Experimental human endotoxemia enhances brain activity during social cognition

Jennifer S. Kullmann,1,2 Jan-Sebastian Grigoleit,1 Oliver T. Wolf,3 Harald Engler,1 Reiner Oberbeck,4 Sigrid Eisenbruch,1 Michael Forsting,2 Manfred Schedlowski,1 and Elke R. Gizewski2,5
1Institute of Medical Psychology and Behavioral Immunobiology, University Hospital Essen, University of Duisburg-Essen, 45122 Essen, Germany, 2Institute of Diagnostic and Interventional Radiology and Neuroradiology, University Hospital Essen, 45122 Essen, Germany, 3Department of Cognitive Psychology, Ruhr University Bochum, 44780 Bochum, Germany, 4Department of Trauma Surgery, University Hospital Essen, 45122 Essen, Germany, and 5University Hospital of Neuroradiology, Innsbruck Medical University, 6020 Innsbruck, Austria

Acute peripheral inflammation with corresponding increases in peripheral cytokines affects neuropsychological functions and induces depression-like symptoms. However, possible effects of increased immune responses on social cognition remain unknown. Therefore, this study investigated the effects of experimentally induced acute inflammation on performance and neural responses during a social cognition task assessing Theory of Mind (ToM) ability. In this double-blind randomized crossover functional magnetic resonance imaging study, 18 healthy right-handed male volunteers received an injection of bacterial lipopolysaccharide (LPS; 0.4 ng/kg) or saline, respectively. Plasma levels of pro- and anti-inflammatory cytokines as well as mood ratings were analyzed together with brain activation during a validated ToM task (i.e. Reading the Mind in the Eyes Test). LPS administration induced pronounced transient increases in pro- (IL-6, TNF-α) and anti-inflammatory (IL-10, IL-1ra) cytokines as well as decreases in mood. Social cognition performance was not affected by acute inflammation. However, altered neural activity was observed during the ToM task after LPS administration, reflected by increased responses in the fusiform gyrus, temporo-parietal junction, superior temporal gyrus and precuneus. The increased task-related neural responses in the LPS condition may reflect a compensatory strategy or a greater social cognitive processing as a function of sickness.

Keywords: peripheral inflammation; social cognition; fMRI; cytokines; endotoxin

INTRODUCTION

Theory of Mind (ToM), a higher-order form of social cognition, comprises the ability to impute mental states of others such as thoughts, intentions, desires and beliefs (Premack and Woodruff, 1978). Owing to the fact that primates, including humans, live in hierarchically organized social groups, ToM ability is essential for the interaction in close relationships and communities to ensure support from others in different aspects of life (Brune, 2001). This capability for social cognition is demonstrably disturbed in patients with neuropsychiatric diseases such as depression and schizophrenia (Frith and Corcoran, 1996; Doody et al., 1998; Kerr et al., 2003; Inoue et al., 2004; Wang et al., 2008). Social processing including ToM ability is known to be mediated by several brain regions, including the prefrontal, medial prefrontal and temporal cortical areas (Mar, 2011). However, the neural mechanisms mediating deficits in social cognition including ToM ability remain incompletely understood.

Alterations in pro-inflammatory peripheral cytokines have been shown to affect neuropsychological functions and are discussed to play a role in the pathophysiology of neuropsychiatric diseases such as schizophrenia (Meyer et al., 2009; Drexhage et al., 2010) or depression (Raison et al., 2006; Irwin and Miller, 2007; Miller et al., 2009). However, the putative link between peripheral immune activation and ToM ability has thus far not been investigated. Vaccination or administration of endotoxin (lipopolysaccharide, LPS), a complex glycolipid found in the outer membrane of gram-negative bacteria, has recently been used in humans as an experimental model to analyze the effects of acute immune activation on neuropsychological functions and brain activity (Brydon et al., 2008; Eisenberger et al., 2009; Harrison et al., 2009a,b; Eisenberger et al., 2010a; van den Boogaard et al., 2010; Kullmann et al., 2013). Intravenous injection of LPS induces a complex psycho-physiological response including the transient release of pro-inflammatory cytokines such as interleukin (IL)-6 and tumor necrosis factor (TNF)-α (Bahador and Cross, 2007) as well as a range of behavioral symptoms including depressed mood, social withdrawal, cognitive impairment, malaise and fatigue, collectively termed ‘sickness behavior’ (Reichenberg et al., 2001; Wright et al., 2005; Dantzer and Kelley, 2007). Whereas a number of studies in rodents observed social withdrawal and a reduction of exploratory behavior during acute inflammation (Larson and Dunn, 2001; Dantzer et al., 2008), social aspects of behavior in humans remain incompletely understood (Eisenberger et al., 2009; Eisenberger et al., 2010b). Furthermore, a study in rhesus monkeys even observed an increase in social interaction during acute inflammation (Willette et al., 2007). Data from experimental animal and human studies suggest that, in particular, pro-inflammatory peripheral cytokines (e.g. IL-1β, IL-6 and TNF-α) play a crucial role in mediating these symptoms by directly or indirectly communicating the peripheral inflammation to the brain (Konsman et al., 2002; Capuron and Miller, 2004; Dantzer, 2006; Ader, 2007).

We have previously shown that activation of right inferior orbitofrontal cortex was significantly increased in response to emotional stimuli during experimental endotoxemia, reflecting enhanced cognitive regulation of emotions as an adaptive response during an acute inflammation (Kullmann et al., 2013). However, effects of acute peripheral inflammation on social cognition, including ToM ability, remain unexplored. Therefore, in an extension of our previous reports, the present study analyzed the effects of endotoxin-induced inflammatory responses on mood and brain activity during a social cognition task (Reading the Mind in the Eyes Test), encompassing ToM mechanisms. We performed a double-blind randomized crossover study...
functional magnetic resonance imaging (fMRI) study with healthy right-handed male volunteers who received an injection of LPS (0.4 ng/kg *Escherichia coli*) or saline to test the hypothesis that acute inflammation-induced alterations in ToM ability are mediated by activity changes in specific brain regions of interest (ROIs) known to mediate ToM ability, including medial prefrontal cortices, fusiform gyri, precuneus and temporal cortical areas (Baron-Cohen et al., 1999; Saxe et al., 2004; Mar, 2011).

**METHODS AND MATERIALS**

**Subjects**

Eighteen healthy right-handed male volunteers (mean age: 26.4 ± 3.1 years, mean body mass index: 25.2 ± 0.2) were recruited by public advertisement (i.e. flyers posted at the University Hospital Essen; Internet-posted advertisements), as previously reported (Kullmann et al., 2013). The majority were medical students (88%, n = 17), all were unmarried and rated their overall health as either good or very good. Mean trait anxiety scores were well within the normal range (32.6 ± 1.0) compared with published normative data (Laux, 1981).

**Screening process**

The in-depth screening process consisted of a physical examination; a personal semi-structured interview, performed by an experienced clinical psychologist; completion of standardized questionnaires and repeated laboratory analyses of blood samples (i.e. complete blood cell count, liver enzymes, renal parameters, electrolytes, coagulation factors and C-reactive protein) before and up to 1 week after completion of the study (see later in the text). Exclusion criteria included age <18 or >40 years; body mass index <17 and >30; any concurrent medical condition, including neurological, psychiatric, cardiovascular, immunological and endocrine conditions; any abnormality of blood laboratory analyses; any evidence of structural brain abnormality on structural magnetic resonance imaging (MRI) scan; MRI-specific exclusion criteria (i.e. phobic anxiety, claustrophobia or ferromagnetic implantations); history of allergies; current use of prescription and non-prescription medications; smoking and regular high alcohol use (>4 drinks per week).

Additional safety measures included a physical examination and normal blood cell counts 6 h post-injection as a pre-condition for subjects being allowed to leave the laboratory. Further, participants were not allowed to drive a vehicle on the days of the study, and underwent follow-up examinations including laboratory analysis of C-reactive protein levels 24 h after each session and 7 days after the final session. Subjects were informed about the study design and were only enrolled after written informed consent had been obtained. The study was conducted in accordance with the declaration of Helsinki and approved by the local ethics committee. Subjects were paid for their participation.

**Study design**

The study used a balanced, randomized, double-blind crossover design, which has previously been described in detail (Kullmann et al., 2013). It consisted of two identical study sessions (at least 7 days apart) during which blood samples and mood ratings were obtained at multiple time points. Subjects received either an intravenous injection of LPS (0.4 ng/kg of body weight) or an identical volume of endotoxin-free normal saline (placebo). We decide to choose a lower dose of LPS (0.4 ng/kg) in this study to avoid the typical more pronounced side effects of the higher LPS dose (0.8 ng/kg) (e.g. nausea, shivering and fever) because this would complicate the interpretation of the data. As previously shown in a dose-dependent comparison (Grigoleit et al., 2011), 0.4 ng/kg of LPS induced pronounced and significant changes in peripheral immune markers, which we believe are sufficiently pronounced to constitute a valid model of sickness behavior. Two hours post-injection, when pro-inflammatory cytokines have been shown to peak after LPS application (Reichenberg et al., 2001; Eisenberger et al., 2010b; Grigoleit et al., 2010; Benson et al., 2012), participants underwent structural MRI scanning followed by two fMRI sessions, consisting first of an emotional processing task (reported elsewhere, Kullmann et al., 2013) and second a social cognition task (Reading the Mind in the Eyes Test). Blood samples were drawn 0.25 h before and 1, 1.75, 3, 4, 6 and 24 h post-injection together with assessments of vital signs (blood pressure, pulse and temperature). Participants also completed mood questionnaires at baseline (−0.25 h) and twice post-injection (3, 6 h).

**fMRI paradigm**

During stimulation, subjects were asked to lie relaxed inside the scanner and try to focus on the presented stimuli. The stimuli were presented visually by a notebook computer running the presentation software package (Neurobehavioral Systems, Davis, CA). The timing of the stimuli was controlled by the timing of the acquisition of magnetic resonance (MR) images, through pulses sent from the MR scanner to the parallel port of the stimulus presentation PC. All stimuli were presented using a screen inside the scanner room and video projection from outside. A mirror was fixed to the head coil to place the screen in the subject’s field of view.

As reported elsewhere (Kullmann et al., 2013), subjects underwent an emotional processing task during which subjects focused on alternating neutral and emotionally evocative visual stimuli drawn from the International Affective Picture System (Lang, 1997). Two different sets of 36 emotional pictures with aversive contents, such as facial mutilation, wounds and dead bodies, and 36 neutral pictures, such as furniture and appliances, which did not elicit strong emotions, were selected. Both sets were comparable with respect to the dimensions valence, arousal and dominance. To avoid any nonrandom version-dependent bias, the stimuli were presented in random order in each block for each subject. A total of six off blocks (each six neutral stimuli) and six on blocks (each six emotional stimuli) were presented. Each picture appeared for 5 s. Thus, each block lasted 30 s.

To assess social cognition performance, including ToM abilities, during the scanning session, we used the German adaptation of the Reading the Mind in the Eyes Test (‘Eyes’ test) (Bölte, 2005), which is based on the original English version devised by Baron-Cohen et al. (2001). In this task, subjects were asked to judge from the expression of another person’s eyes what that other person might be thinking or feeling, e.g. eyes could express panic, grief or desire (Figure 1A).

The test started with a task instruction and two training items. Two different sets of 36 photographed eyes were subsequently presented in...
randomized order in each block. A total of six off blocks and six on blocks were presented in an alternating ABA... design. Each block lasted 30 s and consisted of three consecutive slides with photographs of persons’ eyes. During the control (off) block, subjects were asked to indicate whether each stimulus was a man or a woman (gender judgment). During the on block, subjects were asked to decide which of four simultaneously presented words best described the mental state of the photographed person (ToM judgment). Correct words were counterbalanced to each presentation position. Subjects were briefed to the photographed person (ToM judgment). Correct words were counted and ‘treatment condition’ (LPS, placebo). All regressors were obtained by convolving a box-car function of the event duration with the canonical hemodynamic response function implemented in SPM. Specific effects were tested with appropriate linear contrasts of the parameter estimates for the different regressors resulting in a t-statistic for each voxel. After model estimation, the ensuing first-level contrast images (LPS_toM > placebo_toM > placebo_gender) from each subject were used for second-level analysis, treating individual subjects as a random factor and including nonsphericity correction. Two separate analyses were conducted on the second (group) level: (i) as an initial step, we performed a one-sample t-test on data from the placebo condition to confirm activation in ROIs during the ToM task (ToM > gender). (ii) To directly compare ToM task-induced brain activation in the LPS condition and the placebo condition, paired t-tests were computed (LPS_toM > placebo, placebo_toM > gender > LPS_toM > gender). (iii) To clarify if changes in state anxiety or alertness contribute to (or mediate) changes in activation in ROIs, peak state anxiety scores as well as alertness scores were included as covariates of no interest in the paired t-test within the LPS condition.

Small volume correction (SVC) with family-wise error (FWE) correction for multiple comparisons in specific ROIs at a level of P < 0.05 was performed. ROIs were chosen based on a meta-analysis of neuroimaging findings during non-story-based ToM studies (Mar, 2011), comprising the fMRI results during the ‘Eyes’ test by Baron-Cohen et al. (1999). ROIs included bilateral dorsomedial as well as medial prefrontal cortices (BA8/9 and BA10), superior temporal gyri, temporal-parietal junctions, precuneus and fusiform gyri. SVC was performed with templates constructed from the automated anatomical labelling toolbox in SPM (Tzourio-Mazoyer et al., 2002). All results are reported at P < 0.05 corrected for multiple comparisons, unless indicated otherwise. We additionally performed exploratory whole-brain analyses using a more liberal threshold of P < 0.001 (uncorrected), which are given in table legends. All results are given as Montreal Neurological Institute coordinates.

Questionnaires
Mood was assessed with a validated German questionnaire (‘Mehrdimensionaler Befindlichkeitsfragebogen’, MDBF), designed to estimate state emotions (Steyer et al., 1997). The MDBF has 12 items and three subscales quantifying current mood, alertness and calmness, similar to the Profile of Mood States (McNair et al., 1971). In addition, trait and state anxiety was assessed with the State-Trait-Anxiety Inventory (state version: STAI-S; trait version: STAI-T) (Laux, 1981). STAI-T was recorded during screening process. MDBF and STAI-S were assessed at baseline (~0.25 h) and after administration of LPS and saline (3, 6 h) outside the scanner.

Blood cell counts and cytokine analyses
Total leukocyte numbers and a three-part white blood cell differential count were measured in ethylenediaminetetraacetic acid-treated blood samples using an automated hematology analyzer (KK-21N, Sysmex Deutschland GmbH, Norderstedt, Germany). Plasma for the measurement of cytokine levels was separated by centrifugation and stored at −80 °C until analysis. Concentrations of plasma cytokines were analyzed using multiplexed bead-based assays (Bio-Plex Cytokine Assays, Bio-Rad Laboratories GmbH, Munich, Germany), an increasingly used technique alternative to the common sandwich enzyme-linked immunosorbent assay, which is based on the same principle of measurement but more suitable for screening of high numbers of samples with a wide concentration range (Khan et al., 2004; Elshal and McCoy, 2006; Ng et al., 2010). Briefly, plasma dilutions were incubated in duplicates
with fluorescence-labelled beads that are coupled to monoclonal antibodies against human IL-6, IL-10, TNF-α and IL-1ra. On incubation with the detection antibodies against these cytokines, samples were incubated with streptavidin-PE (Beckton Dickinson, Heidelberg, Germany). At least 100 beads per sample were analyzed on a flow cytometer (FACSCanto II, Beckton Dickinson, Heidelberg, Germany). We have validated this technique in-house with commercially available high-sensitive enzyme-linked immunosorbent assay kits (R&D systems, Minneapolis, USA) and observed high linear correlations \((r > 0.9; P < 0.001)\) between both methods. Absolute cytokine levels were calculated based on the mean fluorescence intensity of cytokine standard dilutions using a four-parameter logistic model (GraphPad Prism 5, La Jolla, CA, USA). Detection limits of the assays were 0.2 pg/ml (IL-6), 0.4 pg/ml (IL-10), 3 pg/ml (TNF-α) and 39.9 pg/ml (IL-1ra).

### Statistical analysis (non-fMRI data)

Statistical analyses were performed using a standard statistical software program (SPSS 17; Inc., Chicago, IL). Absolute changes in immunological, physiological and psychological variables after endotoxin or placebo administration were evaluated by an analysis of variance for repeated measures designs. Only significant interactions (time × treatment) are presented, unless stated otherwise, and these were followed by paired t-tests comparing endotoxin vs saline at specific time points. The social cognition (ToM) performance assessed with the ‘Eyes’ test was calculated using a paired t-test. The alpha level was set at 0.05. All data are presented as mean and standard error of the mean (SEM), unless indicated otherwise.

## RESULTS

### Immunological, physiological and mood responses

Endotoxin administration induced a pronounced inflammatory response reflected by transient increases in pro- and anti-inflammatory cytokines, circulating neutrophils and body temperature (Table 1) (Kullmann et al., 2013). Plasma concentrations of the pro-inflammatory cytokines IL-6 (\(F = 30.7, P < 0.001\)) and TNF-α (\(F = 13.62, P < 0.001\)) significantly increased after LPS administration compared with saline. These concentrations are similar to previously reported studies (Reichenberg et al., 2001; Eisenberger et al., 2010b) using 0.8 ng/kg endotoxin. In addition, LPS injection resulted in significantly elevated plasma levels of the anti-inflammatory cytokine IL-10 (\(F = 25.65, P < 0.001\)) and the soluble IL-1 receptor antagonist IL-1ra (\(F = 21.01, P < 0.001\)).

### Neural responses during the social cognition (ToM) task

To confirm previous neuroimaging findings with regard to brain areas activated during non-story-based ToM tasks including the ‘Eyes’ test (Mar, 2011), we initially conducted a one-sample t-test within the placebo condition. As expected, the ToM > gender contrast activated the following ROIs: right and left dorsomedial prefrontal cortices (BA8/9), left fusiform gyrus, right and left superior temporal gyrus (BA38/23/39/42) as well as the right tempo-parietal junction (BA22) and left precuneus (BA7) \((P < 0.05 \text{ based on ROI analysis using SVE with FWE correction; Table 2})\). Medial prefrontal cortex (BA10) revealed no significant activation. Exploratory whole-brain analysis revealed greater activation of the right cingulate gyrus (BA32), right insula, left postcentral gyrus (BA2), left lingual gyrus (BA18), right and left inferior frontal gyrus (BA46), right and left middle frontal gyrus (BA6), right and left middle temporal gyrus and right inferior occipital gyrus for ToM > gender during placebo condition \((P < 0.001, \text{ uncorrected; Table 2})\).

The LPS condition was also characterized by a rapid and profound increase in the number of circulating neutrophils, peaking 3 h post-injection \((F = 90.55, P < 0.001)\), and by a slight but significant increase in body temperature, with a maximum of 37.7 ± 0.08°C \((vs\ 36.8 ± 0.07°C \text{ in the saline condition)}\) at 3 h post-injection \((F = 16, P < 0.001)\).

LPS application significantly affected mood 3 h post-injection; examination of the MDBF subscales showed impaired mood \((F = 8.11, P < 0.01)\), alertness \((F = 3.77, P < 0.05)\) and calmness \((F = 9.56, P < 0.01)\) and increased state-anxiety 3 h after LPS administration \((F = 4.73, P < 0.05)\) (Table 1).

### Social cognition (ToM) performance

To test whether and to what extent LPS-induced immune activation would affect social cognition (ToM) performance, subjects performed the ‘Eyes’ test. Analysis revealed no significant differences between the LPS and saline conditions in the number of correct responses during ToM judgment (Figure 1B) as well as during control gender judgment \((\text{LPS}_{\text{ToM}}: 11.47 ± 0.51 \text{ vs saline}_{\text{ToM}}: 11.18 ± 0.61; LPS}_{\text{gender}}: 16.35 ± 0.31 \text{ vs saline}_{\text{gender}}: 16.71 ± 0.38; \text{mean correct responses} \pm \text{SEM})\).
(P < 0.05 based on ROI analysis using SVC with FWE correction, Figure 2, Table 3), regions known to be involved in the ability to understand the mental states of others. ROI analysis for medial prefrontal cortices did not reveal any significant activation. Moreover, exploratory whole-brain analysis revealed greater activation of the right lingual gyrus, right insula, right parahippocampal gyrus (BA27), left cingulate gyrus (BA24), left cingulate gyrus (BA24), right medial prefrontal cortex (BA10), right and left middle temporal gyri (BA19/39) and right superior temporal gyrus (BA41), right claustrum, right and left pre- and postcentral gyri (BA6, BA3/7), right inferior parietal lobe, right middle occipital gyrus and right and left cunei (BA18/30) in the LPS-toM-gender > placebo-toM-gender contrast (P < 0.001, uncorrected; Table 3). The placebo-toM-gender > LPS-toM-gender contrast within the ROIs and whole-brain analysis revealed no significant activations.

Changes in state anxiety did not affect brain activity in ROIs, including left fusiform gyrus ([-34, -24, -26], t = 5.37, P < 0.05), right superior temporal gyrus (60, -6, 2), t = 5.63, P < 0.05) and right precuneus (44, -80, 34), t = 6.58, P < 0.05), except for the right temporo-parietal junction (54, -44, 22), t = 4.67, P > 0.05) (all based on ROI analysis using SVC with FWE correction). Further analysis revealed that changes in alertness did not affect activation of left fusiform gyrus ([-34, -26, -26], t = 5.91, P < 0.05) and right superior temporal gyrus (60, -6, 2), t = 4.87, P < 0.05), whereas right precuneus (44, -80, 34), t = 5.14, P > 0.05) and right temporo-parietal junction (54, -44, 22), t = 4.29, P > 0.05) were affected by changes in alertness (all based on ROI analysis using SVC with FWE correction).

### DISCUSSION

To analyze the effects of acute endotoxin-induced peripheral inflammation on social cognition (ToM) task performance and corresponding neural responses, healthy male subjects received an injection of endotoxin (LPS, E. coli) or saline in a balanced, randomized, double-blind crossover design. LPS administration expectedly induced a transient systemic inflammation along with mood impairment, consistent with previous findings (Reichenberg et al., 2009). The behavioral analysis revealed that the inflammatory response had no discernable effect on ToM task performance, indicating that the ability to infer others’ states of mind and to predict how others feel, think and behave is not impaired during an acute inflammatory response in healthy male subjects. However, in the LPS condition, BOLD responses in regions mediating ToM ability (i.e. superior temporal gyrus, temporo-parietal junction) were significantly enhanced. This could be indicative either of a centrally mediated compensatory strategy or of enhanced social cognitive processing as a function of sickness, consistent with previous evidence (Eisenberger et al., 2009).

From an evolutionary viewpoint, our finding that ToM task performance was not affected during an inflammatory response makes sense. The ability to reliably and consistently perceive complex social
information expressed through the eyes of others facilitates the identifi-
cation of potential danger on the one hand and ensures adequate
social communication and prediction of others' behaviors on the other
hand. In fact, one could have also expected increased ToM ability
during low levels of sickness. Either way, the interpretation of our
negative finding with regard to ToM task performance remains specu-
lative. Alternative explanations, including suboptimal sensitivity of the
' Eyes' test, should also be considered, and future studies may consider
the need to find more sensitive methods to assess different aspects of
social cognition performance during endotoxia.

In contrast to the behavioral results, analysis of BOLD responses
with respect to ToM task-related neural activation within specific
ROIs revealed several significant differences between LPS and placebo.
ToM task-related neural activation was significantly enhanced in the
LPS condition in left fusiform gyrus, right temporo-parietal junction,
right superior temporal gyrus and right precuneus, as well as (albeit at
a more liberal statistical threshold) medial prefrontal cortex (BA10).
These effects are interesting, given previous evidence that the superior
temporal gyrus and temporo-parietal junction mediate ToM ability
(Abu-Akel, 2003; Saxe and Kanwisher, 2003; Carrington and Bailey,
2009; Mar, 2011). Especially the superior temporal gyrus is reportedly
involved in 'mentalizing', a concept to describe the understanding of
others' mental states (Frith and Frith, 2003, 1999). In addition, the
fusiform gyrus is relevant for the processing of facial information
related to the social significance of direct gaze (George and Conty,
2008), and the precuneus reportedly mediates imagination processes
required to infer the mental states of others (Mar, 2011). In the absence
of LPS effects on ToM task performance, the enhanced BOLD response in
ToM-relevant brain regions may reflect an enhanced processing effort
during the social cognition (ToM) task, which may constitute a
compensatory strategy of the central nervous system (CNS) to main-
tain normal social cognition performance during states of inflamma-

<table>
<thead>
<tr>
<th>Brain regions</th>
<th>MNI coordinates for LPS_{ToM &gt; gender} &gt; placebo_{ToM &gt; gender} condition</th>
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<tbody>
<tr>
<td>Fusiform gyrus</td>
<td>L −34 −24 −26  5.47*</td>
</tr>
<tr>
<td>Lingual gyrus</td>
<td>R  12 −84  0  3.78</td>
</tr>
<tr>
<td>Insula</td>
<td>R  40 −4 −6  4.45</td>
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<tr>
<td>Parahippocampal gyrus</td>
<td>R  24 −34 −4  27 4.22</td>
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<tr>
<td>Cingulate gyrus</td>
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<tr>
<td>Medial prefrontal cortex</td>
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<tr>
<td>Superior frontal gyrus</td>
<td>R  30 40 38  3.90</td>
</tr>
<tr>
<td>Middle temporal gyrus</td>
<td>R  44 −84 20 19  4.62</td>
</tr>
<tr>
<td>Middle temporal gyrus</td>
<td>L −46 −84 20 39  3.82</td>
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<tr>
<td>Temporo-parietal junction</td>
<td>R  54 22  5.26*</td>
</tr>
<tr>
<td>Superior temporal gyrus</td>
<td>R  60 −6 2 22  5.18*</td>
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<tr>
<td>Superior temporal gyrus</td>
<td>R  52 −6 4  4.51</td>
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<tr>
<td>Superior temporal gyrus</td>
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<tr>
<td>Claustrum</td>
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<td>Precentral gyrus</td>
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<tr>
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<tr>
<td>Postcentral gyrus</td>
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<td>Postcentral gyrus</td>
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<tr>
<td>Inferior parietal lobule</td>
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<tr>
<td>Middle occipital gyrus</td>
<td>R  42 −82 32 19  6.62</td>
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<tr>
<td>Precuneus</td>
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<tr>
<td>Cuneus</td>
<td>L −2 −82 16 18  3.78</td>
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<tr>
<td>Cuneus</td>
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<tr>
<td>Cuneus</td>
<td>L −10 −78 20 18  3.76</td>
</tr>
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H, hemisphere with activation; R, right asymmetrical activation; L, left asymmetrical activation; BA, Brodmann areas.

Paired t-test for LPS_{ToM > gender} > placebo_{ToM > gender} (n = 18). The opposite contrast revealed no significant activations. All P < 0.05 based on ROI analysis using SVC with FWE correction (*) or whole-brain statistics at P < 0.001 uncorrected.

Hence, despite our previous evidence that neuropsychiatric patients demon-
strate impaired ToM task performance (Frith and Corcoran, 1996; Kerr et al., 2003; Inoue et al., 2004; Wang et al., 2008) on the one hand and alterations in pro-inflammatory peripheral cytokines (Irwin and Miller, 2007; Drexhage et al., 2010; Meyer et al., 2009; Miller et al., 2009) on the other hand. Additionally, treatment with cytokines such as IFN-α induces depressive-like symptoms (Raison et al., 2005, 2009). However, the functional link between peripheral immune activation and social behavior is largely unknown. So far, only one previous study in healthy subjects revealed increased self-reported feelings of social disconnection along with the well-known effects on mood after ad-
ministration of a higher endotoxin dose (i.e. 0.8 ng/kg E. coli endo-
toxin) (Eisenberger et al., 2010b). However, no aspects of social behavior and/or social cognition task performance were assessed in this study (Eisenberger et al., 2010b).