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C-Reactive Protein and Affective Inhibition in Bipolar Disorder

Amy T. Peters, Ph.D.[1,2], **Caitlin E Millett, Ph.D.**[2,3], **Jessica Harder, M.D.**[2,3], **Julia Potter, B.A.**[2], **Raina Fichorova, M.D., Ph.D.**[2,3], **Andrew A. Nierenberg, M.D.**[1,2], **Katherine E. Burdick, Ph.D.**[2,3]

[1]Massachusetts General Hospital, Boston, MA

[2]Harvard Medical School, Boston MA

[3]Brigham and Women's Hospital, Boston, MA

Introduction

Bipolar disorder (BD) is often characterized by cognitive deficits that persist during remission of acute symptoms[1]. There can be substantial individual variability in cognitive abilities, but up to 60% of remitted patients demonstrate reduced performance in at least one cognitive domain relative to healthy comparisons[2,3]. One of the most pronounced difficulties in BD is inhibitory control[4,5], the ability to suppress contextually inappropriate responses and behaviors[6]. Inhibitory control difficulties are associated with functional problems, such as greater likelihood of unemployment[7], and even suicidality[8]. The most effective treatments for mood symptoms are not adequate for ameliorating inhibitory deficits, and hence, it is essential to develop a better understanding of underlying biological mechanisms that might offer further targets for treatments.

Inhibitory control is most often studied in the laboratory using "cold cognition" paradigms, which refers to the exertion of cognitive control during affectively neutral tasks[9]. However, in the real world, inhibitory control is also critical for implementation of emotion regulation strategies, the inhibition of unhelpful forms of thought and cognitive biases, and refraining from impulsive or risky behaviors such as substance use or self-injury[10–15]. These different aspects and applications of inhibition may be correlated at a high level in contributing a common "executive functioning" factor, but may also have dissociable components and underlying mechanisms[16,17]. This presents multiple pathways via which failure to exert inhibitory control and integrate inhibition with the detection, evaluation, and filtering of emotional or affectively laden information, may confer vulnerability to mood episode recurrence. Indeed, self-reported negative cognitive style has been linked to recurrence of major depressive episodes[18]. It is therefore plausible that failure to inhibit negative processing biases may also increase risk for recurrent mood episode, particularly depression, which is among the most chronic and unresolved clinical challenges in bipolar disorder[19]. Therefore, from a treatment target perspective, it is of value to know what biomarkers are uniquely or specifically related to "cold cognition" versus those that may have implications for dual cognitive-emotional processes. This can be accomplished by relating biomarkers to emotionally-salient versions of traditionally cold inhibitory control tasks, such as the Affective Go/No-Go, which uses negative, positive, and neutral words as different target response conditions[20] in place of the traditional Go/No-Go inhibitory control task which

lacks affective overlay. Additionally, given that most existing work assessing the relevance of inflammation to affective processing in mood disorders has focused on reward processing and motivation[21], affective inhibition represents an untapped and novel domain to test for the specificity (or the range) of its effects.

A leading potential biological mechanism of affective inhibition dysfunction in BD involves immune dysregulation[22]. Broadly, the hypothesis is that peripheral inflammatory markers that are triggered in response to stress enter the brain through active transport, interaction with circumventricular organs, or via afferent pathways[23]. In turn, this may activate central nervous system inflammatory processes, including brain microglia and neurotransmitter expression, as well as oxidative stress and decreased neuroplasticity, that are thought to contribute to structural and functional brain changes associated with cognitive and behavioral phenotypes[23]. In particular, frontrostriatal inhibitory neurocircuitry, which includes dorsal components implicated in inhibitory control and ventral components implicated in motivational salience, as well as frontolimbic threat processing circuitry, may be particularly vulnerable to the effects of peripheral inflammation[21]. This is possibly because of a high density of glial receptors in these regions and proximity to circumventricular organs as mechanisms of crossover from peripheral to central inflammatory activation[24]. It was previously reported in the primary study of the present cohort that peripheral inflammation is associated with broad cognitive dysfunction, including several aspects of executive functioning that are thought to reflect frontal-subcortical systems function[25]. However, there are no prior studies to our knowledge that address whether peripheral inflammation is also implicated in cognitive-emotional processing, involving both cognitive and affective processing demands, in BD.

To address this gap in the literature, we evaluated the association between C-reactive protein (CRP) levels and affective inhibition accuracy and response times for negative, positive, and neutral stimuli on an affective go/no-go paradigm. We hypothesized that increased CRP would be associated with reduced negative target detection and a response bias (faster response times) during the negative target condition. CRP is an acute phase reactant that is upregulated by proinflammatory cytokines within the innate immune system[26]. We selected CRP as the focal measure of inflammation because it is one of the most studied markers of immune health across many fields of medicine, it is elevated in BD independent of mood state[27], and, due to its relatively long half-life, it is more robust than other commonly measured cytokines to acute changes or measurement confounds affecting sample concentration than are other commonly measured cytokines, including diurnal variation, and dietary, exercise, and sleep patterns[28]. We also acknowledge that CRP is a non-specific marker of inflammation; that is, many different stimuli can lead to its elevation[28]. However, there are few existing studies linking peripheral inflammation and cognitive-emotional processing, particularly in bipolar disorder. As such, our goal was to first establish if there is a relationship between a broad measure of inflammation (e.g., CRP) and cognitive-emotional processing, which could then guide whether further explication of the molecular antecedents involved in the instantiation of a chronic-low grade inflammatory response is warranted, as these may constitute targets for medication treatment.

Methods

Participants

Participants with DSM-V BD I and II (n = 119, age range = 18–65, Table 1 for detail) were recruited from the Icahn School of Medicine at Mount Sinai Hospital. The participants included in the current study represent a subset of that previously reported[25], who were selected based on having data available for both the Affective Go/No-Go Task[20] and CRP. Only 8 healthy control participants had data on both parameters and due to this small sample size, were excluded from further analysis. Diagnosis of BD was determined by the Structured Clinical Interview for DSM-V (SCID-5[29]). Illness features including age at onset, number and type of prior episodes, BD and psychotic subtype, rapid cycling and comorbid axis I diagnoses (current and lifelong) were also derived from the SCID-5.

All participants were outpatients and affectively stable, defined as a Clinical Global Impressions Rating Score ≤ 3[30]. Exclusion criteria included inability to consent, history of head trauma, neurological disorder, or childhood Attention Deficit/Hyperactivity Disorder or learning disability. We chose not to exclude individuals with an adult-onset ADHD diagnosis if it was made after the onset of BD due to the confounding of this diagnosis in the context of a serious psychiatric illness with cognitive implications. Thus, there may be some individuals in this sample with a true adult-onset ADHD but none who met criteria for ADHD during childhood, which is when a clearer and less confounded diagnosis is best made. Additionally, exclusion criteria included current diagnosis of minor or major neurocognitive disorder, substance use disorder within the past three months, an active and unstable medical problem that may interfere with cognition, medication with known adverse cognitive effects (i.e., topiramate, tricyclics, and anticholinergics), agents that enhance cognition (e.g., amphetamine, dopamine agonists), and electroconvulsive therapy (ECT) in the past year. Benzodiazepine use was permitted, but participants were required to refrain from use within 4 hours of testing.

Affective Inhibition

Participants performed the Affective Go/No-Go task from the Cambridge Neuropsychological Test Automated Battery (CANTAB)[20]. This is a continuous performance task that consists of 20 blocks, with two practice blocks followed by 18 testing blocks, where for each block, a target word category and a distracter word category were designated. Then, a series of words were rapidly presented at the center of the screen, and participants were instructed to make a button-press response to words from the target category, while withholding the response to words from the distractor category. There were three categories of words: ‘Positive’, ‘Negative’, and ‘Neutral’. Illustratively (Figure 1), if the target category for a block is ‘Negative’, and distractor category is ‘Positive’, the participants should press the button upon seeing the word ‘Crying’ and withhold the response upon seeing ‘Fun’. Each of the 6 possible target-distracter category combinations were repeated 3 times and order of presentation was counterbalanced across participants. There were 18 trials per block and each word was displayed for 300 msec with a 900 msec inter-stimulus interval (ISI). Participants were instructed to respond as quickly and as accurately as possible.

For each block, the number and percent of target omissions (misses) and commissions (false alarms) were calculated, as well as average response times for target hits and commissions. To evaluate participants' overall accuracy in discrimination of 'Positive', 'Negative', and 'Neutral' words, d' was calculated for each target category, using Z(hit rate) – Z(false alarm rate). D' ranges from 0 (no discrimination) to infinity (perfect discrimination). For blocks where hit or commission rates were either 100% or 0%, effective limits were set of 1-(1/(2*n)) or 1/(2*n), respectively, where n is the number of targets or distractors for the trial. No other behavioral thresholds or accuracy cut-offs were used to optimally model the full range of dimensional performance associations with CRP in the entire sample.

Blood Biomarker Analyses

A research nurse obtained a non-fasting sample of ~16 ml of blood in a serum separator by venipuncture from all participants. The serum samples were stored at −80 °C until batch analyses. The Genital Tract Biology Laboratory at Brigham and Women's Hospital analyzed CRP on electrochemiluminescence (ECL) multiplex-based assay platform using S600 Meso Scale Discovery (MSD) reader (MSD, Gaithersburg, MD). The lab is accredited by the College of American Pathologists. The ECL assays are highly sensitive with a 5-log scale of linearity starting at 2.5 pg/ml. Each sample was diluted to fit the linearity range. Raw readings were transformed by reader software into concentrations and these values were entered in an Excel database. A split quality control sample was run on each ECL assay plate to ascertain reproducibility of measurement showing a 5.6% inter-assay coefficient of variation.

Statistical Analyses

All analyses were performed in the statistical program SPSS (IBM SPSS Statistics version 24). Analyses comparing the current sample with data available for the measures of interest to participants from the overall study were done with a Student's *t* or Chi-squared tests, as appropriate. Accuracy and response times across each target category ('Positive', 'Negative', and 'Neutral') were compared with repeated measures ANOVA. CRP concentrations were not normally distributed (Skewness statistic = 6.31, *SE* = .22), but achieved a normalized distribution with transformation. Log transformed CRP values were used in subsequent correlational and regression analyses.

Pearson's bivariate correlations were used to assess the association of CRP with d' prime and reaction times for 'Positive', 'Negative', and 'Neutral' conditions. Significant bivariate correlations were subsequently subjected to multivariable regression to adjust for potential confounds. In a first step, because residual mood symptoms could be implicated in bias for emotionally valanced words[31], HDRS and YMRS scores were entered as covariates. In a subsequent step, we added additional demographic and clinical characteristics that could plausibly covary with either inflammation or affective cognition, including age, sex, race, education, smoking status, number of psychotropic medications, duration of BD illness, number of mood episodes, and number of psychiatric hospitalizations. Body mass index was only recorded for n = 22 patients in this sample and due to this lack of data could not be adjusted for in analyses. Finally, a stepwise regression was conducted to isolate which

affective inhibition variables (e.g., negative, positive, and neutral d' prime, hits response time, and commissions response time) that best explained variance in CRP.

Results

Affective Inhibition Performance

Affective inhibition performance data is summarized in Table 1 and Figure 2. There was a significant difference for detection accuracy between target word conditions, $F(1.87, 220.32) = 4.10$, $p = .020$. Post-hoc tests indicated that detection of negative target words was lower compared to both positive ($p = .023$) and neutral words ($p = .028$), whereas there was no difference between positive and neutral target words ($p = .880$). Response times did not significantly differ by target word category for either hits, $F(1.83, 212.46) = .61$, $p = .532$, or commissions, $F(1.99, 229.22) = .24$, $p = .784$.

Bivariate correlations between target detection accuracy and response times are reported in Table 2. Greater negative target detection was associated with longer negative hits response times ($r = .26$, $p = .004$) and negative commissions response times ($r = .24$, $p = .008$). Greater positive target detection was associated with longer positive hits response times ($r = .22$, $p = .015$), but not positive commissions response times ($r = .08$, $p = .387$). Neutral target detection was not significantly associated with response times, neither for hits ($r = .17$, $p = .065$) nor commissions ($r = .07$, $p = .466$).

Associations of CRP and Affective Inhibition Performance

Univariate associations between CRP and affective inhibition target detection and response times are displayed in Figure 3. CRP was significantly associated with reduced negative target detection ($r = -.25$, $p = .007$), faster negative hits response time ($r = -.26$, $p = .006$), and faster negative commissions response time ($r = -.23$, $p = .012$). CRP was not significantly associated with positive target detection ($r = -.15$, $p = .111$), positive hits response times ($r = -.13$, $p = .151$), but was related to faster positive commissions response time ($r = -.25$, $p = .006$). CRP was not significantly associated with neutral target detection ($r = -.18$, $p = .054$), neutral hits response time ($r = -.14$, $p = .124$), or neutral commissions response time ($r = -.13$, $p = .155$).

In multivariate regression models, the associations of CRP with reduced negative target detection, faster negative hits and commissions response times, and faster positive commissions response times remained significant model terms after adjustment for both depression and mania symptoms and all additional demographic and clinical covariates (Table 3). However, the overall regression models were significant only for negative target detection and negative hits response times.

In a stepwise regression including all affective inhibition variables as predictors of CRP level, negative hits response times was retained as the sole variable in a significant model predicting CRP ($R^2 = .23$, $F(1, 113) = 6.20$, $p = .014$). Specifically, longer response times were associated with lower CRP ($b = -.002$, $se = .001$, $p = .014$). Tolerance for excluded variables ranged from .42 - .95.

Discussion

The results of the current study indicate that the peripheral marker of inflammation, CRP, was associated with affective inhibition performance in a cohort of euthymic individuals with BD. Specifically, increased CRP was significantly associated with reduced negative target discriminability, which was also significantly reduced compared to positive and neutral target conditions. Additionally, higher CRP levels were associated with faster response times for both negative hits and commissions, and when compared against each other in a stepwise regression, faster negative target response times explained the single-most variance in elevated CRP of all the affective inhibition variables evaluated. Notably, each of these associations were observed after adjusting for several potential confounds to inflammation in bipolar disorder, such as residual mood symptoms, illness course characteristics (medications, psychosis, chronicity), demographic characteristics, and smoking status. Such analyses lend confidence that the observed association between CRP and affective inhibition exists beyond what can be accounted for by demographic and clinical variables that are often disproportionately associated with either BD or inflammation. Taken together, these results add to the existing body of literature which has identified associations between peripheral inflammation and cognitive dysfunction[25], by raising the possibility that peripheral inflammation is also implicated in the integration of cognitive control with emotional processing in patients with BD, particularly for evaluation of negative stimuli.

It is important to draw attention to the fact that CRP was associated with reduced negative target word discrimination – which reflects the combination of both low accuracy in correctly identifying negative words *and* the tendency to incorrectly label positive or neutral words as negative. One potential interpretation is that individuals with BD may be affectively primed to interpret a range of emotionally charged or neutral stimuli as negative and increased immune activation could be involved in the response to this negative affective bias. The observations that increased CRP was associated with faster response times for negative targets and that negative target response times were the sole predictor of CRP levels retained in a stepwise regression, aligns with this possibility and suggests that inflammation may relate to a negativity bias defined by a tendency to more quickly evaluate or judge incoming information as negative. Alternatively, it is also possible that individuals who are less accurate at identifying negative stimuli might mount a stronger or lasting CRP response to regulate or manage unclear emotional inputs.

It is notable that CRP was associated with reduced negative, but not positive or neutral target discrimination. This pattern is suggestive of the possibility that an association of inflammation with reduced inhibitory control is most relevant when attention is primed for a negative, as compared to positive or emotionally ambiguous stimulus, thereby increasing the overall inhibitory demand[32,33]. Indeed, the variance in negative affective target detection explained by CRP (R^2 = .26) is comparable to variance in a composite of non-emotional cognitive measures explained by CRP (R^2 = .25) in a previous study of an overlapping sample[25], where both studies adjusted for similar confounding variables. Mechanistically, as reflected in structural[34–38] and functional[34,39] MRI studies of BD, peripheral inflammation may disrupt the frontal executive neural circuitry thought to be critical for top-down

regulation when emotional sensitivity is most heightened, such as when processing negative information. However, while not statistically significant, the pattern and direction of association of CRP with positive and neutral target conditions was similar, suggesting there may be a lower-level vulnerability between inflammation and inhibition broadly speaking, that crosses a critical threshold when required to identify and integrate negative stimuli. Accordingly, whereas prior studies have largely examined the associations of inflammation with cognition, reward and emotion processing, or mood symptoms separately, there are likely key domains of intersection and interaction amongst these constructs that will be important to continue to dissect to determine which patients and what areas of dysfunction are most vulnerable to the effects of inflammation.

A primary limitation of the study is the cross-sectional nature of the design. Although there are some promising experimental studies linking cytokine administration or systemic inflammatory challenge to both cognitive and affective processing deficits[24], these have not evaluated changes in affective inhibition specifically. Neither have any longitudinal studies focused on this domain, which will be required to fully parse the directionality of the associations observed herein. Moreover, although meta-analysis implicates CRP elevations in euthymic BD and affective inhibition deficits are reported in prior case-control studies, lack of healthy control data precluded our evaluation of whether or not the magnitude of the link between CRP and affective inhibition differs in BD. Importantly, our findings were robust to adjustment for residual mood symptoms and several clinical and demographic features, including many possible confounds to the effects of inflammation. However, we did not collect information on body mass index from all participants and were unable to apply that correction in the current analysis. Additionally, although CRP is generally less vulnerable to diurnal variation than some other cytokines[28,40], we did not have information regarding the time of the blood draw and could not demonstrate this quantitatively in the current sample. Equally, there are several other potential sources of inflammation that we did not monitor in our current sample, including low-grade infections, limited physical activity, poor diet, and related cardiovascular risk factors, which can disproportionately affect individuals with BD[41–44]. Indeed, diets high in fiber and rich in fruits and vegetables[45], as well as exercise[46] have been associated with lower CRP, plausibly through antioxidative properties that reduce oxidative stress[45] and reduced body mass index[46]. Both factors could contribute to temporary fluctuations in CRP that we were unable to adjust for statistically in the current study. It is important in future work to systematically track timing of these activities and their correlation with time of bio-sample acquisition to assess for any covariance. Of note, poor diet, and exercise habits, in addition to shared genetic risk, are factors implicated in the disproportionate incidence of cardiovascular disease in BD[47,48]. Therefore, it will be an especially important area of future inquiry to interrogate the interplay of shared genetic risk for cardiovascular disease and BD, and development of inflammation, cerebrovascular disease, and cognitive and neuropsychiatric sequelae over time. Likewise, we did not formally test for pregnancy nor systematically assess for breastfeeding or menopause in female participants, which can also introduction variation in CRP. Lastly, the correlation of peripheral CRP with cognitive-affective behavioral performance theoretically assumes there are mechanisms by which CRP influences central nervous system function. For instance, activate transport,

blood brain barrier permeability, circumventricular organs, afferent vagal nerve fibers, or monocyte infiltration are plausible[49], but can only be speculated in the present study.

Despite these limitations, the present study advances knowledge on circulating immune function in BD. It adds to an existing body of evidence demonstrating associations between inflammation and cognition or reward sensitivity and motivation separately, by raising the possibility that inflammation is also implicated in the integration of cognitive-affective processing. Our findings also have generated the hypothesis that this association may be more pronounced when stimuli are of negative valence. In future work, additions to study design, such as the inclusion of a control group and longitudinal assessment of broad and specific inflammatory markers, as well as performance-based measures of cognitive and affective processing, will be paramount for determining whether these initial findings observed here align with the notion of an integrated neuroimmune network hypothesis[50]. The neuroimmune network hypothesis suggests that the effects of low-grade inflammation are unlikely to be specific to any one behavioral construct, but rather may have nuanced and interacting influences across multiple domains of clinical risk, including affective processing, cognition, threat sensitivity, and reward. As deficits in each of these areas may come online during different stages of development or be amplified during different stages of the disease process, longitudinal studies assessing the course of these relationships will be especially important for identifying optimal windows for potential intervention or modulation of systemic inflammatory activation in BD.

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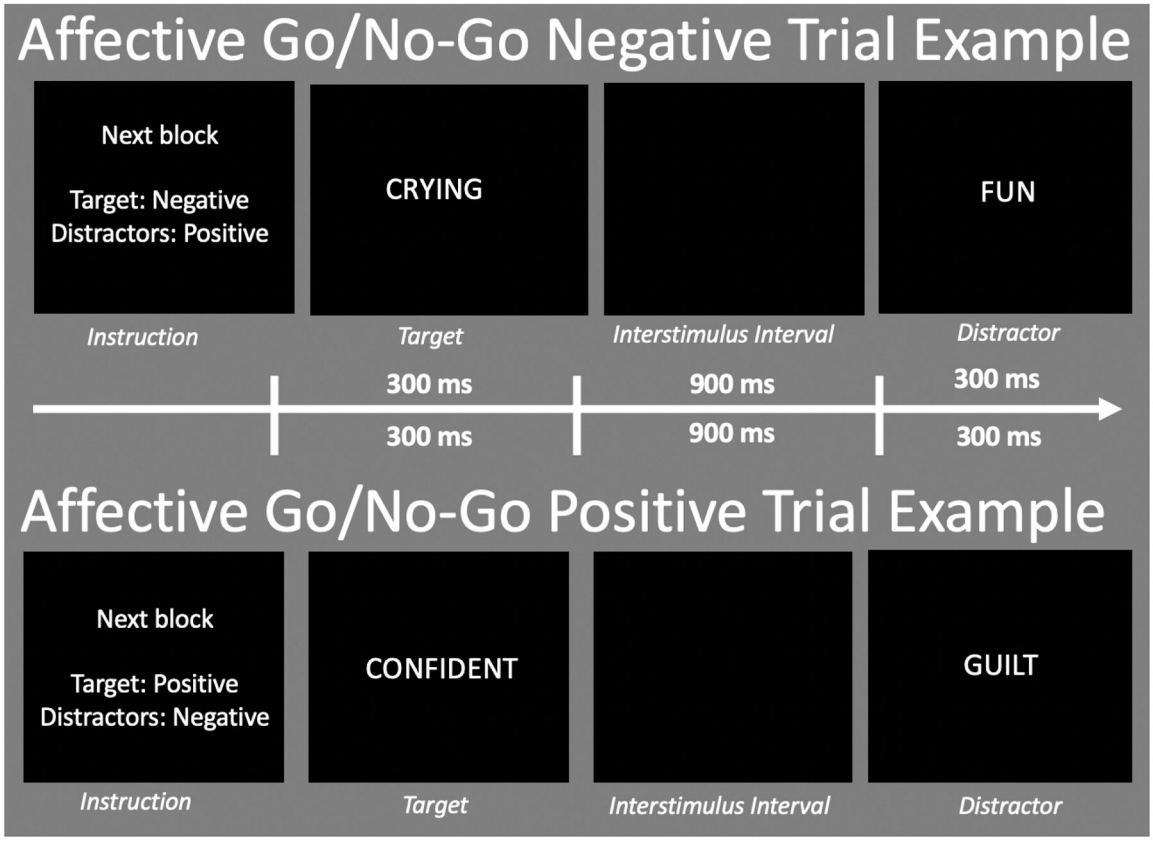

Figure 1.

This is a schematic of the Affective Go/No-Go Task Diagram. In the first representation, the target valence is negative. When a word with negative valence is displayed, the participant presses the response button ("Go" condition"). When a word with a positive valence is presented, the participant must withhold a response ("No Go"). In the second representation, the target valence is positive. When a word with positive valence is displayed, the participant presses the response button ("Go" condition"). When a word with a negative valence is presented, the participant must withhold a response ("No Go").

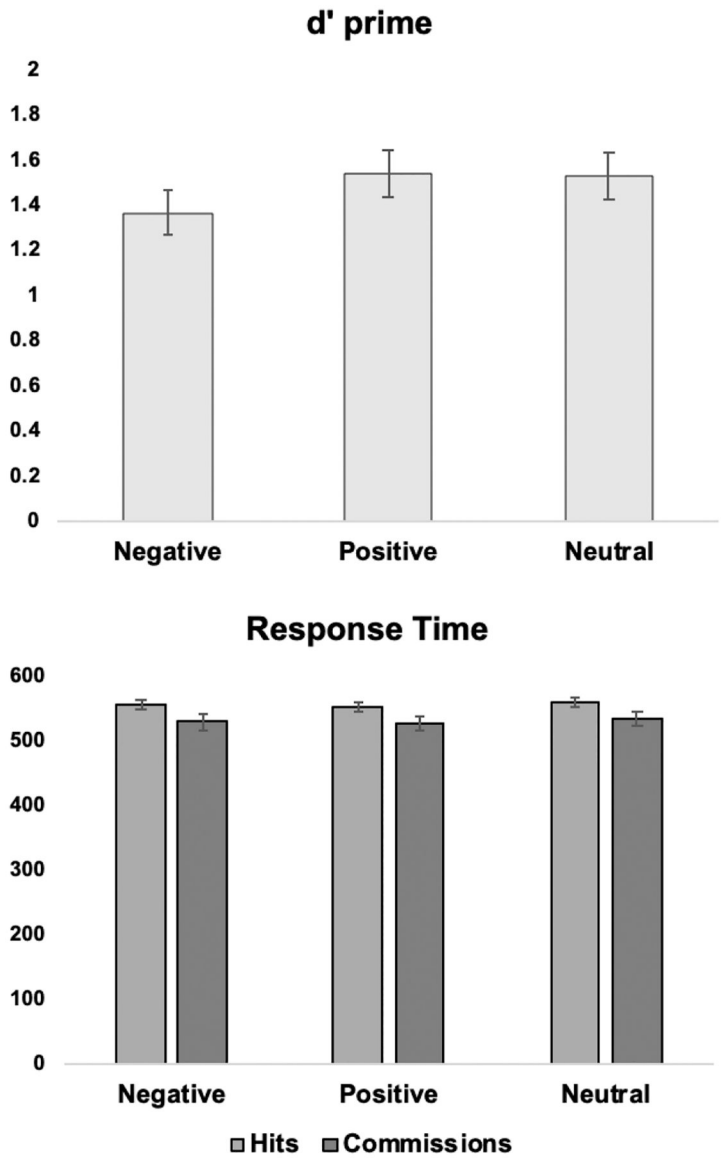

Figure 2.
Average detection accuracy and response times during Affective Go/No-go performance

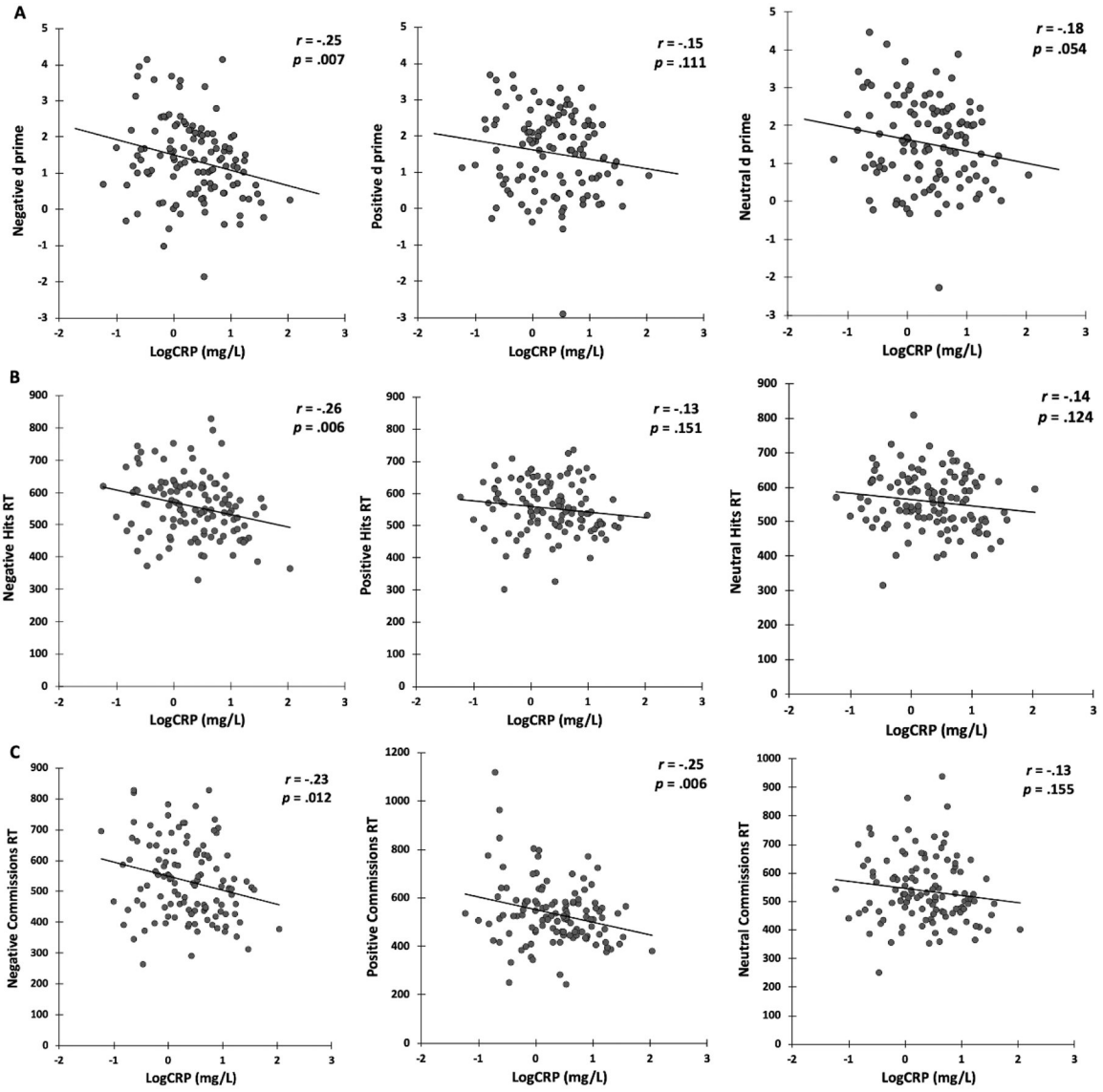

Figure 3.

Univariate associations of CRP and affective inhibition performance measures of: A) d prime; B) Hits RT (Response Times); C) Commissions RT. Negative Commissions RT, n = 118 due to 1 subject with 0% commissions rate. Positive Hits RT, n = 117 due to 2 subjects with 0% hit rate. Neutral Commissions RT, n = 117 due to 2 subjects with 0% commissions rate.

Table 1.

Sample Demographic and Clinical Characteristics (n = 119)

Variable	Mean	SD
Age	47.49	9.9
Education	14.04	2.42
No. Psychotropic Medications	1.61	1.32
Illness Duration	24.1	10.62
No. Hospitalizations	3.44	4.39
No. Mood Episodes	23.37	16.55
Manic Episodes	7.36	8.41
Depressive Episodes	12.49	11.23
No. Suicide Attempts	0.85	2.11
Weeks Since Last Mood Episode	62.83	106.93
	N	**%**
Sex (Female)	49	41.2
Ethnicity (Hispanic/Latino)	24	20.2
Race		
Black	65	54.6
White	51	42.9
Asian	1	0.8
American Indian/Alaska Native	0	0
Other	2	1.7
More than one race	0	0
BD Type I	92	77.3
Current Smoker	48	40.3
Lifetime Psychosis	47	39.5
	Mean	**SD**
Negative		
D Prime	1.37	1.10
Hits RT	555.98	95.59
Commissions RT[a]	533.12	123.67
Positive		
D Prime	1.54	1.13
Hits RT[b]	554.18	80.39
Commissions RT	533.56	130.16
Neutral		
D Prime	1.53	1.13
Hits RT	558.78	80.33
Commissions RT[c]	537.19	115.61

[a] n = 118 due to 1 subject with 0% commissions rate

[b] n = 117 due to 2 subjects with 0% hit rate

[c] n = 117 due to 2 subjects with 0% commissions rate

Table 2.

Bivariate correlations between target detection accuracy and response times

Condition/Variable	Negative			Positive			Neutral		
Negative	**D Prime**	**Hits RT**	**Commissions RT[a]**	**D Prime**	**Hits RT[b]**	**Commissions RT**	**D Prime**	**Hits RT**	**Commissions RT[c]**
D Prime	--								
Hits RT	.26**	--							
Commissions RT[a]	.24**	.73**							
Positive									
D Prime	.73**	.24**	.12	--					
Hits RT[b]	.23*	.76**	.63**	.22*	--				
Commissions RT	.16	.57**	.56**	.08	.70**				
Neutral									
D Prime	.77**	.23*	.20*	.84**	.18*	.14	--		
Hits RT	.18*	.76**	.60**	.16	.82**	.60**	.17	--	
Commissions RT[c]	.14	.64**	.53**	.09	.71**	.55**	.07	.75**	--

*$p < .05$,

**$p < .01$

[a] n = 118 due to 1 subject with 0% commissions rate

[b] n = 117 due to 2 subjects with 0% hit rate

[c] n = 117 due to 2 subjects with 0% commissions rate

Table 3.

Multivariable Modeling of CRP and Affective Inhibition Performance

	Negative D Prime					Negative Hits Response Times					Negative Commissions Response Times[a]					Positive Commissions Response Times				
	B	***SE***	***F* or *t***	**Sig**	**R2**	***B***	***SE***	***F* or *t***	**Sig**	**R2**	***B***	***SE***	***F* or *t***	**Sig**	**R2**	***B***	***SE***	***F* or *t***	**Sig**	**R2**
Step 1			3.459	**0.019**	0.084			3.743	**0.013**	0.090			2.188	0.093	0.055			2.900	**0.038**	0.071
Constant	2.647	0.542	4.880	**0.000**		694.781	46.464	14.953	**0.000**		689.672	62.528	11.030	**0.000**		716.003	64.417	11.115	**0.000**	
logCRP	−0.395	0.159	−2.482	**0.015**		−36.057	13.628	−2.646	**0.009**		−43.822	18.261	−2.400	**0.018**		−49.706	18.893	−2.631	**0.010**	
HDRS	−0.015	0.017	−0.881	0.380		−0.619	1.466	−0.422	0.674		−0.193	1.948	−0.099	0.921		−0.519	2.033	−0.255	0.799	
YMRS	0.047	0.028	1.678	0.096		−4.330	2.417	−1.791	0.076		−2.516	3.216	−0.782	0.436		−3.725	3.351	−1.111	0.269	
Step 2			2.739	**0.002**	0.257			2.257	**0.012**	0.222			1.491	0.133	0.160			1.130	0.343	0.125
Constant	2.229	1.008	2.211	**0.029**		659.458	88.715	7.433	**0.000**		660.543	120.313	5.490	**0.000**		709.198	129.090	5.494	**0.000**	
logCRP	−0.382	0.161	−2.378	**0.019**		−46.677	14.138	−3.302	**0.001**		−54.21	19.293	−2.81	**0.006**		−51.155	20.572	−2.487	**0.015**	
HDRS	−0.017	0.017	−1.005	0.317		−1.175	1.515	−0.776	0.440		−1.662	2.053	−0.809	0.420		−0.481	2.204	−0.218	0.828	
YMRS	0.019	0.028	0.694	0.489		−5.368	2.449	−2.192	**0.031**		−4.035	3.335	−1.21	0.229		−4.380	3.563	−1.229	0.222	
Age	−0.035	0.013	−2.793	**0.006**		−0.390	1.107	−0.353	0.725		−0.467	1.500	−0.312	0.756		−0.513	1.61	−0.319	0.751	
Sex	0.467	0.214	2.182	**0.031**		36.921	18.812	1.963	0.052		43.95	25.731	1.708	0.091		14.877	27.374	0.543	0.588	
Race	−0.004	0.117	−0.035	0.972		−17.276	10.276	−1.681	0.096		−27.991	14.182	−1.974	0.051		−11.482	14.953	−0.768	0.444	
Education	0.097	0.044	2.195	**0.030**		5.936	3.882	1.529	0.129		6.315	5.280	1.196	0.234		4.538	5.649	0.803	0.424	
Smoking Status	−0.233	0.214	−1.093	0.277		−23.632	18.789	−1.258	0.211		4.714	25.463	0.185	0.853		−5.105	27.34	−0.187	0.852	
Lifetime Psychosis	−0.054	0.202	−0.266	0.791		−5.934	17.803	−0.333	0.740		−7.021	24.196	−0.29	0.772		−17.085	25.906	−0.659	0.511	
No. Medications	−0.044	0.079	−0.560	0.577		−15.68	6.978	−2.247	**0.027**		−21.405	9.474	−2.259	**0.026**		−11.024	10.154	−1.086	0.280	
Illness Duration	0.010	0.012	0.882	0.380		1.208	1.044	1.156	0.250		0.749	1.417	0.528	0.598		0.447	1.52	0.294	0.769	
No. Hospitalizations	0.012	0.023	0.500	0.618		2.170	2.036	1.066	0.289		3.021	2.77	1.091	0.278		4.092	2.963	1.381	0.170	
No. Mood Episodes	0.002	0.006	0.251	0.803		−0.445	0.553	−0.805	0.423		0.108	0.749	0.144	0.885		−1.155	0.805	−1.435	0.154	

[a] n = 118 due to 1 subject with 0% commissions rate