Short Communication

Regulation of emotions during experimental endotoxemia: A pilot study

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ABSTRACT

Even though dysfunctional emotion regulation is prominent in depression and a link between depression and inflammation is well established, there is little knowledge about how inflammation affects the regulation of emotions. The aim of this pilot study was to explore the effect of experimentally induced inflammation on the cognitive reappraisal of emotions, and to assess domain specificity by comparing success in regulation of emotions towards two unpleasant stimuli classes (general negative stimuli and disgust stimuli). In a between-subject design, ten healthy participants were injected with an intravenous injection of lipopolysaccharide (2 ng/kg body weight) and eleven were injected with saline. Participants performed a cognitive reappraisal task, in which they had to down-regulate or up-regulate their emotions towards general negative stimuli and disgust stimuli, 5–6 h post-injection. Contrary to our hypotheses, participants injected with lipopolysaccharide reported greater success in down-regulating emotional responses towards unpleasant stimuli as compared to the saline group. In addition, both groups were poorer at down-regulating emotions towards disgust stimuli as compared to general negative stimuli. The current pilot study indicates that cognitive reappraisal of emotions is affected during experimental endotoxemia, and suggests that disgust stimuli might be difficult to reappraise.

1. Introduction

The role of inflammation in the pathophysiology of depression is well-acknowledged (Capuron and Miller, 2011; Danzler et al., 2008; Khandaker et al., 2014). Experimental endotoxemia has allowed to assess the effect of inflammation on emotional processing and its underlying neuronal mechanisms (Dooley et al., 2018; Lasselin et al., 2020a; Schedlowski et al., 2014). Acute inflammation induced by experimental endotoxemia or after typhoid vaccination was found to induce negative/depressed mood (Irwin et al., 2019), and to increase the sensitivity to negative stimuli, such as punishment (Harrison et al., 2016) and social exclusion (Eisenberger et al., 2009). Furthermore, experimental endotoxemia appears to alter cognitive processing of negative information, characterized by a prolonged processing of negative emotional stimuli indicative of a negative emotional bias (Benson et al., 2017). Importantly, emotional and neuronal changes induced during experimental endotoxemia show strong overlap with those implicated in depression (Harrison, 2017; Kraynak et al., 2018; Lasselin et al., 2020a). However, although dysfunctional emotional regulation is a hallmark in depression (Erk et al., 2010; Joormann and Stanton, 2016), it has yet not been investigated how inflammation affects the ability to regulate emotions.

There are several cognitive strategies to regulate emotions. One is cognitive reappraisal, which involves changing the meaning of an emotional situation, i.e. to actively reframe stimuli or situations (Gross, 2002). For instance, a picture of a gun can be reappraised as a toy, and threatful news might be reappraised as fake news. Thus, new rules are actively applied to relations between stimuli and emotional outcomes, involving a change of higher order priors or the models of the world in the emotional domain (Petrovic and Castellanos, 2016). This strategy is particularly efficient to reduce distress and arousal triggered by emotional stimuli, and is associated with lower negative affect and higher well-being (Gross and John, 2003; Haga et al., 2009). Deficient emotion regulation ability is believed to contribute to mental health...
disorders, such as anxiety disorder and depression (Dryman and Heimbeg, 2018), and be part of top-down cognitive control dysfunction in disorders such as attention-deficit/hyperactivity disorder (ADHD) or borderline personality disorder (Petrovic and Castellanos, 2016). However, little is known about how well emotion regulation works in participants with inflammation. Since pro-inflammatory signaling targets brain circuits that are involved in the cognitive reappraisal of emotions (e.g. orbitofrontal cortex, rostral anterior cingulate cortex, amygdala) (Buhle et al., 2014; Harrison, 2017; Kraynak et al., 2018; Lasselin et al., 2020a), capacity for emotion regulation may be affected by inflammation.

Previous research has indicated some general differences in cognitive reappraisal abilities towards disgust stimuli and fear stimuli. In a study by Olatunji et al., (2017), participants watched videos of disgust stimuli or fear stimuli while using one of two top-down regulation strategies: cognitive reappraisal or a response-focused strategy of suppression (i.e. focusing on not expressing emotions with one’s body language). Results showed that disgust-related stimuli were better reappraised using the cognitive reappraisal strategy compared to emotion suppression, but that both strategies were used similarly for the fear stimuli. Importantly, disgust differs from fear in regards to both physiological and cognitive response patterns (Cisler et al., 2009). These findings suggest that cognitive reappraisal outcomes might be different across stimulus classes and be differently affected by contextual factors such as physiological state. Because both an emotional response to inflammatory activation and responding with disgust to avoid harmful microscopic stimuli represent immune defensive behaviors/protect against infection (Curtis and Biran, 2001), it is possible that inflammation affects emotional regulation differently depending on relevance of the class of stimuli that is presented.

The aim of the present study was to explore the effects of acute experimental endotoxemia induced by intravenous injection with lipopolysaccharide (LPS) on cognitive reappraisal of emotions towards general negative stimuli and disgust stimuli. We hypothesized that LPS-injected participants would be poorer at down-regulating their emotional responses and better at up-regulating their emotional responses to unpleasant stimuli, compared to participants receiving saline. Furthermore, we hypothesized that this effect would be domain specific, i.e. be more prominent for disgust-inducing stimuli compared to general negative stimuli.

2. Methods

2.1. Study participants and protocol

The present study was part of a larger study that investigated sickness behavior and the potential predictors of experimental sickness outcomes (ClinicalTrials.gov: NCT02529592), as described in (Lasselin et al., 2017, 2018). In the current study, twenty-two healthy participants randomly received either an intravenous injection of LPS (Escherichia coli endotoxin, Lot HOK354, CAT number 1235503, United States Pharmacopeia, Rockville, MD, USA) at 2.0 ng/kg of body weight, or an intravenous injection of saline (0.9% NaCl). Inclusion criteria included being 18–50 years of age, non-smoker, non-obese, no excessive alcohol consumption, no medication aside from contraceptive pills, and no physiological or psychiatric disorders. One participant in the LPS group was unable to perform the reappraisal task due to dizziness and was excluded. Thus, 10 participants receiving LPS (age: mean(SD) = 23.6 ± 3.0 years, 5 women) and 11 participants receiving saline (age: mean(SD) = 23.2(3.1) years, 3 women) were included in the present study. Further details on the protocol can be found in our previous publications (Lasselin et al., 2017, 2018, 2020b).

2.2. Inflammatory and subjective sickness responses

The inflammatory response was evaluated by measuring plasma interleukin (IL)-6 concentrations. It is known that IL-6 levels start to increase one hour post-injection and return to baseline approximately six hours post-injection (Schedlofski et al., 2014). Therefore, the measurements were taken at baseline and at 1 h, 1.5 h, 2 h, 3 h, 4 h, 5 h, and 7 h after the LPS/saline injection. Concentrations were measured with high-sensitivity multiplex (Human Mag Luminex Performance Assay, RnD Systems, MN, USA). Minimum detectable concentration was 0.28 pg/mL. Two samples (1.5 h and 2 h post-injection) from the group injected with LPS were missing due to difficulties to collect blood samples.

Sickness behavior was measured with the Sickness Questionnaire (SicknessQ), with higher scores indicating stronger sickness behavior (Andreason et al., 2016). The SicknessQ was completed at baseline and at 1.5 h, 3 h, 5 h and 7–7.5 h after the injection.

2.3. Cognitive reappraisal of emotions task

The cognitive reappraisal of emotion task (Ochsner and Gross, 2008) was performed 5–6 h after injection and contained two instructions where the participants were told to down-regulate or up-regulate their emotions when presented with unpleasant stimuli. The unpleasant pictures were of two categories, general negative stimuli (“negative stimuli”), e.g. picturing violent or sad scenes), and pictures that included a dimension of sickness or disgust, such as vomit, open wounds, or rotten food (“disgust stimuli”). Pictures were selected from the International Affective Picture Set database, the Geneva Affective Picture database, the Nencki Affective Picture database, a previous study (Hedman et al., 2016), and a personal database (Ryan et al., 2012; Schaller et al., 2010). General negative stimuli and disgust stimuli were chosen so that they had similar arousal scores and valence scores (based on the values given in the database), as well as similar proportion of faces (Table S1). Two stimuli lists were used and counterbalanced between participants. The participants rated the valence (unhappy/neutral/happy) of the stimuli 7.5 h post-injection. Two pictures in each list were excluded since they were not rated as unpleasant by 50% or more of the participants.

At inclusion, participants received an oral and written explanation of the task and were trained on at least 10 stimuli (5 for each instruction) or until they were feeling comfortable. Participants were told that an arrow would be presented before each stimulus, and that the direction of the arrow would indicate which instruction they should follow. In the case of an upward arrow, they should increase their emotional reaction to make it more unpleasant (up-regulation). By contrast, in the case of a downward arrow, they should decrease their emotional reaction to make it less unpleasant (down-regulation). Several examples of regulation strategies were given (see supplementary material) and participants were free to choose which strategy to use. The experimenter also emphasized the importance to not close their eyes, not look away, and not think about something else while watching the pictures.

The test phase consisted of two blocks, each with 26 trials with randomized order of stimuli and instructions (down-regulation/up-regulation). Participants were standing up, eyes about 70 cm from the screen, but three participants in the LPS group had to sit down during the task. Each trial consisted of a fixation time of 3–5 s, 2 s with presentation of the arrow instruction, followed by 3 s presentation of the stimulus and an unlimited response time (mean response time: LPS = 2.9 ± 1.5sec, saline = 3.0 ± 1.1sec). In each block, there were 10 negative stimuli and 16 disgust stimuli. The task lasted for approximately 13 min, including a one-minute break between blocks. For each stimulus, participants rated on a scale how well they had succeeded in following the instructions, from 1 (did not work at all) to 7 (worked very well).

2.4. Statistics

Linear mixed models were used to assess the effects of LPS administration on plasma IL-6 concentrations and SicknessQ scores. Treatment
(LPS vs. saline), time, and treatment × time were included as fixed factors, and a random slope (time) was used. Plasma IL-6 concentrations were log-transformed and SicknessQ scores were square root transformed to improve normality and homoscedasticity of residuals (see supplementary material for details on mixed linear models).

Two separate generalized estimating equations (ordinal logistic GEE) were used to test the effect of treatment (LPS vs. saline) and stimulus class (disgust vs. negative stimuli), as well as the two-way interaction (treatment × stimulus class), on ratings of emotion regulation performance (ordinal scale) for down-regulation and up-regulation of emotions. Both models included block (first/second block) and stimulus number as repeated variables, with an exchangeable working correlation structure, and list as covariate.

All analyses had a significance level set at \( p < 0.05 \) and were conducted in IBM SPSS statistics 25 independently by the first and last author. Data files and analyses scripts are available at https://osf.io/xr5u7/?view_only=0ede991b8841495bb075e9ab2f9e1c36.

3. Results

3.1. Validation of the model of experimental endotoxemia

IL-6 concentrations and sickness behavior increased in the LPS group as compared to the saline group (Table S2-S3, Figure S1), also when carrying out the reappraisal task, (IL-6: LPS: 86.26 pg/mL, saline: 2.96 pg/mL, \( b(\text{SE}) = 1.25(0.17), p = 0.000; \) SicknessQ: LPS: 10.5, saline: 4.64, \( b(\text{SE}) = 1.81(0.42), p = 0.000 \)) (Figure S1).

3.2. Effect of experimental endotoxemia on cognitive reappraisal of emotions

The LPS group reported being more successful in down-regulating their emotional response towards unpleasant stimuli in general as compared to the saline group (Table 1, Fig. 1a). Furthermore, participants reported being worse at down-regulating emotions towards disgust stimuli as compared to general negative stimuli (Table 1, Fig. 1a). No significant interaction between LPS administration and the stimulus class was found in the down-regulation part (Table 1). No significant effect of LPS administration (vs. saline) or the stimulus class (disgust vs. negative) was found in the up-regulation part of the task (Table 1; Fig. 1b).

Table 1: Effect of LPS administration (vs. saline) on the cognitive reappraisal of emotions task

| Independent variables       | Down-regulation | Up-regulation |
|----------------------------|-----------------|---------------|
|                            | \( b(\text{SE}) \) | \( \text{R(\text{SE})} \) | \( p \) | \( b(\text{SE}) \) | \( \text{R(\text{SE})} \) | \( p \) |
| Stimulus class             |                 |               |       |                 |               |       |
| Disgust stimuli (vs. negative stimuli) | -0.617 (0.197) | 0.002 | 0.376 | 0.083 |
| Treatment                 |                 |               |       |                 |               |       |
| LPS administration (vs. saline) | 0.746 (0.207) | 0.015 | 0.437 | 0.392 |
| Treatment × stimulus class |                 |               |       |                 |               |       |
| LPS administration × disgust stimuli | -0.353 (0.259) | 0.172 | 0.012 | 0.971 |
| Repeated variables         |                 |               |       |                 |               |       |
| Stimulus number            | 0.011 (0.011)   | 0.315 | -0.009 | 0.381 |
| Block                      | -0.251 (0.219)  | 0.253 | 0.107 | 0.428 |
| Covariate                  |                 |               |       |                 |               |       |
| List                       | -0.533 (0.230)  | 0.021 | -0.415 | 0.290 |

Ordinal logistic generalized estimating equation (GEE) models with exchangeable working correlation structures. For both models, the dependent variable was the rating on success in following instructions, a higher score indicating better success. B coefficients represent the changes in log odds of being in a higher step of the scale “success in down-regulating/up-regulating”. Abbreviations: LPS: lipopolysaccharide.

4. Discussion

This pilot study assessed how experimental endotoxemia modulated the cognitive reappraisal of emotional responses to negative and disgust-related images. Because inflammation appears to induce an emotional negative bias, we hypothesized that it would be more difficult to down-regulate emotions towards unpleasant stimuli during experimental endotoxemia. Our findings are contrary to this hypothesis, and instead show that down-regulation of emotions in response to both negative and disgust stimuli was easier for participants who were acutely sick (LPS injection) than for healthy participants (saline injection). Although the effect is rather small (change of \( \approx 10\% \)), the association between cognitive reappraisal and depression has also been found to be small (\( r = 0.17 \) in a meta-analysis of 114 studies, Aldao et al., 2010). The fact that inflammatory activation can increase the sensitivity to negative stimuli such as punishment (Harrison et al., 2016) might be one explanation of the current results, as inflammation could lead to an increased motivation to avoid negative feelings. Alternatively, it is possible that
sick participants refocus their attention from external stimuli towards signals from their own body, as suggested by an inflammation-induced activation of brain processes involved in interoception (Harrison et al., 2009; Lekander et al., 2016). Although the effect of inflammation on emotion regulation capacities in this study was in discrepancy with what is observed during depression, it may suggest that inflammation does affect the cognitive reappraisal of emotions. Further studies will need to disentangle the effects of acute vs. chronic inflammation on this process to provide more information on the role of inflammation in emotion regulation in inflammation-associated depression.

Given that disgust stimuli also can represent an infectious threat, we hypothesized that it would be more difficult for sick participants to down-regulate their emotions in response to disgust stimuli compared to general negative stimuli. Participants were indeed worse at down-regulating emotions when facing pictures of disgusting content (e.g. vomit, open wounds, or rotten food) compared to “typical” negative pictures (e.g. pictures depicting violent or sad scenes), however similarly in both treatment groups. The general difficulty in down-regulating emotions towards disgust relevant stimuli is in line with early work arguing for disgust as cognitively impenetrable (Rozin and Fallon, 1987) and more recent studies indicating that disgust is more resistant to extinction compared to fear (Olatunji et al., 2007; Smits et al., 2002). Moreover, the study took part in a hospital environment, which might have primed the participants, rendering down-regulation of emotions more difficult towards the category of stimuli linked to the context (Fujimura et al., 2013).

This study being a pilot study, a major limitation is the limited sample size, and the current results need to be replicated. However, the endotoxin stimulus induces strong behavioral effects that are easily detectable between groups, and it is not uncommon to use similar group sizes (i.e. about 10 per group) to assess endotoxin-induced behavioral changes (e.g. DellaGioia et al., 2013; Engler et al., 2017; Hannestad et al., 2011; Kox et al., 2014). Therefore, even with a limited statistical power, our findings indicate that our hypothesis that experimental endotoxemia would inhibit down-regulation of emotions and would favor up-regulation of emotions towards unpleasant stimuli is not supported, as the results instead point in the opposite direction. We hope that this finding can be valuable for the direction of future studies. Another limitation is the fact that participants only rated their success in following the instructions, but not their actual feelings (valence) while watching the images. Importantly, however, the level of valence and arousal induced by the two types of stimuli appeared similar, as indicated by the ratings obtained at the end of the study day, although the valence was not very high (65%). Furthermore, information regarding which strategy the participants used was only measured after the training session, but not after the actual task. A protocol with frequent questions during the task could have provided further clues about successful reappraisal strategies used by people. Finally, because of logistic reasons, the task was performed relatively late during the study day, and different findings might be found during the peak of the inflammatory response.

In conclusion, the current pilot study indicates that experimental endotoxemia increased success in down-regulation of emotions towards unpleasant stimuli, and an overall higher success in down-regulating emotions when encountering general negative stimuli compared to disgust stimuli.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2021.01.013.

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