

# Increased neural responses to empathy for pain might explain how acute stress increases prosociality

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## Abstract

Recent behavioral investigations suggest that acute stress can increase prosocial behavior. Here, we investigated whether increased empathy represents a potential mechanism for this finding. Using functional magnetic resonance imaging, we assessed the effects of acute stress on neural responses related to automatic and regulatory components of empathy for pain as well as subsequent prosocial behavior. Stress increased activation in brain areas associated with the automatic sharing of others' pain, such as the anterior insula, the anterior midcingulate cortex, and the primary somatosensory cortex. In addition, we found increased prosocial behavior under stress. Furthermore, activation in the anterior midcingulate cortex mediated the effects of stress on prosocial behavior. However, stressed participants also displayed stronger and inappropriate other-related responses in situations which required them to take the perspective of another person, and to regulate their automatic affective responses. Thus, while acute stress may increase prosocial behavior by intensifying the sharing of others' emotions, this comes at the cost of reduced cognitive appraisal abilities. Depending on the contextual constraints, stress may therefore affect empathy in ways that are either beneficial or detrimental.

**Key words:** psychological stress; neuroimaging; empathy; social cognition; prosocial behavior

## Introduction

Stress is omnipresent in modern human life and known to have a profound impact on behavior and cognition (Starcke and Brand, 2012; Hermans *et al.*, 2014). While its effects on social interactions are only poorly understood, accumulating evidence suggests that prosocial behavior is increased under acute stress (Takahashi *et al.*, 2007; von Dawans *et al.*, 2012; Vinkers *et al.*, 2013; Buchanan and Preston, 2014; Margittai *et al.*, 2015).

Findings such as these are in line with the concept of a 'tend-and-befriend' stress response, which proposes that affiliative behavior increases under stress in order to secure support from others (Taylor *et al.*, 2000). Although originally this hypothesis was proposed as a typical female stress response (Taylor *et al.*, 2000), more recent empirical work suggested that also males may engage in such a response pattern (for a review, see: Buchanan and Preston, 2014). However, the psychological and

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neural mechanisms which may cause such increases in affiliative behavior are largely unexplored.

Empathy—the ability to share the emotions of others—is one potentially promising mechanism. It enables us to emotionally connect to and understand others' emotions. Since empathy has strong links to prosocial behavior (such as altruism or cooperation; e.g. Batson, 2010) and activity in neural systems associated with self-other resonance has been shown to correlate with prosocial behavior (Christov-Moore and Iacoboni, 2016), it is crucial to establish how empathy is affected by stress, and how this in turn may influence prosocial behavior. According to recent neuro-cognitive models empathy entails an automatic, sensory-driven (bottom-up) component, relying upon emotion contagion and vicarious sharing of the other person's affect, and a (top-down) modulation of this automatic response by more deliberately deployed components such as cognitive appraisal, self-other distinction and perspective taking (e.g. for reviews Decety and Lamm, 2006; Shamay-Tsoory, 2011; Zaki and Ochsner, 2012; Singer and Klimecki, 2014). Interestingly, stress has been suggested to increase automatic response tendencies and to decrease control processes (for reviews, see Starcke and Brand, 2012; Hermans et al., 2014; Phelps et al., 2014). We therefore predicted that automatic sensory-driven processes related to empathy will be promoted under stress, while more effortful processes, such as deliberate cognitive appraisals and self-other distinction, will be compromised (Epley et al., 2004). However, another possible prediction would be that both, cognitive-deliberate and automatic-reflexive components of empathy are decreased under stress. Indeed, research on patients suffering from post-traumatic stress disorder has shown diminished cognitive and emotional empathy in these patients (Palgi et al., 2016). In addition, it has been shown that acute stress can increase self-focused attention (Rimmele and Lobmaier, 2012)—which in turn might impair emotion contagion as people might simply pay less attention to the emotions of others.

In order to test these opposing hypotheses, we used functional magnetic resonance imaging (fMRI) to assess how acute stress affects the neural concomitants of these distinct components of empathy, and how this is related to prosocial behavior.

More specifically, we measured brain activity in healthy male volunteers using an experimental paradigm tailored to differentiate automatic and regulatory processes related to empathy for pain (Lamm et al., 2007). Prior research using this and related paradigms has consistently shown that seeing others in pain activates brain regions similar to the ones recruited when experiencing pain oneself (Lamm et al., 2011) leading to an emerging consensus that empathy is underpinned by shared neural representations (Rütgen et al., 2015). This 'empathy for pain network' mainly comprises the anterior insula (AI) and the anterior midcingulate cortex (aMCC), and—for picture-based paradigms, such as the one used here—also the somatosensory cortex (see also Keysers et al., 2010; Lamm et al., 2011).

The present study assessed the effects of stress on such shared neural representations, and their modulation by cognitive appraisal. Since stress has been shown to increase automaticity (Starcke and Brand, 2012; Hermans et al., 2014), our first main hypothesis was that experimentally induced psychosocial stress would *increase* affect sharing, and that this would be indicated by increased neural responses in areas related to shared representations. As empathy has been proposed as a facilitator of prosocial behavior (Batson, 2010), our second main hypothesis was that these increases in affect sharing will be related to increases in prosocial behavior. Finally, since we were also

interested in the effects of stress on regulatory components related to empathy, the experimental paradigm included a condition in which participants had to use cognitive appraisal to reduce their aversive responses to only seemingly painful situations. Prior research using such a manipulation had shown that the associated modulation of empathy is accompanied by activation in prefrontal cortical areas, including orbitofrontal cortex (OFC) and medial and lateral prefrontal areas and the right temporo-parietal junction (Lamm et al., 2007). Based on detrimental effects of stress on control processes and executive functions (Starcke and Brand, 2012; Hermans et al., 2014), our third main hypothesis predicted that cognitive appraisal and self-other distinction will be decreased by stress, and hence also the neural responses in areas related to these functions.

## Materials and methods

### Participants

Seventy-six male participants between 18 and 40 years were included in the study. All participants filled out screening questionnaires before the experiment to assess trait socio-cognitive abilities and social anxiety (see supplementary material for a description of the screening). The study was approved by the ethics committee of the Medical University of Vienna and was performed in line with the latest revision of the Declaration of Helsinki (1964). All participants received between €30 and 40 for participation, depending on how much they shared during one of the experimental tasks. After outlier exclusion (described in the supplementary material), our final sample consisted of 67 participants (35 stress group, 32 control group) for the fMRI analyses and 66 participants (34 stress group, 32 control group) for behavioral data analyses of the empathy for pain paradigm.

### Experimental procedures

Participants first underwent a preparation phase outside the scanner and received instructions for the experimental tasks. Scanning commenced with an anatomical scan and a brief paradigm which helped participants to adapt to the fMRI environment. After the preparation paradigm, the stress paradigm [either stress or control version of the Montreal Imaging Stress Task (MIST); Dedovic et al., 2005] was implemented and immediately afterwards we implemented the empathy for pain paradigm. A more detailed description of the experimental procedures including saliva sampling is provided in the supplementary material.

### Stress paradigm

Stress was induced by an adapted version of the Montreal Imaging Stress Task (MIST; Dedovic et al., 2005) which includes a mental arithmetic challenge under time pressure, together with social evaluative threat. The evaluative threat is induced by a failure to achieve the minimum performance in the arithmetic challenges paired with consistent negative feedback given by the experimenter. In the present study, we used the MIST as a stress induction method only and did not investigate neural activation during the paradigm. Therefore, we only used the experimental (i.e. stress-inducing) condition for the stress group and the control condition for the control group. Furthermore, the extent of social evaluative threat was further increased by showing participants live webcam recordings of an experimenter allegedly watching them and taking notes while they were solving the mental arithmetic challenges in the scanner.

In the control condition, participants were solving mental arithmetic challenges with the same level of difficulty as during the experimental condition, but without time restriction, evaluation of their performance or being watched by the experimenter. Thus, the control condition was designed to match the mental arithmetic aspects of the task, but without the stress components (Dedovic et al., 2005). A detailed description of the stress measures (i.e. saliva sampling and analyses) is provided in the supplementary material.

### Empathy for pain paradigm

We used a paradigm successfully applied before to tap into different components of empathy for pain, including affect sharing, cognitive appraisal and perspective taking (Lamm et al., 2007; Lamm and Decety, 2008). It required participants to watch images of needle injections into a human hand (see supplementary material for a detailed description of the stimuli). In one condition (the *injection* condition), participants were informed that the needle injections were painful for the patients. In another condition (the *biopsy* condition), participants were informed that the target's hand had been anesthetized and that the patients therefore could not feel any pain during this procedure. Importantly, this condition required participants to modulate their automatic aversive response to the only seemingly aversive, but in reality innocuous situation. A third, non-painful, control condition (the *Q-tip* condition) showed the same hands, without anesthesia, being touched by a Q-tip. Behavioral responses were collected via a rating scale presented after each condition block. Participants had to separately rate the level of unpleasantness supposedly experienced by the patient (Rating UNPLEASANT OTHER), and their own unpleasant affect (Rating UNPLEASANT SELF) while watching the images, using a 7-point rating scale ranging from 1 (low unpleasantness) to 7 (high unpleasantness). This enabled disentangling other-related from self-related affective responses to others' pain.

### d2 attention test

In order to assess whether the stress manipulation might also have induced changes in cognitive load and attention, we included an adapted version of the d2 attention test (Brickenkamp and Zillmer, 1998) two times during the experimental session—i.e. 15 min after the onset of the stressor (or control paradigm) (t1) and 45 min after the onset of the stressor/stressor control (t2).

### Prosocial behavior

We used a 'dictator game' (Forsythe et al., 1994) setup as a proxy to measure prosocial behavior. Participants were endowed with €10.- and instructed that they could divide the money between themselves and the next participant of the experiment (who remained anonymous and was neither met before nor after the experiment), according to a ratio that was entirely theirs to decide, on a scale ranging from €0.- to 10.- in €0.50 steps. They were also informed that they would be paid out the money they decided to keep for themselves, plus the money the previous participant had left them (without informing them how much that was until the end of the experiment). Participants then disclosed their decision.

### Statistical analyses of behavioral data

In order to confirm that stress and control group did not differ in variables such as age, socio-cognitive abilities and social anxiety, we computed two-sample t tests for each measure. The effectiveness of the stress induction was tested with repeated-measures ANOVAs with the within-subjects factor *time* (5 repeated measures for cortisol and 8 for subjective stress and mood ratings) and the between-subjects factor *group* (stress, control). Furthermore, we assessed group differences in cortisol response (i.e. prestress to peak  $\Delta$ ) as well as subjective stress response (again, pre-stress to peak  $\Delta$ ) using two-sample t-tests. In case Levene's test indicated unequal variances, we used Welch's t test with corrected degrees of freedom. Behavioral data of the empathy for pain paradigm was analyzed in a repeated-measures ANOVA with the within-subjects factors *condition* (injection, biopsy and Q-tip) and *rating* (unpleasantness for self, other) and the between-subjects factor *group* (stress, control). Greenhouse–Geisser corrections were used when the assumption of homogeneity of covariances was violated (as determined by Mauchly tests of sphericity). Bonferroni-corrected *post-hoc* pairwise comparisons were computed to examine interactions and omnibus main effects. Performance in the two runs of the d2 attention test was assessed by computing the concentration performance (CP) measure as described in Brickenkamp and Zillmer (1998). This measure was included in a repeated-measures ANOVA with the within-subjects factor *time* (run1, run2) and the between-subjects factor *group* (stress, control). We assessed group differences in the prosocial task using the non-parametric Mann–Whitney U test, since due to an over-representation of decisions to share exactly half of the money the data was not following a normal distribution. Furthermore, we tested one-sided due to consistent previous findings of increased prosocial behavior under stress using the dictator game paradigm (Takahashi et al., 2007; von Dawans et al., 2012; Vinkers et al., 2013; Buchanan and Preston, 2014; Margittai et al., 2015) and the fact that our study had been explicitly designed to test possible mechanisms explaining these findings. All data were analyzed using SPSS (v20) and the significance threshold was set to  $\alpha=0.05$ . Effect sizes are reported as  $\eta_p^2$ .

### Statistical analyses of fMRI data

Details on MRI acquisition and preprocessing are reported in the supplemental material. MRI data were preprocessed and analyzed using SPM12 (Statistical Parametric Mapping, <http://www.fil.ion.ucl.ac.uk/spm>). The fMRI time series were analyzed using a block design approach in the context of the General Linear Model (GLM). Effects were modeled in a block-wise fashion by combining the four trials (i.e. the four pictures) in each block into one epoch. The fixation cross block served as an implicit baseline. Single-subject (first-level) models consisted of multiple regressors separately modeling the three conditions (injection, biopsy, Q-tip) based on the time periods in which the 20 blocks for each condition were presented and—as regressors of no interest—the periods during which the instruction screen rating scales were shown. Each effect was modeled as a boxcar function, and then convolved with the canonical hemodynamic response function as implemented in SPM12. Residual head movement effects were accounted for by including the six rigid-body motion parameters (translation and rotation) as nuisance regressors.

Our target contrasts compared the injection condition with the Q-tip condition (INJECTION > QTIP), with the latter serving



as a non-painful control condition, and the biopsy with the Q-tip condition (BIOPSY > QTIP). These first-level contrasts were entered into a second-level random-effects analysis using a flexible factorial model with the factors subject, group (stress, control), and condition contrasts (INJECTION > QTIP, BIOPSY > QTIP). Within this model, we then compared groups (stress and control) in both condition contrasts, in order to enable inferences on the population level (Penny and Holmes, 2004). As the main goal of our study was to assess how stress modulates different processes related to automatic vs regulative components of empathy for pain, we have tailored our design such that the two can be compared to a third, unequivocally non-painful control condition (i.e. hands touched by a Q-tip). Notably, this Q-tip condition also enabled the 'classical' Pain vs No Pain contrast commonly used in empathy for pain studies (for a meta-analysis, see Lamm et al., 2011), allowing us to more directly compare our evidence to previous findings. As we were specifically interested in stress effects on neural responding in the empathy for pain network, we first tested for group differences in regions of interest in the empathy for pain network using coordinates from a meta-analysis of fMRI studies on empathy for pain (Lamm et al., 2011, see supplementary material for a listing of the coordinates). For this ROI analysis, we extracted mean activation from three core empathy for pain network regions (i.e. left and right anterior insula (AI) and anterior midcingulate cortex (aMCC)) using the REX toolbox (<http://web.mit.edu/swg/software.htm>) for region of interest extraction (REX), using 5 mm spheres centered on coordinates reported in (Lamm et al., 2011). In addition to these ROI analyses, we performed whole-brain analyses using family wise error (FWE, voxel-level) correction over the whole brain. The SPM Anatomy Toolbox (Eickhoff et al., 2005) was used to guide anatomical and probabilistic cytoarchitectonic localization of the resulting activation. Additionally, we carried out a psychophysiological interaction (PPI) analysis (described in the supplementary material) to investigate connectivity changes for the results of the main analyses in more detail.

### Correlation brain and behavior

Our main methodological approach was to correlate brain activation from the extracted ROIs of the empathy for pain network with behavioral data. We correlated behavioral data from the unpleasantness ratings during the empathy for pain paradigm, the emotion contagion questionnaire (Doherty, 1997) and the dictator game with brain activation in the ROIs from the empathy for pain network. See supplementary material for a detailed description of these analyses. In addition, we calculated a mediation analysis to investigate the results of the conducted correlations in more detail (described in the results section, Associations between behavioral and fMRI data).

## Results

Stress and control group did not differ in age, social anxiety and trait socio-cognitive abilities such as empathic concern, perspective taking (calculated with sub-scores as recommended by Koller and Lamm (2014)) and emotion contagion (all  $P$ -values  $\geq 0.106$ ). Descriptive statistics of the questionnaire results are provided in the supplementary material.

### Stress manipulation

As expected, individuals of the stress group showed higher cortisol responses as well as higher subjective stress ratings compared to individuals in the control group. All results of the

stress manipulation are described in detail in the supplementary material.

### Self-report affect ratings during empathy for pain paradigm

A  $2 \times 3$  repeated measures ANOVA revealed a significant main effect of condition [ $F(2,128) = 348.399$ ,  $P < 0.001$ ,  $\eta_p^2 = 0.85$ ] and rating [ $F(1,64) = 6.649$ ,  $P = 0.012$ ,  $\eta_p^2 = 0.09$ ], a significant condition  $\times$  rating interaction [ $F(2,128) = 18.604$ ,  $P < 0.001$ ,  $\eta_p^2 = 0.23$ ], and a significant interaction of group  $\times$  condition  $\times$  rating [ $F(2,128) = 3.584$ ,  $P = 0.031$ ,  $\eta_p^2 = 0.05$ ]. All other main effects and interactions were non-significant (all  $P$ -values  $\geq 0.100$ ). Bonferroni-corrected pairwise comparisons showed that the significant three-way interaction was driven by group differences in the ratings between other (Rating<sub>UNPLEASANT OTHER</sub>) and self (Rating<sub>UNPLEASANT SELF</sub>) during the biopsy condition. While in the stress group there was no significant difference between Rating<sub>UNPLEASANT OTHER</sub> and Rating<sub>UNPLEASANTNESS SELF</sub> in this condition ( $P = 0.440$ ), the control group reported higher self-related unpleasantness than other-related unpleasantness when seeing biopsy pictures (Rating<sub>UNPLEASANTNESS SELF</sub> > Rating<sub>UNPLEASANTNESS OTHER</sub>;  $P = 0.011$ ; mean difference = 0.750, SE = 0.285). Supplementary Figure S2 in the supplementary material illustrates this group difference between the unpleasantness ratings for the biopsy condition.

### d2 attention test

Testing for changes in performance in the d2 attention task revealed a significant increase of performance over time [ $F(1,65) = 10.093$ ,  $P = 0.002$ ,  $\eta_p^2 = 0.13$ ], but no group-related differences (all  $P$ -values  $\geq 0.870$ ).

### Dictator game

Prosocial behavior showed a significant group difference [Mann-Whitney  $U(67) = 423$ ;  $Z = -1.830$ ,  $P = 0.034$ ,  $r = 0.22$ ], with higher amounts of money transferred by the stress than by the control group (mean ranks 37.91 vs 29.72; €4.67 vs €3.67 transferred on average).

### fMRI analysis

ROI analyses for the STRESS > CONTROL: INJECTION > QTIP contrast showed significantly higher activation in the stress group in left AI [ $t(65) = 2.427$ ,  $P = 0.018$ ] and aMCC [ $t(65) = 2.745$ ,  $P = 0.008$ ]. The whole-brain analysis complemented this finding by also showing higher activation in left AI and aMCC. In addition, the whole-brain analysis showed higher activation in the stress group in bilateral somatosensory cortex, as well as in inferior frontal gyrus and the right extrastriate body area (EBA, Downing et al., 2001; see Figure 1a). The reverse comparison (CONTROL > STRESS: INJECTION > QTIP) did not reveal any significant differences neither in the ROI, nor in the whole-brain analyses. Assessing effects related to regulatory control with the contrast STRESS > CONTROL: BIOPSY > QTIP also revealed significantly higher activation in the stress group in left AI [ $t(65) = 2.672$ ,  $P = 0.010$ ] in the ROI analysis. The whole brain analysis showed stronger activation in the stress group in aMCC, caudate nucleus (CN), inferior frontal gyrus (IFG) and dorsolateral prefrontal cortex (DLPFC; Figure 1b). The reverse contrast (CONTROL > STRESS: BIOPSY > QTIP) did not reveal any significant differences, neither in the ROI nor in the whole-brain analyses. Since the stress group showed stronger activation for

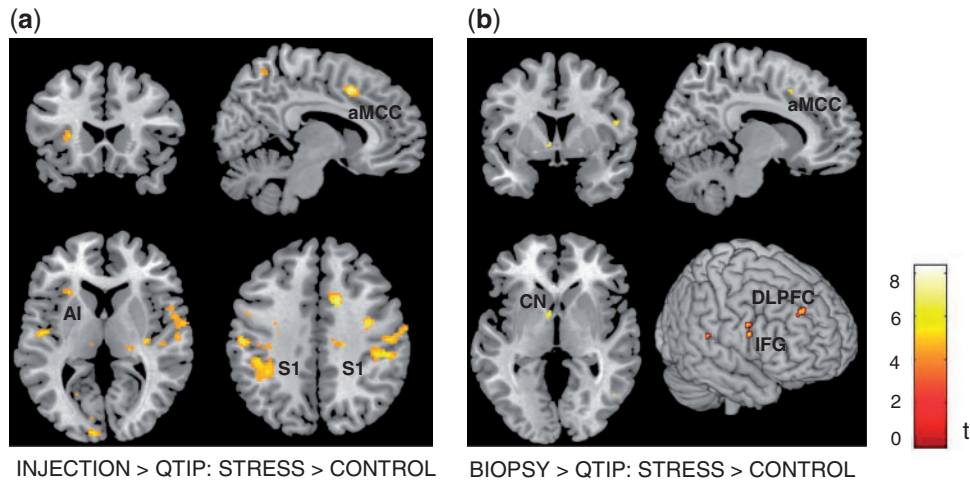


Fig. 1. Activation differences for the group  $\times$  condition contrasts: (a) INJECTION > QTIP: STRESS > CONTROL, showing activation in left anterior insula (AI), anterior midcingulate cortex (aMCC) and bilateral somatosensory cortex (S1) (b) BIOPSY > QTIP: STRESS > CONTROL, showing activation in anterior midcingulate cortex (aMCC), left caudate nucleus (CN), right inferior frontal gyrus (IFG) and right DLPFC. Correction for multiple comparisons was performed using voxel-level family-wise error correction at  $P < 0.05$  over the whole brain.

both target contrasts (i.e. INJECTION > QTIP and BIOPSY > QTIP) in partially overlapping areas of the empathy for pain network, we were interested in assessing the extent of activation overlap in these areas. To this end, we performed a conjunction analysis on the two contrasts STRESS > CONTROL: INJECTION > QTIP  $\cap$  STRESS > CONTROL: BIOPSY > QTIP. This analysis revealed that the stress group showed higher activation in both conditions in aMCC, occipital cortex and caudate nucleus. Table 1 depicts the MNI coordinates of the peak voxels resulting from this analysis. In addition, we also calculated this conjunction analysis using a more liberal threshold for correcting for multiple comparisons [i.e. cluster level family wise error correction at  $P < 0.05$  (selection threshold  $P = 0.001$ )]. We report the results, which show a similar general pattern, in the supplementary material. Finally, for the sake of completeness, we also calculated group differences for the contrast between the two target conditions [i.e. INJECTION > BIOPSY (and reverse)], showing no activation differences.

Additionally, to test whether the group differences specifically resulted from activation differences in our target conditions (i.e. injection, biopsy), as opposed to being the result of unspecific differences in the Q-tip control condition, we assessed potential group differences in the Q-tip control stimuli [contrasts STRESS > CONTROL (and reverse): QTIP > FIXATION]. This did not reveal any activation differences in areas revealed by the results reported above (see supplementary material for a detailed description of the results from this analysis).

### Associations between behavioral and fMRI data

In the stress group, trait emotion contagion in the sub-domain sadness significantly correlated with activation in the left AI ROI during the injection condition:  $r = 0.581$ ,  $P < 0.001$ , using a Bonferroni-corrected threshold level corrected for the three correlations (i.e. with the three coordinate-based ROIs) computed:  $P_{\text{corrected}} = 0.05/3 = 0.017$ . For the biopsy condition, stress group trait emotion contagion in the domain sadness correlated with activation in left AI ( $r = 0.494$ ,  $P = 0.003$ ) and aMCC ( $r = 0.457$ ,  $P = 0.006$ ). For the control group, trait emotion contagion did not correlate with activation in any of the ROIs, neither for the

injection, nor for the biopsy condition (all  $P$ -values  $\geq 0.440$ ). Calculating exploratory correlations between the IRI subscales and neural responding in the empathy for pain ROIs, did not reveal any significant results (all  $P$ -values  $\geq 0.168$ ). Furthermore, across all participants, activation in aMCC ( $r = 0.417$ ,  $P < 0.001$ ) during the injection as well as biopsy condition (i.e. derived from conjunction contrast: INJECTION > QTIP: STRESS > CONTROL and BIOPSY > QTIP: STRESS > CONTROL) correlated positively with the amount of money participants shared in the prosocial task. In addition, activation in the aMCC during the biopsy condition correlated negatively with the difference in ratings of unpleasantness for self and other during the biopsy condition ( $r_{1/4} = 0.300$ ,  $P_{1/4} = 0.017$ ). Thus, higher activation in aMCC was associated with lower self-other distinction in unpleasantness ratings in the biopsy condition. We, in addition, were interested to assess whether the relationship between aMCC activation and prosocial behavior was driven by direct influences of stress on prosocial behavior, mediated by empathy-related aMCC activation. We therefore calculated a mediation analysis with group (stress and control) as the categorical predictor, aMCC activation the mediator, and prosocial behavior the outcome variable. Analyses were conducted using non-parametric bootstrapping procedures operationalized in an SPSS Macro (Preacher and Hayes, 2008). We used 5000 bootstrap resamples of the data. Statistical significance with alpha at 0.05 is indicated by the 95% confidence intervals not crossing zero. We found a significant mediation effect of aMCC activity with respect to the relation between group and prosocial behavior (indirect effect = 0.68, SE = 0.26, 95% CI = [0.26, 1.33]). In addition, this mediation was total, meaning that aMCC activity accounted completely for prosocial behavior, as the direct effect of group did not significantly predict prosocial behavior ( $P = 0.646$ ).

### Discussion

The present study investigated the effects of acute stress on neural mechanisms underlying automatic and regulatory

**Table 1.** MNI stereotactic coordinates of the peak activation voxels resulting from the whole-brain conjunction analysis (using voxel-level family-wise error correction at  $P < 0.05$ ) assessing group differences between stress and control group in conditions injection and biopsy

Area	Peak MNI coordinates x y z	t value	P value (corrected) <sup>a</sup>
(INJECTION > QTIP): STRESS > CONTROL $\cap$ (BIOPSY > QTIP): STRESS > CONTROL			
L occipital cortex	-2 -88 -8	7.52	<0.011
L caudate nucleus	-6 4 -2	6.34	0.002
R operculum parietale (OP4)	56 -12 12	6.31	0.002
R inferior frontal gyrus	50 4 16	5.98	0.006
L cerebellum	-14 -62 -28	5.97	0.006
L inferior parietal cortex	-44 -34 40	5.91	0.008
R inferior frontal gyrus	58 10 22	5.81	0.011
R anterior midcingulate cortex	10 12 44	5.69	0.016
R premotor cortex	32 -2 46	5.63	0.019
R superior temporal gyrus	68 -26 16	5.60	0.022
R lingual gyrus	20 -52 -8	5.59	0.022
R premotor cortex	24 -18 58	5.57	0.024
L precentral gyrus	-50 2 44	5.55	0.025
R posterior insula	36 -16 -6	5.55	0.026
L superior parietal cortex	-40 -46 64	5.50	0.030
L precentral gyrus	-6 8 50	5.43	0.039
R intraparietal sulcus	30 10 42	5.40	0.041

Contrast: (INJECTION > QTIP): STRESS > CONTROL and (BIOPSY > QTIP): STRESS > CONTROL.

<sup>a</sup>Statistical inference was performed using voxel-level family wise error correction at  $P < 0.05$  over the whole brain.

components engaged during empathy for pain. We assessed differences in brain activation, self-report and their relation to prosocial behavior between stressed and non-stressed participants.

Our assessment of how stress modulated these responses revealed three central findings. First, we found that when viewing others in pain, stressed participants showed stronger activation in the empathy for pain network than control participants who were not stressed. Interestingly, stressed participants also showed stronger activation in EBA, i.e. a lateral occipital area specifically associated with the processing of body parts (Downing et al., 2001). This suggests that stress may already influence early visual processing of others' pain. Second, we replicated results of former studies showing increased prosocial behavior under stress (Takahashi et al., 2007; von Dawans et al., 2012; Vinkers et al., 2013; Buchanan and Preston, 2014; Margittai et al., 2015); but see also Steinbeis et al., 2015) and furthermore show that activation in a core area of the empathy for pain network, i.e. aMCC, in response to the pain of others positively correlated with prosocial behavior. An additional mediation analysis further showed that aMCC activity was a full mediator of the effects of stress on prosocial behavior. This provides a potential mechanism of how stress increases prosocial behavior—i.e., by increasing affect sharing with others, rather than affecting prosocial behavior directly. Third, when informed that the stimuli depicted biopsies performed on an anesthetized hand, and hence appeared aversive to participants but in reality were not painful for the patient, stressed participants still showed stronger activation in the empathy for pain network. In line with this, a conjunction analysis revealed that stressed participants showed stronger overlapping activation in a core region of the empathy for pain network, the aMCC, during both the injection and the biopsy conditions. Additionally, activation in left AI and aMCC in response to both, injection and biopsy condition, correlated with trait emotion contagion in stressed participants.

Taken together, this pattern of findings suggests that while stress increases automatic empathic responses, regulatory mechanisms to modulate this automatic affect sharing response seem to be impaired. Our finding of stronger engagement of DLPFC and IFG in the stress group during the biopsy condition might represent some engagement in (not perfectly successful) regulation, since both DLPFC and IFG have been repeatedly associated with emotion regulation and cognitive control (Wager et al., 2008; Ochsner et al., 2013). Although this interpretation would be also in line with a recent study showing decreased efficacy of regions associated with self-control under stress (Maier et al., 2015), it should be noted that both, IFG and DLPFC, have been associated with various other cognitive and emotional processes besides emotion regulation (Duncan and Owen, 2000; Shamay-Tsoory et al., 2009). Furthermore, additional connectivity analyses using DLPFC and IFG as seed regions in order to clarify their engagement in regulatory mechanisms did not reveal any differences between stress and control group in the connectivity of these regions. Thus, our interpretation of this observed activation remains speculative and further research should address the specific mechanisms at play in more detail.

A number of control conditions speak for the specificity of our findings. First, group differences in empathy-related areas cannot be attributed to generalized stress effects on the neural processing of visual or social stimuli, as shown by the absence of group differences for the Q-tip control stimuli. Second, we assessed cognitive load and attention at two time points during the experiment and did not find any group differences. Thus, we can rule out that our findings result from a general effect of stress on participants' cognitive load or attentional processing. Third, potential group differences in socio-cognitive abilities are also unlikely to explain our findings, as the two groups did not differ in several trait socio-cognitive abilities. Interestingly, as indicated by the behavioral data, participants were able to



appropriately rate the target's unpleasantness in the different conditions.

The group  $\times$  condition  $\times$  rating interaction for the biopsy indicates that control participants differentiated more between self- and other-related feelings in that condition, compared to stressed participants. In addition, the magnitude in responding in aMCC during the biopsy condition correlated negatively with differentiation between self and other in the unpleasantness ratings in the biopsy condition—i.e. stronger responding went along with lower self-other differentiation. This might be explained as a lower distinction between self- and other-related emotions in the stress group, and is in line with our prior finding that male participants show decreased self-other distinction under stress (Tomova et al., 2014).

Interestingly, we did not find group differences in neural responding between the two conditions (i.e. the group comparisons for the contrasts: INJECTION > BIOPSY and the opposite BIOPSY > INJECTION). However, it should be noted that due to the multi-dimensional and complex nature of empathy, the two conditions, as designed in this study, are certainly not solely measuring isolated aspects of empathy making direct subtractions of activation strength difficult to interpret. However, future research should address this issue with study designs more suitable to address this aspect more explicitly. In conclusion, our study indicates that stress might have a positive impact on empathy by increasing automatic resonance with the emotions of others, which is associated with increases in prosocial behavior. This, however, comes at the cost of decreased regulation, as exerted by processes such as cognitive appraisal and perspective taking, which may result in inaccurate and misguided empathic responses. Our results therefore indicate that stress does not act on one isolated component of empathy, but affects bottom-up and top-down components in opposing ways. This is in accordance with a recent theoretical account stating that stress causes a shift in brain processing from an executive controlled mode to a salience-driven mode (Hermans et al., 2014). Our results support this account and further extend it into the domain of social cognition. Thus, whether stress is adaptive and beneficial in shaping social interaction and behavior strongly depends on the complexity and requirements of the specific social situation. For example, in simple emergency situations (such as helping a person who has been hit by a car) where fast and automatic reactions are necessary, increased resonance with the emotions of others may lead to more immediate helping behavior. In contrast, in more complex situations (for example someone showing tears of happiness) decreased perspective taking abilities may lead to situations where the context and the emotions of others are misinterpreted, possibly resulting in inappropriate social behavior. These distinct cognitive processing modes and their differential reactivity to stress should be taken into account in future research assessing the effects of stress on social behavior.

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## Supplementary data

Supplementary data are available at SCAN online.

Conflict of interest. None declared.

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