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Communication of health in experimentally sick men and women: A pilot study

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ABSTRACT

The way people communicate their ill-health and the factors involved in ill-health communication remain poorly known. In the present study, we tested how men and women communicate their sickness and assessed whether sickness-related variables (i.e., body temperature, immune response, subjective sickness symptoms) predicted communicative behaviors. Twenty-two participants were filmed during experimentally induced sickness, triggered by lipopolysaccharide administration (2 ng/kg body weight), and after placebo administration, in presence of female care providers. Two trained raters scored participants' communicative behaviors (verbal complaints, moaning and sighs/deep breaths). The physiological and subjective sickness responses were similar in both sexes. Participants were more likely to moan and complain when sick, although the frequency of these behaviors remained low and no clear sex differences was observed. Nevertheless, frequency of sighs/deep breaths was increased amongst sick men but not in women. Sickness-related variables did not predict sigh/deep breath frequency. In this setting, sick men appear to display a lower threshold of expressing their malaise as compared to similarly sick women.

1. Introduction

Efficient verbal and nonverbal communication is vital for getting across one's needs, for successful social interaction (e.g., transmission of correct information, appreciation of other's feelings and intentions) and ultimately for reproduction and survival (Krauss, 2002; Stewart, 1995). Communication is of particular concern in medicine where patients need accurate treatment, symptom relief, and support. This basic premise of care is reflected in the fact that efficient doctor-patient communication leads to better health outcomes, treatment adherence, and patient satisfaction (Heisler et al., 2002; Kelley et al., 2014; Stewart, 1995). However, knowledge on how humans communicate malaise and health status is sparse.

Many sex-specific immune differences exist. Compared to men, women have stronger immune responses to immune challenges (Engler et al., 2016; Karshikoff et al., 2015; Klein et al., 2010), lower thresholds for coughing and asthma exacerbations (Johnston and Sears, 2006; Kelsall et al., 2009) and they consult primary care more often (Hyndman et al., 1994; Morice, 2002). In addition, women appear to exhibit increased mortality risk from sepsis compared to men (Nachtigall et al., 2011; Pietropaoli et al., 2010). On the other hand, males are more likely than females to harbor parasites, have shorter life expectancy, and tend to die more during epidemics (Zuk, 2009). In contrast, men and women generally respond with equal levels of subjective sickness symptoms in experimental studies of sickness (Engler et al., 2016). In both men and women, however, it is not known how either physiological or subjective responses during sickness translate to overt behavior that can serve communicative needs.

There are large individual differences in the way people cope with illness (Kesavayuth et al., 2015), and there is a common belief that men and women communicate their suffering differently when sick (Boynton, 2006; Iheanacho, 2011). In line with this notion, cross sectional findings have shown that men tend to cope less well with multiple illnesses (Kesavayuth et al., 2015) and tend to over-rate symptoms of common cold (Macintyre, 1993). Men may thus appear to over-express their malaise compared to women. Given that men and women appear to rate subjective symptoms similarly and that women exhibit stronger immune response during sickness (Engler et al., 2016; Karshikoff et al., 2015), it indicates that ill-health communication and the sickness response are multifactorial and not necessarily linearly related. On the other hand, it has also been argued that suffering men and women complain about different things rather than complaining at

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different rates (Allen et al., 2006). Importantly, there is a lack of experimental data regarding sex differences in ill-health communication. Notably, communication of sickness is multifaceted, and non-verbal factors may sometimes be more important than verbal ones (Little et al., 2015), particularly when patients do not want or are unable to verbally express complaints (O'Dowd, 2015; Pertl et al., 2014). Healthcare personnel have thus to interpret non-verbal cues of pain or discomfort, such as moaning (Kovach et al., 2000; Van den Bruel et al., 2005) or sighing (Plum et al., 2013; Teigen, 2008). Sighing and deep breaths are not only used for relaxation (Vlemincx et al., 2016) but are, just as moaning, also associated with pain and sickness malaise (Van den Bruel et al., 2005 van der Putten and Vlaskamp, 2011). Sighs and deep breaths may therefore be cues aiding healthcare personnel when judging health and malaise in patients. When assessing communication of sickness, it is therefore important to characterize both verbal communication and non-verbal communication signs.

With this background, the aims of the present study were to experimentally test how men and women express their malaise during sickness and to determine whether sickness-related variables (i.e., body temperature, respiratory rate, immune response, subjective sickness symptoms) could predict ill-health communication. To this aim, twenty-two healthy subjects were injected once with lipopolysaccharide (LPS) at a dose of 2 ng/kg body weight, which acutely activates the immune system and induces a sickness response, and once with saline (placebo). The specific hypotheses were that: 1) sickness engendered by the injection of LPS is accompanied by increased verbal and non-verbal communication about ill-health (i.e., verbal complaints, moans, sighs and deep breaths) in comparison to placebo injection; 2) men and women exhibit distinct ill-health communication, while the physiological response (i.e., increase in body temperature, respiratory rate and inflammatory cytokine concentrations) and the subjective sickness responses (i.e., self-reported sickness symptoms) are similar or stronger in women; and 3) the degree of ill-health communication is not linearly associated with the physiological and subjective sickness responses.

2. Material and methods

2.1. Participants and procedure of experimentally induced sickness using LPS administration

Twenty-two healthy volunteers, 13 males and 9 females (mean age: 23.4, age range: 19–34; see supplementary Table 1 for other baseline characteristics), were included in the study. The protocol of LPS administration is a well-acknowledged model to experimentally, safely and acutely induce sickness in participants, through the acute activation of the immune system (Schedlowski et al., 2014). After LPS injection, the subjective sickness response (including headache, nausea, fatigue) is known to surface about 1 h after the injection, with a peak around 1.5–2 h. The subjective sickness symptoms develop in parallel to the increase in cytokine concentrations and in body temperature and starts to resolve about 4 h after the injection (Lasselin et al., 2017). Several previous studies have shown large to very large effect sizes of how LPS injections affect the sickness response, often using smaller samples and lower doses of LPS (Engler et al., 2016; Karshikoff et al., 2015). The use of a relatively high dose of LPS (2 ng/kg body weight) was to assure a strong activation of the immune system and intense flu-like symptoms in the majority of subjects. To further increase power, the outcomes were measured frequently for four hours post injection. For these reasons, clinically relevant differences in ill-health communications between the LPS and placebo conditions were believed to be measurable using the current sample size. With respect to differences between men and women, a number of previous studies using lower doses (e.g. 0.6 or 0.8 ng/kg body weight) have used similar samples sizes of men and women and reported significant differences in the immune and physiological response between men and women (Engler et al., 2016; Karshikoff et al., 2015). Based on this, the sample size was deemed sufficient to explore significant differential immunological and behavioral changes in men and women after LPS administration at a dose of 2 ng/kg body weight. In all, the aim to analyze possible sex differences should be seen as exploratory since the power to correctly identify small- to mid-sized effect sizes was weak.

This study was part of a larger study aimed at assessing overt signs of sickness and predictors of sickness behavior (ClinicalTrials.gov identifier: NCT02529592), which was conducted according to ethical standards and approved by the regional ethical review board in Stockholm, Sweden (Dnr 2015/1415-32). The analysis of sex differences in health communication was a secondary goal of this larger study, and the hypotheses were defined *a priori,* before the behavioral analysis of the video recordings. The protocol of experimentally induced sickness has been described elsewhere (Lasselin et al., 2017), followed a double-blind, placebo-controlled, cross-over design, and was conducted in the Center for Clinical Research at Danderyd Hospital, Stockholm, Sweden. Briefly, subjects were included if they were healthy (no somatic or psychiatric disease), did not consume medication (contraceptive pills were allowed), were non-smokers and non-excessive alcohol consumers. Volunteers received LPS (*Escherichia coli* endotoxin O113:H10, Lot HOK354, CAT number 1235503, United States Pharmacopeia, Rockville, MD, USA) at 2.0 ng/kg body weight intravenously once and physiological saline (placebo condition) intravenously once, in a randomized order with 3–4 weeks of wash-out. A designated caregiver, either a physician or a research nurse, was present for each subject (e.g., for blood draws, caring, medical monitoring), as well as a research assistant and an additional research nurse that also interacted with the subjects across the study day. All volunteers and research staff were blinded, except the physician for safety purposes. All persons involved in this study, including the physician, were blinded to the hypotheses of the current study. All participants signed a written informed consent after a complete explanation of the study and received a remuneration of 3500 SEK (about 370 EUR/430 USD).

2.2. Sickness-related variables

Body temperature was assessed using a tympanic thermometer (Braun Thermoscan, Mexico) just before and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5 and 7 h after LPS/placebo injection. Although tympanic temperature may not exactly reflect the body core temperature (Niven et al., 2015; Yeoh et al., 2017), this was chosen for its feasibility and because it was less invasive compared to alternative methods. Respiratory rate was recorded at the same time points than body temperature, using the monitor IntelliVue X2 (Philips, Boeblingen, Germany).

Subjective sickness symptoms were assessed using the Sickness Questionnaire (SicknessQ) just before, 1.5, 3, 5 and 7 h after the injection. The SicknessQ comprises ten items that assess subjective symptoms of sickness at the moment of completion, such as "I want to be still", "I feel nauseous", "I feel tired". The total score ranges from 0 (no symptoms) to 30 (very high sickness symptoms) (Andreasson et al., 2016). Due to the relatively high dose of LPS, the SicknessQ was conducted by the caregiver, rather than self-completed, 1.5 h after the injection.

Blood samples were drawn before the injection and 1, 1.5, 2, 3, 4, 5 and 7 h after the injection in order to assess inflammatory marker concentrations. Plasma concentrations of the pro-inflammatory cytokines interleukin (IL)-6, tumor necrosis factor (TNF)-α and IL-8 were assessed using high-sensitivity multiplex (Human Mag Luminex Performance Assay, LHSCM000, LHSCM206, LHSCM208, LHSCM210, RnD Systems, MN, USA). Logarithm-transformed concentrations of IL-6 were used in the current study as an index of cytokine production, as previously described (Lasselin et al., 2017). Additional analyses with TNF-α and IL-8 are reported in the supplementary material (Supplementary Tables 2 and 3, Supplementary Fig. 1).