unipolar depression, controlling for affective state and medication status. Specifically, we sought to determine whether increases in the positive APP, CRP, and decreases in the negative APP, TFN, could be detected in bipolar and unipolar subtypes of depression.

2. Methods

2.1. Subjects

A group of 171 subjects participated in this study: 79 BPI, 24 bipolar II (BPII), 46 unipolar MDD outpatients of the Depression Research Unit at the University of Pennsylvania Medical Center, and 22 healthy controls. Healthy volunteers were recruited from the staff of the Psychiatry Department at the University of Pennsylvania and were free of any current or past psychiatric disorder or any serious medical illness as determined by reported history during brief clinical interview. None had been taking any psychotropic or other medications. Diagnoses of

affectively ill outpatients were made using DSM-IIIR criteria (American Psychiatric Association, 1987), according to a modified version of the Structured Clinical Interview for DSM-IIIR, Patient Version (Spitzer et al., 1989). Medication status (lithium, other antidepressants, lithium plus antidepressants in combination, neuroleptics, benzodiazepines, lithium plus neuroleptic in combination, or medication-free) and affective state (euthymic, depressed, manic/hypomanic) were determined for the time of blood draw by retrospective chart review. Medication status was determined on the basis of patient report. Affective state was based upon the clinical impression noted by the research psychiatrist at the time the patient was seen. Due to the retrospective nature of the study, severity ratings were not directly available from the chart review and were therefore not included in the analysis. Patients and controls with any reported evidence of inflammatory, infectious, or allergic diseases in the 2 weeks prior to the study were excluded, and all subjects were free of any drugs known to interfere with immune function for 4 weeks prior to blood sampling. Additionally, subjects with chronic medical illnesses known to affect the immune system were also excluded from the study.

2.2. Study design

Blood samples were drawn into 10-ml serum separator tubes. The blood was allowed to clot, centrifuged, and serum was removed and frozen at -20°C until assayed for CRP and TFN levels. Both CRP (Laurent et al., 1985) and TFN (Stoddard et al., 1984) concentrations are reported to remain stable for extended periods at -20°C.

2.3. Laboratory assessments

Serum concentration of the positive APP, CRP, was evaluated by qualitative latex agglutination technique (RapiTex CRP; Behringwerke, Marburg, Germany). Results were referenced against positive (>6 mg/l) and negative (<6 mg/l) control sera provided in the RapiTex kits, and all samples were assayed in the same assay to eliminate inter-assay variability. Concentration of TFN was assessed by immunonephelometric technique (Ritzmann and Daniels, 1975) using a Behring nephelometer (Behringwerke). All TFN samples were assayed in the same assay to eliminate interassay variability. The intra-assay coefficient of variation was $<3\%$ The standardized laboratory reference range was 200–400 mg/dl.

2.4. Statistical analysis

Relationships between variables were assessed by means of logistic regression analysis for CRP and linear regression analysis for TFN. Differences between sample means were ascertained with one- and two-way ANOVA, unpaired *t*-test (with Bonferroni–Dunn correction, as appropriate), and chi-square statistics.

3. Results

3.1. Demographic data

Table 1 shows the clinical features (age, gender and medication status) of the 171 subjects in this study. Age varied significantly among groups: the BPI group was significantly older (51.5 ± 14.3 years) than the BPII (42.3 ± 13.0 years), MDD (44.4 ± 11.6 years), and control (41.1 ± 11.5 years) subjects (Anova, $F=6$, $p=0.0006$). There were also between-group differences in gender ratio which approached statistical significance ($\chi^2=7$, $p=0.07$) with the percentage of males distributed in each group as follows: the BPI group was 45.6% male; the BPII group, 25% male; MDD group, 45.6% male; and the control group, 63.6% male. Medication status was determined and categorized as follows: lithium monotherapy, antidepressant monotherapy, lithium plus antidepressants in combination, neuroleptics, benzodiazepines, lithium plus neuroleptics in combination, or medication-free. Numbers and percentages of patients within each diagnostic subgroup that were on each treatment regimen are given in Table 1. Medication status appeared to differ for each affective subgroup. In addition, age varied significantly across medication subgroups (Anova, $F=4$, $p=0.0004$). However, using a Bonferroni–Dunn test to correct for multiple comparisons given the large number of medication subgroups, the only significant difference that was seen on unpaired *t*-

Table 1
Subject characteristics

	BPI ($n = 79$)	BPII ($n = 24$)	MDD ($n = 46$)	Control ($n = 22$)
Age, years±S.D.	51.5±14.3[a]	42.3±13.0	44.5±11.6	41.1±11.5
(range)	(22–79)	(26–71)	(22–71)	(24–68)
Gender (% male)	45.6	25.0	45.6	63.6
Lithium monotherapy (%)	69.2	30.4	26.3	–
Antidepressant monotherapy (%)	2.6	17.4	10.5	–
Lithium plus antidepressant (%)	21.8	21.7	7.9	–
Neuroleptic monotherapy (%)	0.0	0.0	2.6	–
Benzodiazepine monotherapy (%)	0.0	0.0	5.3	–
Lithium plus neuroleptic (%)	1.3	0.0	0.0	–
Medication-free (%)	5.1	30.4	47.4	100.0

[a] $F = 6$, $p = 0.0006$.

tests was between the patients on lithium monotherapy (mean age±S.D. = 52±15 years) and those who were medication-free (mean age±S.D. = 41±10 years; $t = 4$, $p < 0.0001$).

Affective state at the time of blood draw (euthymic, depressed, or hypomanic/manic) is delineated for each diagnostic subgroup in Table 2A. A greater percentage of the BPI patients were euthymic at the time of blood draw (59.7%) as opposed to only 22.3% of BPII and 12.8% of MDD patients. As expected, more of the medication-free patients were in a depressed state at the time of blood draw: 100% (29/29) of medication-free patients, 26% (18/68) of patients receiving lithium, and 80% (8/10) of patients on an antidepressant (Table 2B).

3.2. CRP seropositivity in depressive subtypes

Controlling for the influence of affective state, diagnostic subtype, gender, age and medications in a logistic regression analysis, the frequency of positive CRP results (i.e., CRP level >6 mg/l) showed only a trend towards greater CRP positivity in the MDD group (odds ratio = 31.15, Wald $\chi^2 = 2.93$, $p = 0.087$) but not the BPI subgroup (odds ratio = 13.17, Wald $\chi^2 = 1.67$, $p = 0.196$). BPII individuals ap-

Table 2
(A) Mood state in affective subtypes

	Euthymic (%)	Depressed (%)	Manic/hypomanic (%)
BPI ($n = 79$)	59.7	33.8	6.5
BPII ($n = 24$)	22.3	77.3	0.0
MDD ($n = 46$)	12.8	87.2	0.0
(B) Mood state in medication subgroups			
Lithium monotherapy ($n = 68$)	67.6	26.5	5.9
Antidepressant monotherapy ($n = 10$)	20.0	80.0	0.0
Lithium plus antidepressant ($n = 25$)	32.0	64.0	0.0
Neuroleptic monotherapy ($n = 1$)	0.0	100.0	0.0
Benzodiazepine monotherapy ($n = 2$)	0.0	100.0	0.0
Lithium plus neuroleptic ($n = 1$)	0.0	100.0	0.0
Medication-free ($n = 29$)	0.0	100.0	0.0

Table 3
CRP and TFN in affective subtypes

	CRP[a,b] (% positive)	TFN[c] (mg/dl±S.D.)
BPI ($n = 79$)	8.9	328±63
BPII ($n = 24$)	0.0	331±62
MDD ($n = 46$)	23.9	331±60
Total affective ($n = 149$)	12.1	329±62
Control ($n = 22$)	4.5	340±64

[a] Positive CRP response (qualitative assay) defined as >6 mg/l.
[b] Odds ratio = 31.15, Wald $\chi^2 = 2.93$, $p = 0.087$, logistic regression of BPI, BPII, MDD, control group.
[c] d$F = 3$, $F = 0.2$, $p = 0.87$, linear regression of BPI, BPII, MDD, control group.

peared distinct from MDD, BPI and control groups in their CRP responses (0% CRP positive vs. 23.9%, 8.9%, and 4.5% positive, respectively), but this difference was not significant (Table 3). Logistic regression further revealed a significantly decreased rate of CRP positive results in those patients on lithium monotherapy (odds ratio = 0.05, Wald $\chi^2 = 4.99$, $p = 0.025$) with a trend towards a lower rate of CRP positivity in the lithium plus antidepressant combination group (odds ratio = 0.06, Wald $\chi^2 = 3.46$, $p = 0.063$). There were no significant effects of gender (Wald $\chi^2 = 1.28$, $p = 0.258$) or age (Wald $\chi^2 = 0.48$, $p = 0.490$) on CRP results.

Additionally, affective state, independent of diagnostic subtype of mood disorder, did not have a significant overall influence on CRP positivity by logistic regression analysis. Euthymic patients had a similar frequency of CRP positivity (10.7%) as patients in a depressed state (10.4%). In contrast, patients who were hypomanic or manic at the time of blood draw had a 0% rate of positive CRP responses, but the total numbers in this group were small.

3.3. TFN levels in depressive subtypes

Linear regression analysis revealed no significant influence of diagnostic subtype, affective state, medication status, or age on TFN concentrations (Table 3). There was a nonsignificant trend for men to have lower TFN levels than women (mean TFN±S.D. for men was 321.9±51.4 and for women was 337.9±68.7; $t = -2$, $p = 0.081$).

In addition, TFN levels did not vary as a function of CRP results (mean TFN concentration for CRP positive group = 331±60 mg/dl vs. 331±62 mg/dl

Table 4
Psychotropic medication effects on CRP and TFN

	CRP[a] (% positive)	TFN (mg/dl±S.D.)
Lithium monotherapy ($n = 71$)	8.5[b]	328±65
Antidepressant monotherapy ($n = 10$)	10.0	336±76
Lithium plus antidepressants ($n = 25$)	8.5[c]	328±63
Neuroleptic monotherapy ($n = 1$)	100.0	393
Benzodiazepine monotherapy ($n = 2$)	0.0	332
Lithium plus neuroleptic ($n = 1$)	0.0	370
Medication-free ($n = 51$)	13.7	333±60

[a] Positive CRP response (qualitative assay) defined as >6 mg/l.
[b] Odds ratio = 0.05, Wald $\chi^2 = 4.99$, $p = 0.025$.
[c] Odds ratio = 0.06, Wald $\chi^2 = 3.46$, $p = 0.063$.

for CRP negative group; $t = -0.02$, $p = 0.98$) (Table 4).

4. Discussion

This study noted a significant reduction in CRP positives in patients on lithium monotherapy and a trend towards decreased CRP positivity in patients on lithium in combination with an antidepressant. Contrary to previous reports, the influence of diagnostic subtype on CRP results was not significant when affective state, gender, age and medication status were controlled by logistic regression analysis, with only a trend towards a higher rate of CRP positivity associated with the MDD, but not the BPI patient subtype. No relationship was found between diagnostic subtypes and levels of the negative APP, TFN. Although the TFN results could not be explained by differences in age, medication status, or affective state, there was a trend for male gender to be associated with a decreased level of TFN. The normalizing effects of lithium that were seen for CRP were not observed in the TFN analyses.

Previous reports of the systemic immune response accompanying depression have described increases in positive APP such as CRP along with decreases in negative APP such as TFN (Maes et al., 1991, 1992b, 1995b; Healy et al., 1991). The present investigation only found a trend towards the type of CRP elevations noted in prior reports of depressed populations (Maes et al., 1992c; Sluzewska and Rybakowski, 1993; Sluzewska et al., 1994; Seidel et al., 1995) and failed to confirm prior reports of hypotransferrinemia (Maes et al., 1992c; Maes, 1993). Positive CRP responses were most frequent in the MDD group, with a slight elevation in BPI patients, yet no BPII patients demonstrated positive results. A higher frequency of positive responses in MDD as compared to controls (23.9 vs. 4.5%, respectively), and the small increase in positive responses in BPI relative to controls (8.9 vs. 4.5%, respectively), however, is consistent with previous studies of CRP in states of depression (Maes et al., 1992c; Sluzewska and Rybakowski, 1993; Sluzewska et al., 1994; Seidel et al., 1995). The smaller size of the BPII group may have accounted for the absence of CRP positivity in such patients. Alternatively, it could be hypothesized on the basis of the trend towards a greater rate of CRP elevation in MDD patients as opposed to either BPI or BPII patient subgroups that the acute phase response is more characteristic of unipolar as compared to bipolar subtypes. Another explanation is that such results might be linked to accumulating evidence that the BPII subtype may be a biologically distinct subgroup (Coryell et al., 1995; Akiskal et al., 1995). However, perhaps the most likely explanation relates to the significant impact of lithium therapy in reducing CRP positivity. Patients on lithium monotherapy (who were more likely to belong to the BPI patient subgroup) or on lithium plus antidepressant therapy (who were more likely to belong to either the BPI or BPII patient subgroup) had a lower rate of CRP positives than those who were medication-free or on other psychotropic agents.

The lack of significant hypotransferrinemia in our study could not be explained by any of the clinical variables for which we controlled in the analysis, including age, medication status, or affective state, although there was a trend towards decreased TFN levels in men. Given the dose-dependent, enhancing influence of lithium on urinary excretion of TFN (Jensen et al., 1995), it is conceivable that the absence of significant results could reflect a net effect of lithium at both the kidney level (reducing circulating serum TFN concentrations by increasing urinary TFN excretion) and at the hepatic level (normalizing a putative decrease in hepatic synthesis and secretion of TFN due to hypotransferrinemia). It is also possible that patient numbers were too small in each subgroup to achieve the statistical power needed to detect an effect of small size.

The current analysis was not able to assess the potential impact of important clinical variables such as age of onset, duration of current episode, episode severity, presence or absence of melancholia or atypical features, or treatment refractoriness. Similarly, factors which could have affected both the psychiatric and control groups, such as acute or chronic psychosocial stressors, were also not evaluated with the use of objective rating scales. Evidence that such variables may influence parameters of systemic immune activation comes from several sources. Severe psychosocial distress has been linked to a host of aberrations in cell-mediated and humoral

immunity (Calabrese et al., 1987), and patients with severe depressive illness, with a presumed accompaniment of greater distress, are more likely to have altered APP responses in comparison to patients with minor or nonmelancholic depression (Maes et al., 1993b). One study comparing medication-free depressed patients who had failed to respond to antidepressants during previous episodes of depression with patients who had a history of good antidepressant treatment response found greater concentrations of CRP and other positive APPs such as AGP and interleukin-6 (IL-6) in the refractory group (Sluzewska et al., 1995). Although the patients classified as treatment refractory had been tried on a mean of three previous treatments for depression, the antidepressant trials were limited to tricyclic antidepressants, α-2 autoreceptor antagonists, or nonselective monoamine oxidase inhibitors, and did not include any mood stabilizers such as lithium or carbamazepine. As another study from the same laboratory found that depressed patients who went on to respond to lithium augmentation of antidepressant therapy had both significantly greater CRP levels at baseline (on the failed antidepressant) and greater reductions in CRP after lithium potentiation (Rybakowski et al., 1995), it is possible that the patients classified as treatment-refractory in the previous study (Sluzewska et al., 1995) may have similarly had the capacity to respond to lithium. If so, baseline CRP elevations during a depressive episode might play a role in the identification of patients who would ultimately respond to lithium and/or lithium augmentation.

The effect of lithium on CRP results is consistent with prior studies assessing acute phase responses in depression. Subchronic administration of lithium (4 weeks) has been shown to decrease serum levels of APP such as α-1-acid-glycoprotein and CRP in depressed populations (Rybakowski et al., 1993a,b). In addition, despite evidence that treatment with the antidepressant fluoxetine (Sluzewska et al., 1994, 1995) but not venlafaxine (Sluzewska et al., 1995) may decrease concentrations of positive APP such as α-1-acid-glycoprotein and α-1-antichymotrypsin, we did not see an effect of other antidepressants on CRP levels. The absence of such an effect may be confounded by the neuropharmacologic heterogeneity of the antidepressant medications being administered in this study. However, the fact that the medication-free group showed an increased rate of CRP positivity (13.7%) as compared to the lithium (8.5%), antidepressant (10%), or lithium plus antidepressant group (8.5%) may be suggestive of a small medication effect that could not be detected due to insufficient numbers of subjects in each group. Inherent biases with regard to these issues also exist in the present analysis due to absence of assessments for history of treatment refractoriness and the enrichment of the study population with patients who were either euthymic and on lithium (who by definition were both treatment- and lithium-responsive) or medication-free and depressed (who were more likely to meet criteria for past or current treatment resistance or refractoriness). One study of immune parameters including serum levels of soluble interleukin-2 receptors (a measure of immune activation), phenotypic lymphocyte markers, and mitogen stimulation in euthymic bipolar patients did not find any evidence of immune activation, nor were results influenced by lithium administration (Rapaport, 1994). Thus, the observation of the present study that lithium is associated with reduction of the acute phase response contrasts somewhat with the findings of Rapaport. However, Rapaport's study did not specifically measure acute phase proteins and was instead assessing other parameters of immune activation. Lithium's effect on immune function is likely to be complex, and perhaps most appropriately described as normalizing as opposed to simply enhancing all immune parameters. The results here indicate that lithium may have the capacity to reverse immune activation (as reflected by elevations of CRP) which may be associated with some forms of mood disorder.

It is also possible that other autoimmune factors may have influenced CRP results. Rheumatoid factor, for instance, can cause false positive results in a latex agglutination test such as the one used in the CRP analyses in this study, although the assay utilized herein is not affected rheumatoid factor levels below 1200 IU/ml (RapiTex CRP, 1993). None of the subjects had known rheumatoid arthritis nor any other clinically obvious rheumatologic or autoimmune disorder. In a separate analysis, autoantibodies to a wide variety of antigens were not found to be elevated in this patient population,

although rheumatoid factor was not specifically assessed. This assessment included autoantibodies commonly found in affective populations (especially bipolar patients on lithium) such as those directed to thyroid microsomal and thyroglobulin which were also noted to be in normal range (Hornig-Rohan et al., 1996). Lastly, although there are inherent limits in the qualititative nature of the CRP assay, the relevance of quantitative assessments of CRP is greatest where very recent changes (i.e., less than 24 h) in acute phase response are being evaluated (Peter, 1989), which was not the case in this analysis.

There are obvious limitations to this type of retrospective study. Heterogeneity of medications and of affective state in the patient subgroups may have played a role in influencing results. Age effects on CRP and TFN results were not evident, even though the patient groups did differ significantly in age. Mean age was greater for BPI patients; in addition, patients on lithium monotherapy were also significantly older, given that most of the BPI patients in our sample were on lithium. However, the absence of such effects of age, gender and affective state on APP levels lends further support for the influence of lithium and possibly of diagnostic subtype on the acute phase proteins examined in this study. Lastly, although there are inherent limitations associated with the use of psychiatric staff for recruitment of control subjects, the control group was screened carefully for current or historical diagnoses of psychiatric or medical illness.

The affirmation of lithium's capacity to reduce CRP responses, in conjunction with previous data from our group and others, highlights the importance of controlling for medication effects in assessments of APP responses in depression. The possibility that such reductions in CRP may be more evident in lithium responders than in those refractory to the therapeutic effects of lithium deserves further study; the ability to utilize APP patterns to enhance accuracy in classifying patients into diagnostic subgroups may assist in the biologic characterization of affective subtypes and has the potential to lead to more appropriate treatment selection. Prospective studies evaluating both baseline and post-lithium APP responses in patients who are categorized according to lithium response or nonresponse, current mood state, affective severity, age of onset, and presence or absence of other immune disturbances such as autoimmune disorders (e.g., autoimmune thyroid disease) are needed to amplify our understanding of this interesting finding.

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