Short Communication

Inflammation and positive affect: Examining the stress-buffering hypothesis with data from the National Longitudinal Study of Adolescent to Adult Health

Cara L. Blevins, Sara J. Sagui, Jeanette M. Bennett

Health Psychology Graduate Program, The University of North Carolina at Charlotte, USA
Department of Psychology, The University of North Carolina at Charlotte, USA

Article info

Article history:
Received 16 February 2016
Received in revised form 14 July 2016
Accepted 17 July 2016
Available online 18 July 2016

Keywords:
Positive affect
Perceived psychological stress
Inflammation
Stress protective
Young adulthood

Abstract

The present study examined the influence of positive affect (PA) on levels of inflammation within the context of Pressman and Cohen's (2005) stress-buffering model, which suggests that PA confers protective health benefits through its ability to mitigate the pathogenic influence of stress. We hypothesized that greater PA would buffer against the influence of perceived psychological stress (PPS) on systemic inflammation, operationalized as C-reactive protein (CRP, mg/L). Specifically, we predicted that PA would moderate the relationship between PPS and CRP. Cross-sectional data were drawn from Wave IV (2008–2009) of the National Longitudinal Study of Adolescent to Adult Health (Add Health). Participants (n = 3093) ranged in age from 25 to 34 years old (M = 29.0 ± 1.79). Using a moderated hierarchical regression analysis, PPS and PA significantly interacted to predict levels of CRP (p < 0.05). Examination of the simple slopes revealed a disordinal interaction between PPS and PA, such that higher PA was protective against elevated CRP levels, but only when individuals also reported greater levels of PPS. Thus, the data partially support the stress-buffering model of PA and extend existing evidence regarding the complexity by which PPS and PA influence health. Findings also provide caution of future assumptions that relationships among PA, PPS, and physical health markers, such as CRP, are always positive (e.g., PA) or negative (e.g., PPS) in nature.

1. Introduction

Acute inflammatory responses are essential components of recovery from infection or injury. Chronic elevations in proinflammatory biomarkers, such as levels of C-reactive protein (CRP; e.g., >1 mg/L), are associated with a range of chronic illnesses including cardiovascular disease (CVD), type-II diabetes, and metabolic syndrome (Ansell et al., 2003; Dockray and Steptoe, 2010; Kiecolt-Glaser et al., 2003; McDade et al., 2006; Ridker, 2003). Systemic inflammation can be influenced by a variety of innate factors including biological (e.g., age, sex, medication use) and psychosocial (e.g., race, perceived stress, socioeconomic status) characteristics (Bennett et al., 2013; O’Connor et al., 2009).

The experience of perceived psychological stress (PPS; Cohen et al., 2007; Lazarus and Folkman, 1984) has been associated with impaired immune function and a greater propensity to illness and infection (Kiecolt-Glaser et al., 2003; McDade et al., 2006; Robles et al., 2009). PPS has been shown to upregulate CRP production and enhance expression of proinflammatory cytokines including interleukin-6 (IL-6), interleukin-1 beta (IL-1β), and tumor necrosis factor-alpha (TNF-α; Ershler and Keller, 2000; Kiecolt-Glaser et al., 2003; McDade et al., 2006). Burgeoning research suggests that intrinsic positive psychosocial processes, such as positive affect, may protect or buffer against stress and inflammation, conveying salutary benefits (Chida and Steptoe, 2008; Meyer et al., 2014; Pressman and Cohen, 2005; Steptoe et al., 2005).

Positive affect (PA) refers to the experience of feelings or moods that reflect pleasurable engagement with the environment, such as happiness, interest, and enthusiasm (Watson et al., 1988). PA can be experienced at both the state and trait levels. State PA is typically assessed as one’s report of how s/he has felt over a short period of time (i.e., day or moment), while trait PA represents a report of how one “typically” feels or the average of multiple measures of state PA (Polk et al., 2005; Pressman and Cohen, 2005). The strongest associations between PA and health have been noted at the trait level (Pressman and Cohen, 2005; Robles et al., 2009), and
prospective studies have associated trait PA with decreased morbidity and all-cause mortality (Chida and Steptoe, 2008; Kubzansky et al., 2001), as well as with attenuated inflammatory response to acute psychological stressors (Robles et al., 2009; Steptoe et al., 2008).

To describe the specific mechanisms by which PA influences health, Pressman and Cohen (2005) proposed a theoretical framework consisting of two general models. The direct effects model suggests that PA broadly influences physiological systems and behavior, regardless of its effect on perceptions of and responses to stress. Alternately, the stress-buffering model suggests that PA may protect or “buffer” against the negative influence of stress on health and behaviors.

A wide range of studies have supported assumptions that PA conveys health protective benefits; however, little work has utilized the Pressman and Cohen (2005) stress-buffering framework to examine specific mechanisms by which PA protects against stress’ detrimental effects on physical health. Therefore, the present study sought to examine the influence of PA on systemic inflammation within Pressman and Cohen’s (2005) stress-buffering framework. Specifically, this study hypothesized that PA would moderate the relationship between PPS and CRP.

2. Methods

2.1. Participants

Publically available cross-sectional data from Wave IV of the National Longitudinal Study of Adolescent to Adult Health (Add Health; Harris et al., 2009) were used to examine our hypothesis and included individuals who participated in finger stick dried blood spot (DBS) collection (N = 4543). CRP values ranged from 0.08 mg/L to 95.2 mg/L. Individuals with CRP levels ≥ 6.25 mg/L (n = 1034; see Data Analysis section for explanation) and abnormal sleep values (n = 149) were removed from the analyses. Listwise deletion was used to account for missing data, yielding a final sample of n = 3354 for the unadjusted model and n = 3093 for the adjusted model.

Among the 3093 participants, average BMI was 27.76 ± 6.13 kg/m², mean age was 29 ± 1.79 years, and average CRP levels were 1.92 ± 2.61 mg/L. In addition, 50.7% were female, 36.7% reported smoking at least 1 cigarette in the past 30 days, and 67.4% stated they sleep between 7 and 9 h on a regular basis. Approximately 70.6% of individuals identified as White; 19.4% identified as Black; and 10% identified as Asian, Native American, Other or Hispanic, All Races. Overall, 13.2% of respondents endorsed no physical activity over the past seven days, 31% endorsed more than one physical activity per day, and 67% reported being active on three or less days over the past seven, including participation in individual or team sports (e.g., baseball or golf) or organized exercise (e.g., aero- bics or weight lifting). In regards to education and income, approximately 14.6% of participants completed high school or an equivalent degree, 33.9% completed some college, and 35% finished a bachelor’s degree or higher; approximately 44.6% reported an annual household income of $49,999 or less, and 16.3% endorsed an income over $100 K. Please see Supplemental Table 1 for additional information summarizing participant characteristics.

2.2. Measures

Positive affect (PA) was assessed with a single-item taken from Section 14: Social Psychology and Mental Health. Respondents indicated on a four-point Likert scale (0 = never or rarely to 3 = most of the time or all of the time) the degree to which they felt happy during the past seven days. Prior research suggests that a single-item happiness measure can accurately predict mortality or longevity (Kawamoto and Doi, 2002; Steptoe and Wardle, 2011). Further, measures utilizing the ‘past week’ time frame have previously been used to assess stable reflections of affect (e.g., Ostir et al. (2000)). Higher scores on this measure indicated greater PA.

Perceived psychological stress (PPS) was assessed using Cohen and colleagues’s (1983) four-item Perceived Stress Scale that examines stressful life appraisals. Responses were noted on a five-point Likert scale (0 = never to 4 = very often) and reflected the frequency with which feelings and thoughts have occurred throughout the past month in relation to stressful situations. This questionnaire was included only in Wave IV thereby precluding analyses with this measure in earlier waves. Internal consistency reliability in this sample was acceptable (α = 0.73).

Negative affect (NA) has previously been related to PPS and inflammatory processes (Raison et al., 2006; Taylor et al., 2006) and was therefore included as a critical covariate in our analyses. To mirror the assessment of PA, NA was taken from a single-item asking respondents the degree to which they felt sad during the past seven days on a four-point Likert scale (0 = never or rarely to 3 = most of the time or all of the time). This is supported by previous work suggesting that a single-item of sadness drawn from the Center for Epidemiological Studies – Depression (CES-D) scale can accurately predict mortality among cognitively intact adults (St. John and Montgomery, 2009). Higher scores on this measure indicated greater NA. Information detailing the calculation of all other study covariates (i.e., age, body mass index [BMI], socioeconomic status [SES], tobacco use, exercise, sleep, and anti-inflammatory medications) can be found in the Supplemental Materials.

2.3. Immunological assay

Dried blood spots (DBS) were collected via finger stick immediately following the completion of study questionnaires and stored −70°C freezer until assayed at the University of Washington, Department of Laboratory Medicine (see Whitsel et al. (2012), for full assay protocol). A high-sensitivity sandwich enzyme linked immunosorbent assay (ELISA) method was used to quantify CRP (mg/L); the limit of detection was 0.035 mg/L, and intra- and inter-assay coefficients were 8.1% and 11%, respectively. For a small sub-sample (n = 87), plasma samples were also collected; DBS and plasma levels were highly correlated (r = 0.98; Whitsel et al., 2012).

2.4. Data analysis

Two hierarchical moderated regression models (unadjusted and adjusted) were used to test the hypothesis via SPSS (Version 23). Continuous covariates were transformed to z-scores and categorical covariates were weighted effect coded (Hayes and Matthes, 2009). Serum CRP levels can be as high as 1.6 times that of DBS levels (Brindle et al., 2010); therefore, to be conservative, reported analyses and data reported in the main and Supplemental Materials only include participants with CRP values < 6.25 mg/L (i.e., estimated to have < 10 mg/L in the blood as values greater than 10 mg/L can be indicative of acute infection; see Pearson et al. (2003) and McDade et al. (2006) for review). In addition, CRP data were natural log transformed before analysis to achieve a residual distribution that was approximately normal.

An interaction term was computed as the product of the z-scored PPS and PA variables. The adjusted model controlled for age, sex, race, BMI, SES, NA, anti-inflammatory medication use, and relevant health-behaviors including current tobacco use, current levels of exercise, and sleep duration (Janicki-Deverts et al., 2010; McDade et al., 2006; O’Connor et al., 2009).
3. Results

3.1. Zero-order correlations

For the primary variables of interest, PA was negatively associated with PPS ($r = -0.53$, $p < 0.001$) and NA ($r = -0.50$, $p < 0.001$). Greater PPS was linked with elevated NA ($r = 0.51$, $p < 0.001$). Neither PPS nor PA were significantly related to CRP levels; however, greater NA was associated with higher CRP levels ($r = 0.04$, $p < 0.05$).

Examination of potential confounds revealed that higher BMI, being female, and having moderate sleep levels were associated with increased CRP levels ($r = 0.39$, $p < 0.001$; $r = 0.12$, $p < 0.001$; $r = 0.04$, $p < 0.05$, respectively). As expected, more exercise and greater education were related to lower levels of CRP ($r's = -0.08$, $p's < 0.05$). Neither age, tobacco use, income, race, chronic nor acute anti-inflammatory medications were significantly linked with CRP levels. For a detailed review of all descriptive statistics and zero-order correlations, see Supplemental Table 1.

3.2. Unadjusted hierarchical regression

Neither PPS nor PA as individual predictors accounted for a significant proportion of the variance in CRP ($R^2 = 0.00$; $p > 0.10$). The inclusion of the interaction term in step two ($\beta = -0.04$, $p < 0.05$) incrementally predicted CRP ($\Delta R^2 = 0.002$, $p < 0.05$) indicating that together, PPS and PA have an interactive effect that increases the predictive validity beyond the second step. As with the unadjusted model, the pattern of findings remained the same when including participants whose CRP levels were $\geq 6.25$ mg/L. The interaction maintained significant whether or not the adjusted model included negative affect (NA) as a covariate; furthermore, the trending significant relationship between NA and CRP in step two disappeared in step three of the regression model.

The simple slopes (Fig. 1; Hayes and Matthes, 2009) demonstrate a moderating effect of PA on CRP such that individuals with higher PA experienced reduced levels of CRP when PPS was elevated (simple slope at $+1$ SD of trait PA, $\beta = -0.07$, $p < 0.05$). In contrast, there was no relationship between stress and CRP when PA was lower (simple slope at $-1$ SD of PA, $\beta = -0.01$, $p > 0.05$). Thus, Pressman and Cohen’s (2005) stress-buffering model was partially supported.

4. Discussion

This study examined associations among perceived psychological stress (PPS), positive affect (PA), and systemic inflammation (i.e., CRP). Results supported prior work (Dockray and Steptoe, 2010; Meyer et al., 2014; Pressman and Cohen, 2005) indicating that levels of PA were inversely related to levels of PPS. A direct

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Summary of moderated multiple regression analyses for variables predicting C-reactive protein levels.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1</strong></td>
<td><strong>Step 2</strong></td>
</tr>
<tr>
<td>Unadjusted (Intercept)</td>
<td>$0.24^{*}$ 0.02</td>
</tr>
<tr>
<td>PPS</td>
<td>$-0.01$ 0.02</td>
</tr>
<tr>
<td>PA</td>
<td>$-0.01$ 0.02</td>
</tr>
<tr>
<td>PPS*PA</td>
<td>$-0.04^{*}$ 0.02</td>
</tr>
<tr>
<td>Adjusted (Intercept)</td>
<td>$0.29^{*}$ 0.08</td>
</tr>
<tr>
<td>Age</td>
<td>$0.00$ 0.02</td>
</tr>
<tr>
<td>Female</td>
<td>$0.13^{*}$ 0.02</td>
</tr>
<tr>
<td>Race-White</td>
<td>$-0.01$ 0.09</td>
</tr>
<tr>
<td>Race-Black</td>
<td>$0.05$ 0.32</td>
</tr>
<tr>
<td>Education</td>
<td>$-0.05^{*}$ 0.02</td>
</tr>
<tr>
<td>Income</td>
<td>$0.04^{*}$ 0.02</td>
</tr>
<tr>
<td>BMI</td>
<td>$0.02^{*}$ 0.02</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>$0.01$ 0.02</td>
</tr>
<tr>
<td>Exercise</td>
<td>$0.06^{*}$ 0.02</td>
</tr>
<tr>
<td>Low sleep duration</td>
<td>$0.06^{*}$ 0.02</td>
</tr>
<tr>
<td>Moderate sleep duration</td>
<td>$0.01$ 0.01</td>
</tr>
<tr>
<td>Chronic anti-inflammatory use</td>
<td>$0.07^{*}$ 0.08</td>
</tr>
<tr>
<td>Acute anti-inflammatory use</td>
<td>$-0.01$ 0.03</td>
</tr>
<tr>
<td>NA</td>
<td>$0.02$ 0.02</td>
</tr>
<tr>
<td>PPS</td>
<td>$-0.04^{*}$ 0.02</td>
</tr>
<tr>
<td>PA</td>
<td>$0.01$ 0.02</td>
</tr>
<tr>
<td>PPS * PA</td>
<td>$-0.03^{*}$ 0.02</td>
</tr>
</tbody>
</table>

Note. Unadjusted $n = 3354$. Adjusted $n = 3093$. $\beta$ = standardized beta weight; S.E. = standard error; BMI = Body Mass Index; NA = Negative Affect; PA = Positive Affect; PPS = Perceived Psychological Stress. The interaction term is the product of the z-scored PPS and PA variables.

$^{*} p < 0.10$.

$^{a} p < 0.05$.$^{b} p < 0.01$.$^{c} p < 0.001$. 

$^{d} p < 0.001$. 

In step two, PPS and PA as individual predictors did not account for a significant proportion of the variance in CRP levels above and beyond control variables ($\Delta R^2 = 0.00$; $p = 0.11$). Importantly, the addition of PPS and PA allowed for a trending significant relationship between NA and CRP levels in the expected direction ($\beta = 0.04$, $p < 0.10$) that mirrored the zero-order correlation.

The inclusion of the interaction term in step three ($\beta = -0.03$, $p < 0.05$) incrementally predicted CRP levels ($\Delta R^2 = 0.001$, $p < 0.05$), indicating that together, PPS and PA have an interactive effect that increases the predictive validity beyond the second step. As with the unadjusted model, the pattern of findings remained the same when including participants whose CRP levels were $\geq 6.25$ mg/L. The interaction maintained significant whether or not the adjusted model included negative affect (NA) as a covariate; furthermore, the trending significant relationship between NA and CRP in step two disappeared in step three of the regression model.
relationship was not observed between PPS and CRP levels or PA and CRP levels. However, the inclusion of an interaction term allowed for the impact of PPS on CRP to be observed as a function of individual differences in PA, thereby partially supporting the Pressman and Cohen (2005) stress-buffering model.

Specifically, under conditions of increased PPS, higher PA buffered against elevated systemic inflammation. However, the model was only partially supported because there was no direct association between PPS and CRP for PA to buffer against. As depicted in Fig. 1, inflammation was elevated regardless of PA level when PPS was lower. Therefore, rather than a direct buffer of stress, the data suggest that under conditions of greater stress, higher PA may be better described as a protective factor against elevated inflammation.

The disordinal nature of the interaction between PPS and PA may explain the lack of a main effect for either PPS or PA on CRP levels in this sample (for detailed explanation, see Cohen et al. (2003) and Widaman et al. (2012)), highlighting that the salutary effect of PA may be contextually dependent. High-arousal PA (i.e., excitement) and low-arousal PA (i.e., contentment) can have unique effects on inflammatory processes (Dockray and Steptoe, 2010; Pressman and Cohen, 2005) and differentially impact various inflammatory biomarkers (Moreno et al., 2016). In the present study, at the lowest levels of PPS, individuals with higher PA were not protected against elevated CRP levels. Consequently, higher PA does not appear to be a globally protective factor. Rather, it is possible that the effect of PA on inflammation might only be detected within specific contexts (i.e., higher levels of PPS), adding to the complexity of how PA and stress influence health.

Additionally, our results defy the linear negative relationship often assumed between stress and health implying that individuals who report little to no stress should be the healthiest. Accumulating research challenges this assumption, demonstrating the detrimental effects of diminished stress appraisals and stress reactivity on health and chronic disease risk (Lovallo, 2011; Sagui and Levens, 2016; Sapolsky, 2015). This body of work largely suggests that an individual’s affect can be used to shift stress appraisals closer to a state in which adaptive behavior and physiological health can be attained or maintained, thereby representing an important area of future research.

Using a clinical lens, individuals with higher PA-higher PPS had an estimated 0.3–0.5 mg/L reduction in CRP levels compared to lower PA-higher PPS and lower PPS individuals, regardless of PA level. This benefit mirrors the attenuation of CRP levels due to aerobic and resistance exercise training interventions as well as changes in diet and sleep (Estruch et al., 2006; Kohut et al., 2006). Accordingly, PA may represent an additional mechanism that helps protect individuals from the health adverse impact of higher PPS. Future work should examine the clinical utility of PA interventions to improve physical health in high stress populations while considering theoretically related covariates (e.g., depression, tobacco use, sleep, exercise, etc.; Janicki-Deverts et al., 2010; McDade et al., 2006; O’Connor et al., 2009).

Results also revealed that PA and NA were differentially related to levels of CRP, thus fueling ongoing scientific discourse questioning whether PA and NA are at two ends of the same spectrum or if PA represents a separate experience from NA (see Pressman and Cohen (2005) for review). At the trend level, NA was directly related to CRP levels in step two of the adjusted regression model, while PA demonstrated a significant interactive effect with PPS to predict CRP levels in step three. Therefore, the findings suggest that PA may be a potential antecedent mechanism which allows individuals to appraise stressful situations in a way that is health-protective (Folkman and Moskowitz, 2000) above and beyond the main effects of NA. However, a more comprehensive assessment of PA and NA (i.e., assessing frequency, duration, and intensity) covering a wider breadth of positive and negative emotions is necessary to sufficiently conceptualize these affective factors as orthogonal and to distinguish the impact of PA on health outcomes beyond merely the absence of NA (Andreasson et al., 2013; Pressman and Cohen, 2005).

The lack of main effect for PA or stress on CRP levels may also highlight the uniqueness of the sample—community dwelling, young adults. Previously, direct relationships among chronic stress,
PA, and inflammation have been largely demonstrated within middle-age, elderly, or chronically-ill populations (Dockray et al., 2010; McDade et al., 2006; Roy et al., 2010; Steptoe et al., 2008). In the present study, young-adult participants were, on average, overweight and sedentary with unadjusted CRP levels indicative of intermediate CVD risk (Ridker, 2003). However, despite these less healthy characteristics, the youthfulness of the sample may have offset the confound of dysregulated immunity or other physiological systems that previous populations had due to aging or chronic disease (e.g., Ferrucci et al. (2005), Franceschi et al. (2000), McEwen (1998)). The cumulative negative allostatic changes (McEwen, 1998) are, perhaps, necessary for adequate detection of PA’s and stress’ direct effect on inflammation. Future work should continue to explore the influence of stress and affect on inflammatory processes in young adulthood, as this represents a critical developmental period for prevention and intervention efforts (Berenson et al., 1998).

Results from this study are promising and extend current empirical findings; however, this research has several limitations. First, the cross-sectional design provides results that are correlational in nature, limiting absolute conclusions about directionality of the results. PPS was not assessed in earlier waves of Add Health data collection, hence precluding the examination of prospective causality among PPS, PA and CRP. Consequently, subsequent research should consider employing a longitudinal and experimental design to test for causal links between PA and PPS in adolescence and corresponding levels of inflammation in young adulthood. Further, while CRP is a robust inflammatory marker associated with chronic illness, future work should extend these analyses to include other proinflammatory biomarkers associated with chronic illness, such as IL-6 and TNFα (e.g., McDade et al. (2006)).

Additionally, study findings demonstrated smaller effect sizes, particularly the incremental predictive validity of the interaction term. Alternative conceptualizations of traditional constructs (i.e., testing an affective construct in physical health domains) can be associated with smaller effect sizes (Cortina and Landis, 2009), and although these results should be interpreted with caution, the statistical and substantive clinical significance of the observed moderating role of PA in stress and inflammatory processes is an important contribution to the affective science and health literature.

Finally, the present study assessed affect with a single-item that asked the degree to which the respondents felt happy or sad during the past seven days. This study sought to build on existing literature supporting the use of a single item to assess PA or NA (Kawamoto and Doi, 2002; St. John and Montgomery, 2009; Steptoe and Wardle, 2011) and suggesting that individuals are generally good at identifying their emotions over the past week (Ostir et al., 2000; Watson et al., 1988). However, self-report measures of affect, especially PA, can vary widely across studies, thereby limiting the generalizability of findings (Moreno et al., 2016). In addition, the cross-sectional assessment of affect with focus on the past 7 days limits the ability to definitively conclude that results reflect experiences of trait affect.

Future studies should seek to address the complexity of the PA and NA constructs, including more time-sensitive measures of discrete and socially-oriented positive emotions (Fredrickson, 2001), level of arousal (Moreno et al., 2016; Sin et al., 2015), and separate hedonic PA versus eudaimonic PA experiences (Fredrickson et al., 2013). Moreover, as stress, affect, and inflammation can vary from day-to-day, it may also be beneficial to examine momentary, naturalistic affective processes to capture a more representative measurement of these time-dependent variables (Sin et al., 2015). Therefore, additional studies should consider utilizing experiential sampling methods or multilevel, within-subject designs to better understand the impact of affective experience on health and well-being.

In conclusion, the present study partially supports Pressman and Cohen’s (2005) stress-buffering model, suggesting that PA is stress-protective and may carry anti-inflammatory benefits for young adults experiencing higher levels of stress. Positive affect may also represent a modifiable aspect of emotional health that could protect individuals against elevated chronic inflammation. Results extend evidence regarding the complexity by which stress and PA influence physical health. Caution is directed to future assumptions that PA has a linear salutary effect on physical markers like CRP as it appears stress levels play a contextual role.

Conflict of interest statement

All authors declare that there are no conflicts of interest.

Acknowledgments

This research uses data from Add Health, a program project directed by Kathleen Mullan Harris and designed by J. Richard Udry, Peter S. Bearman, and Kathleen Mullan Harris at the University of North Carolina at Chapel Hill, and funded by grant P01-HD31921 from the Eunice Kennedy Shriver National Institute of Child Health and Human Development, with cooperative funding from 23 other federal agencies and foundations. Acknowledgement is due Ronald R. Rimduse and Barbara Entwistle for assistance in the original design. Information on how to obtain the Add Health data files is available on the Add Health website (http://www.cpc.unc.edu/addhealth). No direct support was received from grant P01-HD31921 for this analysis.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bbi.2016.07.149.

References


