Brain, Behavior, and Immunity 57 (2016) 255–262

Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Full-length Article

Towards an integrative picture of human sickness behavior

Eric C. Shattuck*, Michael P. Muehlenbein

Laboratory for Evolutionary Medicine, Department of Anthropology, University of Texas at San Antonio, San Antonio, TX, United States

ARTICLE INFO

Article history:
Received 3 March 2016
Received in revised form 22 April 2016
Accepted 6 May 2016
Available online 7 May 2016

Keywords:
Sickness behavior
Cytokines
Meta-analysis
Psychoneuroimmunology
Depression

ABSTRACT

Sickness behavior, a coordinated set of behavioral changes during infection and elicited by the pro-inflammatory cytokines tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β), is well studied in non-human animals. Over the last two decades, several papers have expanded this research to include humans. However, these studies use a variety of research designs, and typically focus on a single cytokine and only a few of the many behavioral changes constituting sickness behavior. Therefore, our understanding of human sickness behavior remains equivocal. To generate a more holistic, integrative picture of this phenomenon, a meta-analysis of the human sickness behavior literature was conducted. Full model results show that both IL-6 and IL-1β have significant relationships with sickness behavior, and the strength of these relationships is affected by a number of study parameters, such as type of immune stimulus and inclusion of controls. In addition to research design heterogeneity, other issues to address in future studies include an unequal focus on different cytokines and different sickness behaviors.

1. Introduction

Sickness behavior, a collection of behavioral changes occurring early in infection, has been well described and thoroughly researched, both experimentally and observationally, in a variety of animal species (e.g., Aubert et al., 1997; Avitsur and Yirmiya, 1999; Hetem et al., 2007; Willette et al., 2007; Ashley et al., 2009), including humans. Sickness behavior is elicited by the actions of the pro-inflammatory cytokines tumor necrosis factor-α (TNF-α) and interleukins 1β and 6 (IL-1β and IL-6) which are released as part of the acute phase response (APR; Baumann and Gauldie, 1994). Sickness behavior is comprised of lethargy, decreased appetite, reduced social behaviors and mobility, decreased libido, cognitive disturbances (e.g., changes in memory and reaction times), weight loss, hyperalgesia, and depressed affect[1] (Miller et al., 2005).

Whether subjects are humans or non-human animals, sickness behavior research utilizes a variety of methods. For methodological reasons, studies of natural infection are rare, and most researchers prefer the use of immunostimulants, namely endotoxin or poly i:c, in order to trace the development of inflammation and sickness behavior from a known point of origin. Endotoxin has also used in human sickness behavior research, as have common vaccines (e.g., Vollmer-Conna et al., 2004; Janicki-Deverts et al., 2007; Eisenberger et al., 2010). Experimental inoculation with live virus is another, extremely rare, means of eliciting sickness behavior (Janicki-Deverts et al., 2007). Studies of one or only a few sickness behavior symptoms, rather than the entire suite of behaviors, are the norm. Finally, a number of different psychometric and/or objective measurements have been used to determine the presence and severity of sickness behavior in humans.

As a consequence of varying methodologies and a relative dearth of research, we have an incomplete picture of human sickness behavior. We therefore conducted a meta-analysis in an attempt to generate a integrative picture of this phenomenon. Research questions included determining which of the three dominant research designs (natural infection, use of LPS, or use of vaccines) shows the strongest and most consistent association with sickness behavior, whether differences in study design affected results, whether any of the three pro-inflammatory cytokines discussed above (TNF-α, IL-6, and IL-1β) showed stronger associations with sickness behavior relative to the others, and if any particular cytokine is more strongly associated with individual "symptoms" of sickness behavior (e.g., lethargy, reduced social behaviors, etc.). Because cells encounter a variety of cytokines during an

---

* Corresponding author at: Laboratory for Evolutionary Medicine, Department of Anthropology, University of Texas at San Antonio, One UTSA Circle, San Antonio, TX 78249, United States.

E-mail address: eric.shattuck@utsa.edu (E.C. Shattuck).

URL: http://www.biologicalanthropology.org (E.C. Shattuck).

[1] We use the term "depressed affect" here as opposed to "depression" to distinguish the transient state of low mood induced by sickness/inflammation from pathological "depression," which could be due to a number of different causes (Halbreich, 2006).

http://dx.doi.org/10.1016/j.bbi.2016.05.002

immune response, rather than just one (Vilček, 2003), it is feasible that sickness behavior, as a whole, is driven by multiple cytokines. We also examined the role(s) of participant sex, age, and ethnicity on sickness behavior, three variables that affect immune responses (Baik et al., 2000; Carroll et al., 2010) or cytokine levels (Shattuck and Muehlenbein, 2015, Tables 2 and 3 therein) and therefore could plausibly shape sickness behavior (McLinden et al., 2012). Finally, we examined the literature for statistical evidence of publication bias (i.e., unpublished results with null results).

2. Methods

Articles included in the analysis were found by searching PubMed, Web of Science, and Medline. Because there are few articles specifically examining sickness behavior in humans, we broadened our search criteria to include studies that examined at least one sickness behavior "symptom." Keywords and search terms used were: human sickness behavior; experimental human endotoxemia and behavior; IL-6 and human behavior; IL-6 and human mood; TNF-α and human behavior; TNF-α and human mood; IL-1β and human behavior; IL-1β and human mood. The bibliographies of the studies were searched for any relevant studies not found in the database search. Non-English language studies were excluded, as were review papers. To avoid any implicit and unanticipated bias, only those studies examining the effects of cytokines on mood and behavior, rather than the effects of mood or behavior on cytokine levels, were included. To achieve this, the hypotheses and methods of each study were examined when directionality was not immediately apparent based on the title. Studies explicitly hypothesizing that mood states or behavior would affect cytokine levels were excluded, while those hypothesizing the reverse were included. If the direction of the effect was still uncertain, the methods were consulted to determine whether the researchers tested the effects of some condition (e.g., infectious or chronic disease) on cytokine levels. Of the 215 studies found in the bibliographies ($N = 59$) and databases ($N = 156$), 92 were selected for inclusion in the analysis based on the above criteria. Within those papers, a further subset of 46 papers reported Pearson's or Spearman's correlations. Because these correlational measures comprised the majority of statistical tests used, and to maintain consistency in the meta-analysis, we excluded any papers using different statistical measures. Spearman's and Pearson's correlations were transformed into Fisher's z scores for analysis. Finally, many individual papers included multiple relevant analyses (e.g., correlation between IL-6 and depressed affect as well as IL-6 and fatigue). Therefore, our dataset represents 174 analyses from 46 publications (Fig. 1; all citations can be found in the Supplementary materials). Three independent researchers extracted the data from the publications. Approximately 5% of papers yielded questions of inclusion, and these were resolved through discussion among the researchers.

Random-effects meta-analyses were conducted in R (http://www.R-project.org), using the metafor package (Viechtbauer, 2010). Random-effects models differ from fixed-effects models in that they do not assume that true effect sizes remain constant among studies. Thus, these models are more conservative and preferred in instances where high inter-study heterogeneity is expected (Borenstein et al., 2009), as was the case with the present study. Subgroup analyses were conducted for all categorical variables, and meta-regressions were conducted for continuous variables (i.e., age, percent male, and percent ethnic minority). Categorical variables were: treatment used to generate a cytokine response, sickness behavior outcome measured (e.g., depressed affect, fatigue, cognitive disturbance, etc.), and type of controls included in the study. The treatment variable categories were LPS/endotoxin, vaccination, no treatment, and a separate category that included all other "treatments" or conditions (e.g., cancer, heart failure, kidney disease, etc.). Categories for the type of controls used in the study were placebo controls and matched controls receiving no treatment.

Inter-study heterogeneity was assessed with the I^2 statistic. This statistic, based on the Q statistic, expresses the ratio of true heterogeneity to total variation in observed effects (Borenstein et al., 2009). A very low I^2 indicates that all or most of the observed variance in effect sizes is illusory, while a large I^2 suggests that there may be underlying reasons for the variance (Borenstein et al., 2009).

Finally, to address possible publication bias, funnel plots were used in conjunction with Rosenthal's fail-safe N calculation and the trim and fill method (Duvall and Tweedie, 2000). Rosenthal's fail-safe N is a computation of the number of studies, with an assumed effect size of zero, required to make the p-value nonsignificant (Borenstein et al., 2009). A small fail-safe N value might be indicative of a true effect size of zero, while a large value lends confidence to the effect size estimate (Borenstein et al., 2009). The trim and fill process imputes the number of missing studies needed to produce a symmetrical funnel plot. These missing studies are then included in the calculation of effect size, giving a theoretically unbiased estimate of effect size.

3. Results

The full model, including all three cytokines in the analysis, gave an effect size of 0.131 ($p < 0.0001$) and an I^2 of 83.83% (Table 1, Supplementary Fig. S1). Studies using LPS/endotoxin and natural infection as stimuli showed greatly increased effect sizes (0.263 and 0.401, respectively). Depressed affect and fatigue were the outcomes most strongly associated with this model ($d = 0.160$, $p < 0.0001$ and $d = 0.177$, $p < 0.001$, respectively). The use of both placebo controls and non-treatment controls in studies increases the strength of cytokine-sickness behavior associations ($d = 0.351$, $p = 0.003$ and $d = 0.201$, $p = < 0.0001$, respectively). Finally, age approaches significance ($p = 0.052$) as a moderating variable in these studies (Table 2).

3.1. IL-6 subgroup analysis

The majority of observations found a positive association between IL-6 and sickness behavior (Fig. S2). Table 3 shows the results of all subgroup analyses for studies measuring IL-6, while Table 4 shows the results of the meta-regressions. Interleukin-6 is a statistically significant ($p < 0.0001$) biomarker in human sickness behavior studies, with a relatively small (*sensu* Cohen, 1988) effect size of 0.1634. There is a high degree of heterogeneity ($I^2 = 85.87\%$) due to differences in study design or other parameters. A combination of all other treatments increases the effect size somewhat ($d = 0.1978$, $p < 0.0001$), while the use of natural infection to examine relationships between IL-6 and sickness behavior yields a greatly increased effect size ($d = 0.4198$, $p < 0.0001$). However, this last result should be interpreted with some caution, as the thirteen observations come solely from three studies.

In terms of individual aspects of sickness behavior, IL-6 shows significant relationships with depressed affect ($d = 0.1492$, $p = 0.0003$) and fatigue ($d = 0.2585$, $p = 0.001$), though a lack of relationship with other aspects of sickness behavior could be due to small sample sizes. Studies that include matched, non-treatment controls find a larger effect size than those that do not include controls ($d = 0.2352$ vs. 0.1366, respectively). Age, proportion of male participants, and proportion of non-Caucasian participants have no effects (Table 4).