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# Effect of direct eye contact in PTSD related to interpersonal trauma: an fMRI study of activation of an innate alarm system

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**In healthy individuals, direct eye contact initially leads to activation of a fast subcortical pathway, which then modulates a cortical route eliciting social cognitive processes. The aim of this study was to gain insight into the neurobiological effects of direct eye-to-eye contact using a virtual reality paradigm in individuals with posttraumatic stress disorder (PTSD) related to prolonged childhood abuse. We examined 16 healthy comparison subjects and 16 patients with a primary diagnosis of PTSD using a virtual reality functional magnetic resonance imaging paradigm involving direct *vs* averted gaze (happy, sad, neutral) as developed by Schrammel *et al.* in 2009. Irrespective of the displayed emotion, controls exhibited an increased blood oxygenation level-dependent response during direct *vs* averted gaze within the dorsomedial prefrontal cortex, left temporoparietal junction and right temporal pole. Under the same conditions, individuals with PTSD showed increased activation within the superior colliculus (SC)/periaqueductal gray (PAG) and locus coeruleus. Our findings suggest that healthy controls react to the exposure of direct gaze with an activation of a cortical route that enhances evaluative 'top–down' processes underlying social interactions. In individuals with PTSD, however, direct gaze leads to sustained activation of a subcortical route of eye-contact processing, an innate alarm system involving the SC and the underlying circuits of the PAG.**

**Keywords:** PTSD; social cognition; fMRI; childhood abuse; dorsomedial prefrontal cortex; superior colliculus

## INTRODUCTION

Mutual eye-to-eye contact is a crucial element of social interactions as it allows us to identify the intentions and emotions of others (Baron-Cohen, 1995; Tomasello and Carpenter, 2007). The ability to attribute mental states of others, such as desires, beliefs, opinions, perceptions or attitudes, is commonly referred to as 'mentalizing' (Morton *et al.*, 1991), 'theory of mind' (Premack and Woodruff, 1978), or 'mind reading' (Whiten, 1991). Results from behavioral and psychophysiological investigations suggest that direct gaze provokes these social cognitive processes, whereas averted gaze does not (Kampe *et al.*, 2003; Conty *et al.*, 2007). Direct gaze when compared with averted gaze also facilitates the identification and differentiation of emotional facial expressions of anger and happiness (Adams and Kleck, 2005; N'Diaye *et al.*, 2009; Schrammel *et al.*, 2009; Pinkham *et al.*, 2011) and enhances their perceived intensity (Adams and Kleck, 2005). Furthermore, reaction times for detecting direct gaze are significantly shorter than for detecting averted gaze (Conty *et al.*, 2007). These findings suggest that direct gaze is a rich source of information that recruits more processing resources than averted gaze, possibly reflecting the involvement of theory of mind and mentalizing processes (Conty *et al.*, 2007).

### The effect of emotion on direct *vs* avert eye contact

The facilitated identification of emotions in direct vs averted gaze is not found for all emotions. Emotions that are associated with a behavioral tendency to avoid rather than approach others (e.g. fear, sadness) are better recognized during averted when compared with direct gaze. In contrast, approach-related emotions (e.g. happiness, anger) are better recognized during direct gaze (Adams and Kleck, 2005). Interestingly, neutral faces elicit greater negative affect when gaze is direct rather than averted, suggesting that showing no facial expression at all may in some cases signal some kind of threat (Hess *et al.*, 2007). Schrammel *et al.* (2009) demonstrated an increased emotional experience and a greater emotional expression (a pronounced facial electromyograph) for virtual characters that created mutual eye-to-eye contact with the subjects. Although the effect of direct gaze is often modulated by the valence of the facial expression displayed, these results support the idea of a neurobiological distinction between direct and averted gaze processing.

### Neural mechanisms of direct gaze processing in healthy controls

In healthy individuals, processes evoked by direct eye contact such as mentalizing are assumed to occur automatically with little cognitive effort (Leslie, 1987; Kampe *et al.*, 2003). However, eye contact does not directly activate brain areas associated with mentalizing but is thought to be initially detected by an implicit and automatic subcortical route hypothesized to include the superior colliculus (SC)/periaqueductal gray (PAG)[1], pulvinar and amygdala (de Gelder *et al.*, 2011; but also see Pessoa and Adolphs, 2010; for review on the effect of eye contact see Senju and Johnson, 2009). This subcortical pathway then modulates the activation of cortical brain areas associated with reflective social cognitive processes, including mentalizing, such as the fusiform gyrus, superior temporal sulcus, medial prefrontal and orbitofrontal cortices (Liddell *et al.*, 2004; Johnson, 2005).

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[1] Because of their spatial proximity and functional overlap in this context, PAG and SC are summarized as SC/PAG (Kober *et al.*, 2008).

Although the subcortical route of direct gaze processing may be anatomically and functionally related to a more general automatic face-detecting pathway (Johnson, 2005), there is ambiguity surrounding the purpose of the subcortical route. A common viewpoint is that the subcortical face pathway serves to detect potential signals of threat as it is most consistently activated by negative, especially fearful, facial expressions (Johnson, 2005). Direct eye contact, irrespective of the emotional facial expression displayed may be a signal of threat under some social contexts or in populations that experienced negative events accompanied by eye contact, and the subcortical face processing route may function to detect this potential threat (Senju and Johnson, 2009). Elements of the subcortical pathway, however, have also been found to be activated during neutral and positive-affect expressions (Zald, 2003; Johnson, 2005). The subcortical pathway may therefore also serve to facilitate processing of biologically salient stimuli, including faces irrespective of emotional valence (Johnson, 2005), or eye contact specifically, as eye contact has been suggested to be an emotionally relevant stimulus (Emery, 2000).

Perceived eye contact is initially detected by the SC/PAG, which then projects to the thalamic pulvinar, the amygdala and, via the locus coeruleus (LC), specific regions of the frontal cortex, in particular prefrontal and motor areas, to initiate a frontally driven automatic orienting response to fear signals and to generate plans and intentions (Halgren and Marinkovic, 1995; Panksepp, 1998; Liddell *et al.*, 2005). As described above, this subcortical pathway may entail an evolutionary benefit by serving to prepare organisms quickly and unconsciously for potential threat and has therefore been referred to as an 'innate alarm system' (Liddell *et al.*, 2005). Activation of both the deep layers of the SC as well as the underlying circuits of the PAG are associated with anxiety-related responses (de Sudré *et al.*, 1993; Almeida *et al.*, 2006; Broiz *et al.*, 2011). Furthermore, the PAG is assumed to be the anatomical root of an altered state of consciousness—'primary-process consciousness'—that does not enable thoughts or clearly defined perceptions but is characterized by primitive feelings and bodily awareness (Panksepp, 1998; Watt, 2000).

The subcortical route is thought to interact with reflective cognitive processes such as mentalizing that are modulated by task demands and serve to evaluate the ongoing social interaction. These processes are observable by presenting direct facial expressions overtly and for a prolonged period, which is commonly done in studies comparing the effects of direct *vs* averted gaze. Areas activated during general mentalizing tasks, such as the dorsomedial prefrontal cortex (DMPFC) as well as the temporoparietal junction (TPJ) and the temporal poles (TP) (Vogeley *et al.*, 1999; Kober *et al.*, 2008; Van Overwalle, 2009; Frewen *et al.*, 2011), overlap substantially with the regions activated by direct *vs* averted gaze (Senju and Johnson, 2009).

Two studies using functional neuroimaging compared direct and averted gaze with regard to neutral facial expressions and found bilateral occipitotemporal activations, including the posterior superior temporal sulcus as a correlate of biological motion and socially relevant gaze processing (Kuzmanovic *et al.*, 2009; Ethofer *et al.*, 2011). Results showed that not only the direction of gaze is important but also pointed to the significance of the duration of gaze. Specifically, with increasing gaze duration (1, 2.5, or 4s), response within the medial prefrontal cortex increases, as does response within the anterior and posterior cingulate cortex and medial orbitofrontal cortex, likely serving to evaluate the ongoing social interaction and supporting evidence for activation of the reflective cognitive pathway following the subcortical automatic route (Kuzmanovic *et al.*, 2009). Dynamic animations of virtual characters mimicking a social interaction are increasingly used since this method mimics approaching a real human social interaction under controlled conditions. For example, Schilbach *et al.* (2006) examined the neural processes involved in mentalizing by presenting dynamic virtual characters that showed facial expressions serving as social cues. The characters entered the screen and then either turned directly toward the subject, creating mutual eye-to-eye contact, or 30° to the left or right of the observer and thus appearing to look at someone else. The virtual characters then showed socially relevant facial expressions (e.g. a smile) or arbitrary facial movements (e.g. lip biting). As a main finding, the DMPFC was activated when the subjects were gazed at directly, regardless of the kind of facial expression. Similarly, analyzing participants' gaze behavior with the same paradigm revealed longer fixation durations for direct than averted gaze, which can be understood as an indicator for deeper processing in the case of direct gaze (Mojzisch *et al.*, 2006).

Not only gaze direction is important for the direction of social attention, Langton (2000) showed that congruency of gaze and head direction during direct gaze facilitated processing of cues in a Stroop-type interference paradigm, as indicated by shorter reaction times compared with incongruent gaze and head orientation. These results show that congruency of head orientation and gaze is mutually influential on the allocation of attention in social interactions (Langton, 2000). Body orientation is used as a cue for spatial direction, the direction another individual is moving to (Emery, 2000). Congruency of head direction/body orientation and gaze as well should therefore be regarded as a variable of interest in the examination of the effect of eye contact.

### Facial processing in posttraumatic stress disorder

People who have experienced childhood abuse often learn to avoid direct gaze due to it provoking their abuser. As eye contact is fundamental to emotional attending and mentalizing, direct eye contact is often perceived as threatening in individuals who were abused as children (Krill and McKinnon, 2010; Wilkinson, 2010). Moreover, individuals with posttraumatic stress disorder (PTSD) exhibit abnormal neural responses during social cognitive processing (reviewed by Lanius *et al.*, 2011). It is therefore plausible that persons with PTSD related to childhood abuse will show altered neurobiological response during mutual eye-to-eye contact. To our knowledge, no study has investigated the differential effect of direct *vs* averted gaze in individuals with PTSD. However, functional neuroimaging studies examining the effect of fearful and angry *vs* happy as well as fearful *vs* neutral facial expressions that are presented in direct gaze typically find increased amygdala reactivity accompanied by a hypoactivation of the medial prefrontal cortex in individuals with PTSD when compared with healthy controls (Rauch *et al.*, 2000; Shin *et al.*, 2005; Williams *et al.*, 2006; Fonzo *et al.*, 2010). An event-related potential (ERP) study by Felmingham *et al.* (2003) compared angry *vs* neutral faces and found that individuals with PTSD showed reduced ERP responses to both angry and neutral facial expression within the temporal and occipital cortex, whereas controls exhibited greater activation to angry facial expression. These results hint toward difficulties discriminating threatening from non-threatening stimuli and a hyporeactivity of the posterior temporo-occipital cortex. How can the results of facial processing in PTSD be understood? Threat-related stimuli seem to induce hyperactivation within the amygdalae accompanied by hypoactivation within cortical areas, especially within the dorsal prefrontal cortex. This pattern may reflect a sustained activation of the initial implicit and automatic subcortical route of eye-contact processing, the 'innate alarm system'. Although in controls the subcortical activation is quickly followed by controlled and conscious processes of cognitive evaluation (Liddell *et al.*, 2004; Senju and Johnson, 2009), this second path of direct gaze processing may not occur as rapidly, if at all, in patients with PTSD.

Previous research shows that the emotional expression of faces displayed has a significant impact on neural responses in individuals with PTSD. Heightened responses within the subcortical route of direct gaze processing and decreased responses in cortical brain regions are, as described above, often found when contrasting facial displays of threat with happy or neutral faces, and negative or threat-related stimuli when compared with neutral and positive stimuli often provoke hypervigilance in individuals with PTSD (e.g. Kimble *et al.*, 2010). However, neuroimaging studies rarely compare response to positive *vs* neutral facial expressions in individuals with PTSD. The latter point may be particularly relevant to individuals who suffer from PTSD related to interpersonal violence since the distinction between positive and threat-related or negative stimuli may not be as clear in this population. In this regard, it is important to note that individuals with interpersonal trauma not only often exhibit decreased positive affect but also increased negative affect in response to what would normally be considered pleasant stimuli and events (Frewen *et al.*, 2012). Therefore, even general positive stimuli may not be experienced as positive in individuals with PTSD. This may also be the case during direct eye contact in an interpersonal/interactional setting, particularly in persons with a history of childhood trauma.

The latter point of view is supported by a recent study that examined brain activation to emotional facial expressions (happy, angry, fearful, sad and neutral) when compared with scrambled pictures in youth with a history of interpersonal trauma and current posttraumatic stress symptoms (PTSS) and healthy subjects (Garrett *et al.*, 2012). Group differences in activation of the amygdala/hippocampus, ventromedial prefrontal cortex and insula were associated with angry facial expressions but not fearful or sad faces. Greater activation in the PTSS group in response to neutral faces was noted in the amygdala, accompanied by reduced activation within the dorsolateral prefrontal cortex. These results suggest that angry facial expressions may be especially relevant to individuals with interpersonal trauma and that neutral faces may also be interpreted negatively or with ambiguity. Happy faces led to increased activation in the ventrolateral prefrontal cortex but decreased activation in the dorsolateral prefrontal cortex. The difference in activation of the ventrolateral prefrontal cortex was greatest in subjects that met the full diagnostic criteria for PTSD. Moreover, happy faces were the only stimuli that elicited marked sensitization of activation from early to late phase in the insula in healthy controls with no change occurring in the PTSS group. Lack of sensitization to happy faces may be related to anhedonia or numbing symptoms reported in PTSS (Garrett *et al.*, 2012). Taken together, youth with PTSS showed abnormal brain activation to neutral faces as well as emotional expressions. Increase of activation within the left amygdala was not limited to threat-related stimuli but also occurred with the presentation of neutral faces. Beyond that, hypoactivation of dorsal prefrontal areas was also existent while watching happy facial expressions. Altered brain activation during direct gaze in individuals with interpersonal trauma may not be therefore restricted to threat-related stimuli (Garrett *et al.*, 2012).

Previous studies of facial processing in PTSD have to be interpreted with caution in relationship to the literature examining the neural circuitry underlying eye contact. First, the PTSD studies only used facial expressions involving direct gaze. Second, the PTSD studies present facial stimuli in stills, thus weakening the context of social interaction.

### Objectives and hypotheses

The aim of the present study was to gain insight into the neurobiological process mediating mutual eye-to-eye contact in healthy individuals *vs* those with PTSD related to prolonged childhood abuse by administering Schrammel *et al.*'s (2009) virtual reality paradigm adapted to functional magnetic resonance imaging (fMRI). We hypothesized that healthy controls would respond to direct gaze with increased activation in brain regions associated with mentalizing [DMPFC (Kober *et al.*, 2008), TPJ (Frewen *et al.*, 2011) and TP (Kober *et al.*, 2008)]. In comparison, we expected individuals with PTSD to respond to direct gaze with heightened activation in brain areas associated with the subcortical route of direct gaze processing, the innate alarm system [LC, SC/PAG and amygdala (Liddell *et al.*, 2005; Senju and Johnson, 2009; de Gelder *et al.*, 2011)].

## METHODS

### Participants and measures

The sample consisted of 32 female participants: 16 healthy comparison subjects and 16 patients with a primary diagnosis of PTSD. Demographics, clinical severity and comorbidity characterizing the present sample can be seen in Table 1. Healthy comparison subjects and PTSD subjects did not differ in age, $t_{(30)} = -0.70$, $P = 0.490$. However, significantly less PTSD subjects were currently employed $X^2_{(df=1,n=32)} = 5.93$, $P = 0.015$. PTSD was, in all cases, caused by a traumatic history of childhood abuse as indicated by interview and assessment with the Childhood Trauma Questionnaire (CTQ)—Short Form (Bernstein *et al.*, 2003). The PTSD diagnosis was confirmed via the Clinician-Administered PTSD Scale (CAPS, Blake *et al.*, 1995) that assesses the frequency and intensity of each of the 17 PTSD symptoms determined in the *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, 2000). In our sample, all subjects scored above the common cutoff of 50 for the CAPS (Blake *et al.*, 1995), scores ranging from 50 to 100 (mean = 71.50, s.d. = 15.63). The *Structured Clinical Interview for DSM-IV Axis I Disorders* (First *et al.*, 1996) was administered to ascertain Axis I comorbidities. Individuals with a history of lifetime bipolar disorder, lifetime psychotic disorders, lifetime neurological disorder, current substance abuse in remission for less than 3 months, serious head

**Table 1** Demographics and diagnostic information of full sample and subgroups

| Variable | Full sample ($N = 32$) | Controls ($n = 16$) | PTSD ($n = 16$) |
|---|---|---|---|
| Demographic | | | |
| Mean (s.d.) age | 32.06 (12.03) | 30.56 (12.61) | 33.56 (11.63) |
| % employed (full or part time) | 84.38 | 100 | 68.75 |
| Severity of PTSD | | | |
| Mean (s.d.) on CAPS | – | – | 71.50 (15.63) |
| Comorbidities | | | |
| Mean (s.d.) present number | 0.77 (1.26) | – | 1.50 (1.41) |
| Mean (s.d.) lifetime number | 1.03 (1.33) | 0.13 (0.35) | 1.88 (1.36) |
| Comorbid Axis I conditions (%) | | | |
| Alcohol dependence | 3.13 | – | 6.25 |
| Major depressive disorder | 28.13 | – | 56.25 |
| Panic disorder w/wo agoraphobia | 12.50 | – | 25.00 |
| Social phobia | 6.25 | – | 12.25 |
| Specific phobia | 3.13 | – | 6.25 |
| Generalized anxiety disorder | 3.13 | – | 6.25 |
| Somatization disorder | 3.13 | – | 6.25 |
| Undifferentiated somatoform disorder | 15.63 | – | 31.25 |
| Childhood trauma history | | | |
| Mean (s.d.) on CTQ-PA | 7.94 (4.71) | 5.13 (0.34) | 10.75 (5.37) |
| Mean (s.d.) on CTQ-EA | 11.53 (7.23) | 5.94 (1.61) | 17.13 (6.23) |
| Mean (s.d.) on CTQ-SA | 10.22 (6.91) | 5.00 (0) | 15.44 (6.36) |
| Mean (s.d.) on CTQ-PN | 8.81 (4.43) | 5.56 (1.37) | 12.06 (4.02) |
| Mean (s.d.) on CTQ-EN | 12.00 (6.33) | 7.50 (1.37) | 16.50 (5.98) |

*Diagnostic and Statistical Manual of Mental Disorders* (4th ed.) not listed were not present in the sample. CAPS = Clinician-Administered PTSD Scale; w/wo = with or without; CTQ-SF = Childhood Trauma Questionnaire—Short Form; PA = physical abuse; EA = emotional abuse; SA = sexual abuse; PN = physical abuse; EN = emotional abuse.

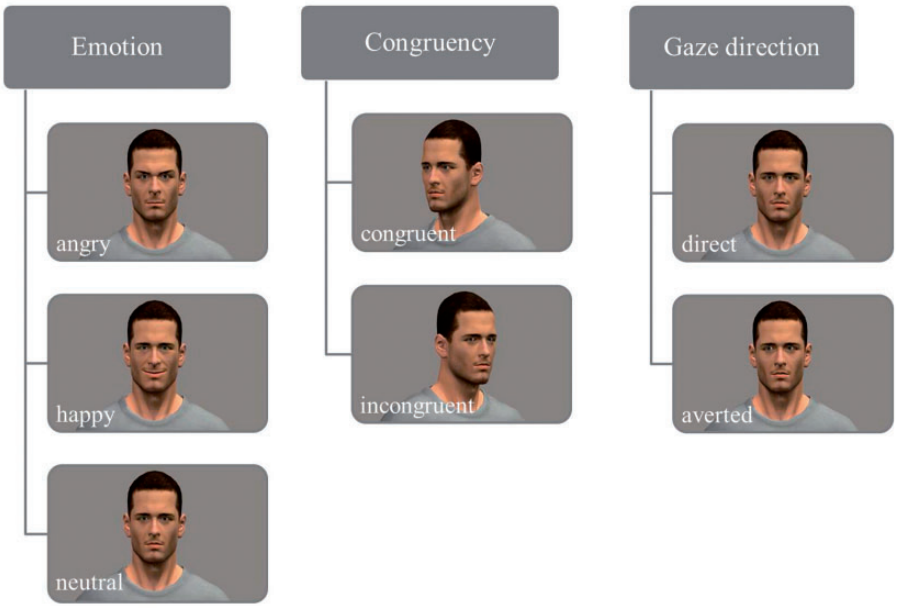


**Fig. 1** Factors examined within this study—emotion (three levels: angry, happy and neutral), congruency of body posture and gaze (two levels: congruent and incongruent) and gaze direction (two levels: direct and averted).

injury or metallic implantations (to account for imaging requirements) were excluded. All participants completed the CTQ (Bernstein *et al.*, 2003), a well-validated measure to assess the extent of exposure to traumatic events during childhood and adolescence. Participants were recruited via advertisements posted within the community and local mental health treatment centers; all participants provided informed consent. Study procedures were approved by the Health Sciences Research Ethics Board of Western University, Canada.

### Behavioral task description and procedure

Stimuli and course of events was modeled from the paradigm developed by Schrammel *et al.* (for a detailed description of stimulus material and development, see Schrammel *et al.*, 2009) and consisted of three-dimensional dynamic animations of four virtual characters moving across the screen. This approach was preferred over presenting two-dimensional static images to create a more realistic course of events, because Pönkänen *et al.* (2011) have shown that an effect of direct compared to averted gaze was only observable when a static facial expression was presented 'live' on a computer-controlled liquid crystal shutter; a digital photograph (pictorial stimulus) of the same person did not lead to any effect of gaze direction.

The stimulus material was composed of video sequences displaying a virtual character that moves across the screen and then either turns toward the observer directly or at 30° to the left or right, the latter usually making the impression that the character is looking at someone or something else. In contrast to Schrammel *et al.* (2009), who depicted male and female virtual characters, only the male characters were used in this study as they were rated slightly higher on naturalness, dominance and sociability (Schrammel *et al.*, 2009). Each video sequence conformed to a fixed interval of 8.8 s that can be divided into three epochs.

At first, the character entered the screen from the left or the right (2 s). Then the character's body posture and head turned either toward the observer or at 30° to the left or the right of the observer. Concurrently, the character's gaze either turned toward the observer implicating a mutual eye-to-eye contact (direct gaze) or at 30° (averted gaze), and displayed an angry, happy or neutral facial expression (4.8 s). This resulted in four different combinations of body posture and gaze as turning of body posture and gaze were independent. Conditions that displayed virtual characters with equally oriented body posture and gaze were denoted congruent. Finally, in the third epoch, the character turned away and left the screen (2 s). The different combinations of gaze, body posture and emotions are depicted in Figure 1.

In total, participants saw 48 video sequences with four clips for each combination of within-subjects factors [gaze direction (two levels: direct *vs* avert) × congruency (two levels: congruent *vs* incongruent) × emotion (three levels: happy, angry, neutral)] in a randomized order. In all sequences, the character was presented in front of a gray background with only his head and shoulders visible (see Figure 1). The character's hair color (light or dark) as well as the direction of his entrance (from the left or right) was counterbalanced throughout the 48 trials. Participants were merely instructed to watch the video sequences attentively.

Video sequences were presented in two sessions of 8 min and 54 s each, acquiring 178 3 s whole brain imaged volumes. Each session began with a 30-s resting and entailed 24 repetitions of the following blocks: 4.7-s fixation condition, 8.8-s video sequence and 7.5-s fixation cross. Video sequences were displayed via an external projector and viewed via a mirror system.

Immediately after the scanning session, participants were shown still pictures of the facial expressions of the characters and were asked: "What emotion is the character expressing?" and "How do you feel while watching this character?". For both questions, stimuli were rated on a one to nine negative to positive Likert scale.

### Imaging descriptions

All imaging data were collected using a 3.0 T whole-body MRI scanner (Magnetom Tim Trio, Siemens Medical Solutions, Erlangen, Germany) with the manufacturer's 32-channel phased array head coil.

Orthogonal scout images were collected and used to prescribe a three-dimensional T1-weighted anatomical image of the whole head with 1 mm isotropic resolution (MP-RAGE, TR/TE/TI = 2300 ms/2.98 ms/900 ms, flip angle = 9°, FOV (*X*, *Y*, *Z*) = 256 mm × 240 mm × 192 mm, acc. factor = 4, total acq. time - 3 min 12 s). The anatomical volume was used to determine the angle

of the transverse plane passing through both the anterior and posterior commeasures midsagittally and as the source image for interindividual spatial normalization. A set of 64 contiguous, 2 mm-thick imaging planes for blood oxygenation level-dependent (BOLD) fMRI were prescribed parallel to the AC-PC plane and positioned to ensure coverage of the top of the brain.

BOLD fMRI images were acquired with the manufacturer's standard gradient-echo EPI pulse sequence (single-shot blipped EPI) using an interleaved slice acquisition order and tridimensional prospective acquisition correction. EPI volumes were acquired with 2 mm isotropic resolution and the following parameters: FOV = 192 mm × 192 mm, 94 × 94 matrix, TR/TE = 3000 ms/20 ms, flip angle = 90°, 64 slices, 178 measurements.

### Analyses

Imaging data were analyzed using Statistical Parametric Mapping 8 (Wellcome Trust Centre for Neuroimaging, London, UK) implemented in MATLAB 7.2 (Mathworks Inc., Sherborn, MA). To preprocess the data, volumes were normalized to the first volume collected to correct for head -movement and spatially smoothed (8 mm kernel). Voxelwise general linear models with design matrices composed of epoch-related regressors were applied to analyze the fMRI data statistically. All events were convolved with the standard hemodynamic (gamma) response function. Baseline responses were assessed from average activation patterns during the last 3 s of the fixation cross. BOLD-response associated with the video clips was calculated based on average response patterns occurring during the centered 3 s of the 8.8-s lasting video sequences to specify for analysis of that moment in the time course during which trials differed from each other (head is turned and emotion displayed). At the single-subject level, a single BOLD-response contrast map was created for each combination of within factors (e.g. direct–congruent–angry *vs* fixation cross) accounting for differences in the magnitude of the BOLD signal. The results of these preliminary fixed effects analyses were carried forward into random effects analyses.

Data on control subjects were collected and analyzed before individuals with PTSD were investigated. We analysed the data retrieved from control subjects in a full factorial design to explore factors of the paradigm that lead to differences in response rate in controls. Accordingly, appropriate contrasts were analyzed on a second level to explore the main and interacting effects of gaze direction, congruency with body posture and emotion. The full factorial determined clusters of voxels that fell below a height threshold of $P = 0.005$ (uncorrected) and above an extent threshold of $k = 30$ voxels. Our choice of thresholds was guided by Lieberman and Cunningham (2009), who suggest that combined intensity and cluster size thresholds such as $P < 0.005$ with a 10 voxel extent produce a desirable balance between Types I and II error rates. To decrease the likelihood of Type I errors in the full-factorial and one-sample *t*-tests, we set the extent cluster threshold at $k = 30$ since further analyses were based on these results. For subsequent two-sample *t*-tests, we set the *k* value to 10. Follow-up *t*-tests on controls and PTSD subjects were conducted only within factors that were statistically significant within the results of the full factorial. The full factorial yielded a significant main effect of gaze and congruency, but no main effect of emotion or possible interactions (see below). We thus compared congruent (cong) and incongruent (incong) trials in which gaze was direct (D) *vs* averted (A), independent of emotional expression. Group comparisons (PTSD *vs* control) were applied for the congruent condition only.

Primary hypotheses regarding the differential effect of direct gaze were tested employing an region-of-interest (ROI) approach. We hypothesized that the DMPFC, TPJs and TPs (bilaterally) would respond to direct relative to averted gaze in control subjects. In contrast to controls, we hypothesized that subjects with PTSD would lack this activation but would show an increased response in the left SC, the left LC and the amygdala. Coordinates were retrieved independently for the mentioned areas from previously published research and were as follows: DMPFC—MNI −4, +52, +30; TP—MNI ±50, +8, −26 (Kober *et al.*, 2008); left TPJ—MNI −56, −58, +26; right TPJ—MNI +60, −60, +20 (Frewen *et al.*, 2011); left LC—MNI −2, −36, −23, left SC—MNI −0.5, −24, −8; left amygdala—MNI −18,+1, −20; right amygdala—MNI +28, +4, −12 (Liddell *et al.*, 2005). These coordinates served as a point of origin for a spherical search region (ROI) with a radius of 10 mm delineated within the MNI space. Given the a priori hypotheses for the study, contiguous voxels were determined according to the family-wise error rate of 0.05 (reported as $P_{SVC}$ for 'small-volume-corrected').

## RESULTS

### Facial expression ratings

Ratings of the displayed expression and the feelings while watching the virtual characters were submitted to separate 2 × 3 repeated-measures analyses of variance (ANOVAs), with group as a between-subjects factor (control and PTSD) and expression as a within-subjects factor (angry, happy and neutral). As the assumption of sphericity was violated for the within-subjects factor, the degrees of freedom were corrected by using the Greenhouse–Geisser adjustment in both analyses. In *post hoc t*-tests, we corrected for inhomogeneity of variance when necessary by reporting results of Welch's *t*-test. Means and standard deviations for both ratings are presented in Table 2.

With regard to ratings of the displayed expressions, the main effects of group ($F_{1,\ 30} = 10.07$, $P = 0.003$) and expression ($F_{1.32,\ 39.69} = 224.14$, $P < 0.001$) were significant. For reasons noted within the introduction, it was nevertheless of a priori interest to compare responses between individuals with *vs* without PTSD regarding specific facial expressions. *Post hoc t*-tests revealed that the main effect of group traced back to between-group differences in ratings for happy facial expressions. The PTSD and control groups did not differ in their ratings of angry and neutral facial expressions; however, happy facial expression were rated significantly less positive by the PTSD group, $t_{20.95} = 2.71$, $P = 0.013$. Across groups, ratings of facial expressions differed between all three emotions. Angry facial expressions were rated significantly more negative than neutral ones ($t_{31} = -12.67$, $P < 0.001$), and neutral facial expressions were rated significantly more negative than happy faces ($t_{31} = -12.76$, $P < 0.001$).

With regard to ratings of feelings while watching the virtual characters, the main effects of group ($F_{1,\ 30} = 17.15$, $P = < 0.001$) and expression ($F_{1.35,\ 40.57} = 50.89$, $P < 0.001$) were significant. *Post hoc t*-tests revealed that the main effect of group traced back to differences

**Table 2** Means and standard deviations for ratings of the facial expression displayed and feelings while watching still pictures of the virtual characters

| Facial expression | Mean (s.d.) | |
|---|---|---|
| | Control group | PTSD group |
| Rating of facial expressions | | |
| Angry | 2.64 (0.88) | 2.35 (1.02) |
| Neutral | 4.87 (0.29) | 4.75 (0.43) |
| Happy | 8.05 (0.68) | 6.93 (1.50) |
| Rating of feelings | | |
| Angry | 4.16 (0.72) | 3.09 (1.23) |
| Neutral | 4.98 (0.37) | 4.67 (0.61) |
| Happy | 6.60 (1.08) | 5.45 (1.38) |

in ratings for angry ($t_{24.11} = 3.01$, $P = 0.006$) and happy facial expressions ($t_{30} = 2.63$, $P = 0.013$). Feelings during neutral facial expression did not differ significantly between PTSD and control groups. Across groups, ratings of feelings differed significantly between all three facial expressions. Subjects felt more positive during happy expressions when compared with neutral ($t_{31} = 5.58$, $P < 0.001$) and angry faces ($t_{31} = -7.89$, $P < 0.001$), and subjects felt more positive during neutral when compared with angry facial expressions ($t_{31} = -6.29$, $P < 0.001$).

### Neuroimaging: functional BOLD response

#### *Control subjects: full factorial design*

The whole brain analysis revealed a significant main effect of gaze and congruency; results are reported Tables 1 and 2 in the supplementary material. Follow-up *t*-tests indicated that BOLD response increased within several ROIs for the contrast (D > A), including the left anterior cingulate, right frontal as well as left parietal and occipital cortical areas, whereas no areas of the brain increased in BOLD response for the reverse contrast (A > D). Follow-up *t*-tests concerning the main effect of congruency showed different patterns of BOLD response only in the 'incongruent > congruent' contrast. Controls showed increases in BOLD response rate within the right middle frontal and temporal gyrus as well as bilateral cuneus. No regions revealed a significant increase in response rate for a main effect of emotion or possible interactions at $P_{UNC} < 0.005$.

#### *Region of interest analyses (control and PTSD subjects)*

*Congruent body posture.* In control subjects, the DMPFC (MNI: −10, +58, +34, $t_{(15)} = 4.74$, $P_{SVC} = 0.018$) and by trend the left TPJ (MNI: −60, −50, +30, $t_{(15)} = 3.68$, $P_{SVC} = 0.079$) revealed increased BOLD responses to mutual eye-to-eye contact (contrast: $D_{cong} > A_{cong}$). The SC and LC did not show a significant BOLD response during direct gaze. In contrast, the PTSD group responded to mutual eye-to-eye contact (contrast: $D_{cong} > A_{cong}$) with increased activations within left SC/PAG (MNI − 2, −30, −8, $t_{(15)} = 4.02$, $P_{SVC} = 0.040$) and bilateral LC (MNI + 2, −32, −22, $t_{(15)} = 4.50$, $P_{SVC} = 0.020$). SC activity was observed within a large cluster that also encompassed activity within the LC. Figure 2 illustrates this effect. The DMPFC, left LPJ and TPs did not show an increase in BOLD response in subjects with PTSD.

Direct comparisons between groups revealed significantly increased BOLD response in controls when compared with PTSD subjects (controls > PTSD) during direct *vs* averted gaze in the left TPJ (MNI: −60, −50, +30, $t_{(30)} = 3.52$, $P_{SVC} = 0.041$) and the right TP (MNI: +54, +16, −30, $t_{(30)} = 3.47$, $P_{SVC} = 0.046$), whereas differences between groups for the DMPFC were not significant (see Figure 2). In contrast, PTSD subjects revealed a significantly increased BOLD response of the left SC/PAG (MNI − 4, −30, −6, $t_{(30)} = 3.87$, $P_{SVC} = 0.020$) (see Figure 2). Results of the applied whole brain analyses for the described contrasts are displayed in Table 3.

*Incongruent body posture.* The contrast $D > A_{incong}$ revealed a trend toward an increased BOLD response in the DMPFC during direct *vs* averted gaze (MNI: −10 + 54 + 24, $k = 64$, $t_{(15)} = 3.81$, $P_{SVC} = 0.059$, $P_{UNC} = 0.001$) in controls. In subjects with PTSD, we did not observe any differences in response rate in our ROIs.

### Whole brain analyses

#### *Congruent body posture*

*Within-group analyses.* In control subjects, the main effect of direct gaze yielded significant variation in responses mostly within cortical areas, such as the right and left middle and medial prefrontal cortex, right inferior frontal gyrus, bilateral inferior parietal lobule, bilateral precuneus, left superior temporal gyrus, left fusiform gyrus, right cuneus, left inferior occipital gyrus and right lingual gyrus. Furthermore, the right globus pallidus and left hippocampus displayed an increase in activation. Individuals with PTSD showed significantly increased activation predominantly within subcortical areas, including the bilateral thalamus, right globus pallidus, right caudate, left putamen, left SC, bilateral LC and left claustrum. Response within the right inferior and superior frontal gyrus, left temporal gyrus and right cuneus was also noted.

*Between-group analyses.* The comparison of controls with PTSD subjects (controls > PTSD) revealed increased responses exclusively within cortical brain areas, including the right middle frontal gyrus, right precentral frontal gyrus, left supramarginal gyrus, left precuneus, right postcentral gyrus, left middle temporal gyrus and right superior temporal gyrus. The reverse contrast (PTSD > control) yielded significantly elevated responses within subcortical areas, including the left thalamus, left caudate, left insula and the left SC. In addition, the right inferior and left superior frontal gyrus displayed an increased response in PTSD subjects.

#### *Incongruent body posture*

*Within-group analyses.* In controls, the contrast $D > A_{incong}$ displayed significant response within the left insula, right caudate, bilateral anterior cingulate, left cingulate gyrus, right subcallosal gyrus, left inferior and medial frontal gyrus, and right superior frontal gyrus. The same contrast yielded significant response only within the left mammillary body and left posterior cingulate in the PTSD subgroup.

## DISCUSSION

The aim of the present study was to gain insight into the neurobiological effects of mutual eye-to-eye contact in healthy controls when compared with individuals with PTSD related to prolonged childhood abuse. Controls exhibited increased BOLD response during direct *vs* to averted gaze within the DMPFC, left TPJ and right TP but not in the SC/PAG. Under the same conditions, individuals with PTSD showed increased activation within the SC/PAG and LC, during direct *vs* averted gaze, irrespective of the emotion the virtual character displayed; no increase in BOLD response was observed in brain regions involved in social cognition, including the DMPFC, TPJ and TPs. These effects were only observable when gaze and body posture were congruent.

In the current study, we presented angry, happy and neutral virtual characters overtly and prolonged. We therefore hypothesized that healthy subjects would respond to mutual eye-to-eye contact with activation in brain areas associated with the reflective, cognitive route of direct gaze processing, serving to mentalize and evaluate the ongoing social interaction (Liddell *et al.*, 2004; Kuzmanovic *et al.*, 2009). This hypothesis was supported by our results. Specifically, we found that direct *vs* averted gaze with congruent body posture entailed increased activation within the DMPFC, left TPJ and right TP likely reflecting evaluative processes. These results are consistent with studies investigating general mentalizing tasks (Vogeley *et al.*, 2001; Saxe *et al.*, 2006; Kober *et al.*, 2008; Van Overwalle, 2009; Schilbach *et al.*, 2010) as well as research focusing on the differential effect of direct gaze by presenting pictorial stimuli that render a dynamic gaze shift in a virtual reality paradigm (Schilbach *et al.*, 2006; Kuzmanovic *et al.*, 2009; Ethofer *et al.*, 2011). Particularly, activation within the DMPFC is often replicated when examining the differential effect of direct gaze, supporting again that direct when compared with averted gaze provokes higher-level social cognition. Although activation within

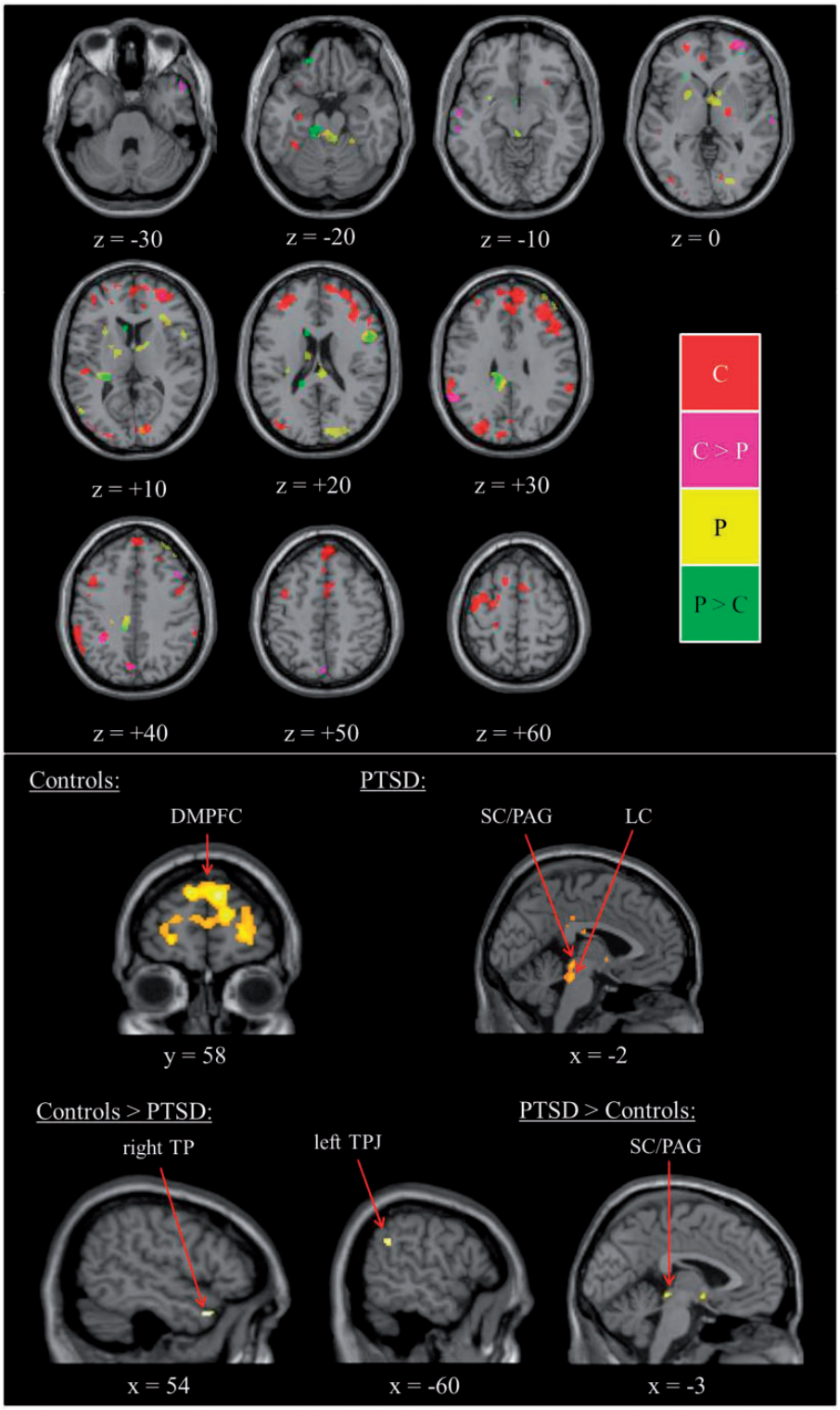


**Fig. 2** Brain areas showing increased BOLD response during direct *vs* averted gaze (*vs* implicit baseline) for controls (C; $n = 16$; $P < 0.005$; $k > 30$) and individuals with PTSD (P; $n = 16$; $P < 0.005$; $k > 30$) as well as for the between-group comparisons controls > PTSD (C > P; $P < 0.005$; $k > 10$) and PTSD > controls (P > C; $P < 0.005$; $k > 10$). Upper three rows display all brain activation observed in transverse slices from $z = -30$ to $z = +60$. Bottom two rows display regions of interest showing increased activation during direct gaze when compared with averted gaze (*vs* implicit baseline) within the controls and PTSD group as well as between groups (bottom row). PTSD = posttraumatic stress disorder; DMPFC = dorsomedial prefrontal cortex; TP = temporal pole; TPJ = temporoparietal junction; SC = superior colliculus; PAG = periaqueductal gray; LC = locus coeruleus; MNI coordinates in brackets.

the DMPFC has not been shown when the stimuli are presented for a very short amount of time, activation in this region seems to enhance with increasing gaze duration (Kuzmanovic *et al.*, 2009). Our findings in healthy controls therefore suggest that longer exposure to direct gaze enhances evaluative 'top–down' processes affecting the ongoing social interaction in healthy individuals, reflecting the second pathway of direct gaze processing. This interpretation is also supported by the results of whole brain analyses, which revealed significant increases

**Table 3** Main effect of direct gaze congruent and incongruent with body posture in controls and PTSD subjects

| Gyrus/sulcus | Hemisphere (right/left) | Extent *k* | Stat. $t_{(15)}$ | $\alpha$ *P* | MNI local max. | | | BA |
|---|---|---|---|---|---|---|---|---|
| | | | | | *x* | *y* | *z* | |
| Congruent | | | | | | | | |
| Controls | | | | | | | | |
| Globus pallidus | R | 67 | 4.76 | <0.001 | 20 | −10 | 0 | – |
| Hippocampus | L | 41 | 3.86 | 0.001 | −30 | −14 | −18 | – |
| Inferior frontal gyrus | R | 2499 | 5.75 | <0.001 | 34 | 30 | 20 | 9, 10, 46 |
| Superior frontal gyrus | L | 83 | 5.71 | <0.001 | −12 | 16 | 56 | 6 |
| Middle frontal gyrus | L | 833 | 5.43 | <0.001 | −42 | 12 | 42 | 4, 6, 9 |
| Middle frontal gyrus | L | 400 | 5.36 | <0.001 | −32 | 44 | 18 | 9, 10 |
| Inferior frontal gyrus | L | 35 | 4.58 | <0.001 | −26 | 16 | −16 | 47 |
| Dorsomedial frontal gyrus | R/L | 156 | 4.03 | 0.001 | 4 | 10 | 52 | 6, 24 |
| Medial frontal gyrus | R | 38 | 3.87 | 0.001 | 10 | 48 | 6 | 10, 32 |
| Superior frontal gyrus | R | 31 | 3.44 | 0.002 | 30 | −14 | 64 | 6 |
| Medial frontal gyrus | R | 43 | 3.43 | 0.002 | 2 | 24 | 44 | 8 |
| Inferior parietal gyrus | R | 81 | 4.97 | <0.001 | 64 | −40 | 32 | 40 |
| Inferior parietal gyrus | L | 409 | 4.85 | <0.001 | −60 | −40 | 36 | 40 |
| Precuneus | L | 49 | 3.74 | 0.001 | −6 | 72 | 40 | 7 |
| Superior temporal gyrus | L | 68 | 4.46 | <0.001 | −48 | −26 | 8 | 22, 41 |
| Fusiform gyrus | L | 59 | 3.77 | 0.001 | −34 | −44 | −20 | 20 |
| Cuneus | R | 89 | 4.41 | <0.001 | 16 | −82 | 8 | 17, 18 |
| Inferior occipital gyrus | L | 602 | 4.29 | <0.001 | −38 | −80 | −4 | 18, 19 |
| Lingual gyrus | R | 44 | 3.59 | 0.001 | 18 | −60 | −4 | 19 |
| Precuneus | R | 37 | 3.39 | 0.002 | 4 | −72 | 26 | 31 |
| PTSD | | | | | | | | |
| Thalamus/globus pallidus | R | 247 | 5.00 | <0.001 | 10 | −2 | 6 | – |
| Thalamus/putamen | L | 248 | 4.73 | <0.001 | −10 | −10 | 16 | – |
| Locus coeruleus | R/L | 155 | 4.50 | <0.001 | 2 | −32 | −22 | – |
| Superior colliculus | L | 155 | 4.02 | <0.001 | −2 | −30 | −8 | – |
| Claustrum | L | 35 | 3.45 | 0.002 | −28 | 14 | 8 | – |
| Posterior cingulate gyrus | L | 322 | 6.82 | <0.001 | −10 | −34 | 32 | 23 |
| Inferior frontal gyrus | R | 306 | 5.25 | <0.001 | 52 | 8 | 18 | 5, 44 |
| Superior frontal gyrus | R | 93 | 3.87 | 0.001 | 32 | 52 | 36 | 9 |
| Inferior frontal gyrus | R | 50 | 3.36 | 0.002 | 36 | 24 | 10 | 13 |
| Middle temporal gyrus | L | 43 | 4.59 | <0.001 | −54 | −66 | 10 | 19 |
| Fusiform gyrus | R | 31 | 3.80 | 0.001 | 34 | −40 | −24 | 20,36 |
| Cuneus | R | 290 | 4.32 | <0.001 | 18 | −84 | 16 | 18, 19 |
| Controls > PTSD | | | | | | | | |
| Middle frontal gyrus | R | 114 | 3.65 | <0.001 | 32 | 58 | −6 | 10 |
| Precentral gyrus | R | 27 | 3.28 | 0.001 | 44 | 22 | 40 | 9 |
| Precentral gyrus | R | 13 | 3.17 | 0.002 | 22 | −22 | 70 | 6 |
| Middle frontal gyrus | R | 18 | 3.05 | 0.002 | 30 | 52 | 10 | 10 |
| Supramarginal gyrus | L | 51 | 3.52 | 0.001 | −60 | −50 | 30 | 40 |
| Precuneus | L | 60 | 3.28 | 0.001 | −2 | −74 | 48 | 7 |
| Postcentral gyrus | R | 30 | 3.26 | 0.001 | 28 | −34 | 74 | 3 |
| Superior temporal gyrus | R | 19 | 3.47 | 0.001 | 54 | 16 | −30 | 38 |
| Superior temporal gyrus | R | 10 | 3.39 | 0.001 | 66 | −18 | 0 | 22 |
| Middle temporal gyrus | L | 29 | 3.29 | 0.001 | −66 | −22 | −6 | 21 |
| PTSD > controls | | | | | | | | |
| Superior colliculus | L | 16 | 3.87 | <0.001 | −4 | −30 | −6 | – |
| Caudate | L | 57 | 3.72 | <0.001 | −10 | 14 | 18 | – |
| Inferior frontal gyrus | R | 115 | 3.82 | <0.001 | 52 | 8 | 22 | 44 |
| Superior frontal gyrus | L | 30 | 3.50 | 0.001 | −18 | 48 | −18 | 11 |
| Incongruent | | | | | | | | |
| Controls | | | | | | | | |
| Insula | L | 406 | 4.83 | <0.001 | −36 | 18 | 20 | 13 |
| Caudate | R | 63 | 4.09 | <0.001 | 10 | 4 | 10 | – |
| Cingulate gyrus | L | 34 | 5.29 | <0.001 | −6 | −48 | 42 | 31 |
| Anterior cingulate | R | 87 | 5.11 | <0.001 | 10 | 32 | 6 | 24 |
| Anterior cingulate | L | 303 | 4.60 | <0.001 | −8 | 36 | −6 | 32 |
| Subcallosal gyrus | R | 268 | 4.57 | <0.001 | 16 | 4 | −16 | 34 |
| Inferior frontal gyrus | L | 60 | 5.39 | <0.001 | −34 | 26 | −14 | 11, 47 |
| Superior frontal gyrus | R/L | 197 | 4.73 | <0.001 | 6 | 44 | 58 | 8, 9 |
| Inferior frontal gyrus | L | 181 | 4.68 | <0.001 | −54 | 20 | 8 | 45 |
| Medial frontal gyrus | R/L | 188 | 4.35 | <0.001 | −10 | 58 | 18 | 9, 10 |
| PTSD | | | | | | | | |
| Mammillary body | L | 33 | 5.22 | <0.001 | −6 | −8 | −16 | – |
| Posterior cingulate | L | 44 | 3.80 | 0.001 | −8 | −50 | 4 | 29, 30 |

of BOLD response in almost exclusively cortical brain areas, such as prefrontal and frontal, inferior parietal as well as superior temporal regions.

In comparison, individuals with PTSD responded to mutual eye-to-eye contact with an increased activation in the LC and particularly the SC/PAG, across all emotions displayed by the virtual character. These results support our hypothesis that, in individuals with PTSD, direct gaze leads to a sustained activation of the subcortical route of eye-contact processing rooting in the SC as well as the underlying circuits of the PAG as described by Senju and Johnson (2009). This subcortical pathway may be anatomically and functionally related to a more general face-processing pathway that has been described as an innate alarm system and may serve to detect potential signals of threat (Liddell *et al.*, 2005). This view is supported by studies finding that pharmacological and electrical stimulation of the dorsal PAG or the deep layers of the SC evokes anxiety-related responses in animals, for example, active defensive behaviors like running (Sudré *et al.*, 1993; Lovick, 2000; de Almeida *et al.*, 2006; Broiz *et al.*, 2011). The dorsal PAG and the deep layers of the SC may thus represent the anatomical locus of panic behavior (Lovick, 2000). A recent study by the Georgetown University Medical Center (2009) supports this view and suggests that activation of the deep layers of the SC elicits defensive behaviors, such as an exaggerated startle, hypervigilance, cowering and escape. These symptoms are commonly observed in individuals with PTSD (American Psychiatric Association, 2000). However, there has been discussion as to whether the subcortical face processing pathway can be interpreted as an alarm system. Activation of the subcortical route may also represent a reaction toward a biologically salient and emotionally relevant stimuli, in general, including faces that are not necessarily threatening (Johnson, 2005).

In the present study, the whole brain results reveal that activation of the SC/PAG was accompanied by heightened responses of the LC as well as increased activation within the thalamus and the inferior and superior frontal gyrus. These results yield further evidence to suggest activation of the subcortical pathway of direct gaze processing as these brain regions were also found to be activated by Liddell *et al.* (2005). The crude sensory representation of the threat-related stimulus developed in the PAG/SC reaches frontal cortical areas via the thalamus and the LC. Activation in frontal areas enables the response to the potentially threatening stimuli with a reflective orientating response that serves to highlight the stimulus for attentional processing (Halgren and Marinkovic, 1995; Liddell *et al.*, 2005). The LC supports this process by facilitating processing of stressful, highly salient stimuli and contexts (Aston-Jones *et al.*, 1996; Jones, 2003; Liddell *et al.*, 2005) and plays an important role in enhancing attentional processes by sending projections to the pulvinar and the SC (Berntson *et al.*, 2003). Although there is evidence that the LC receives direct descending efferent projections from the PAG/SC (Mantyh, 1983), Liddell *et al.* (2005) assume that this activation is mediated by the amygdala. In the present study, we did not observe increased activation of the amygdala, suggesting that activation within the LC was either mediated by a different structure than the amygdala or that the current methodology is not sensitive to increased amygdala activation. Specifically, the prolonged presentation (8.8 s) of the stimuli in the current study may have prevented the observation of amygdala activation through activation of specific top–down mechanisms that can regulate activation of this region (Kuzmanovic *et al.*, 2009; Adams *et al.*, 2011).

In individuals with PTSD, direct gaze did not enhance activation in areas associated with higher-level social cognitions, such as the left TPJ and the right TP. These findings suggest that an evaluation of the social interaction with the virtual character may not occur, at least not rapidly. The latter may be related to the fact that activation of the deep

layers of the SC and the underlying circuits of the PAG have been suggested to be linked to an altered state of 'primary-process consciousness' that is based on basic neural representations of pain, fear, anger, separation distress, sexual and maternal behavior (Panksepp, 1998; Watt, 2000) and not to involve more complex thoughts or clearly defined perceptions. We thus suggest that activation of the SC/PAG during direct eye contact in individuals with PTSD may signify an altered, 'lower-level' state of consciousness that does not encompass an ability to reflect about others' purposes and intentions.

The hyperresponsiveness of this alarm system may be related to its frequent and sustained activation during prolonged childhood abuse. The latter may in turn lead to a malfunctioning of the SC/PAG and may be an important factor leading to the development of defensive behaviors, such as an exaggerated startle, hypervigilance, cowering and escape, as observed in PTSD (Lovick, 2000; Georgetown University Medical Center, 2009). Given that our results did not vary across different emotions, it is possible that mutual eye-to-eye contact in subjects with PTSD signaled a threat irrespective of the expression displayed by the character, including when no emotional expression was displayed. Ratings of emotional expressions show that especially happy facial expression are rated less positive in subjects with PTSD. This may be due to the potentially contradictory meaning of a happy face in an abusive relationship. Moreover, emotional responses elicited in the subjects were rated significantly more negative in the PTSD group for all three facial expressions. A limitation that is important to note, however, is that still pictures of the facial expressions of the characters and not the video sequences that were used in the fMRI scanner were used to obtain subjective ratings. The videos create a more interpersonal impression and may therefore be perceived differently, which should be examined in a future study. In addition, the displayed emotions were limited to angry, happy and neutral facial expressions. Future studies should also examine other emotions such as fear or sadness that constitute a behavioral tendency of avoidance, especially because the comparison of fearful and happy faces yielded activation of subcortical brain areas in individuals with PTSD in previous studies (Rauch *et al.*, 2000; Shin *et al.*, 2005; Fonzo *et al.*, 2010). The results reported in this study resulted from video sequences that displayed virtual characters with congruent body posture and gaze. In the incongruent condition, effects were reduced in healthy individuals and below threshold in patients with PTSD. Controls also showed a trend toward enhanced activation within the DMPFC during direct *vs* averted gaze. Direct when compared with averted gaze may therefore be associated with higher-level social cognition in the incongruent condition, even though future studies will have to examine this further. In patients with PTSD, however, we did not observe any increase in brain activity within our ROIs. We thus assume that the subcortical route of eye-contact processing remained inactivated during direct gaze in the incongruent condition. As body orientation is used as a cue for spatial direction, the direction another individual is moving to (Emery, 2000), discrepancies concerning the self-relevance of the direct gaze may have occurred in the incongruent condition. An averted body posture even in combination with direct gaze may signal a tendency toward moving away rather than approaching the individual. In our study, only body posture and gaze were regarded independent from each other, body posture and head direction were always equally aligned. Future studies should therefore examine whether the subcortical route of eye-contact processing is activated when body posture and gaze are incongruent and head direction and gaze are congruent when a virtual character appears to look over its shoulder (averted body posture, but direct head and gaze direction). This may provide a more realistic course of events as we usually do not only shift our gaze to a new stimulus but also adjust our head position.

Several limitations of the current study are worth noting. First, by using dynamic animations of virtual characters, we aimed to mitigate the methodological limitations that arose when using pictorial stimuli as described by Pönkänen *et al.* (2011). However, we did not present a 'live' person creating mutual eye-to-eye contact but instead used virtual characters. Saygin *et al.* (2011) found that gazing at a robot with biological appearance led to notable differences in brain activity when compared with a human and robot with non-biological appearance that exhibited an activation pattern similar to each other. These results may be explained by unpredictability of the robot with biological appearance, which may also be a factor in the present study. Comparison of the effects of mutual eye-to-eye contact appearing with a virtual character to a 'live' person in future studies may therefore be fruitful. In addition, the effect of the virtual characters' gender (Fonzo *et al.*, 2010) should be evaluated in future investigations. Furthermore, we did not examine a group of trauma-exposed individuals without PTSD. However, we have previously found that recruiting trauma-exposed individuals who exhibit CTQ scores similar to the ones in the present PTSD group in the absence of psychiatric diagnoses is not feasible. In addition, comorbid anxiety disorders in the present sample may have contributed to the observed effects, especially since anxiety is known to be associated with hyperactive-orienting behaviors and an inability to disengage from threatening stimuli (Bar-Haim *et al.*, 2007). Forthcoming studies should also examine behavioral and autonomic measures in conjunction with the BOLD response. Finally, future research directions include examination of how the neural response in traumatized individuals to others' gaze impacts on their ability to interact with others, including within psychotherapy and in the parenting role.

## SUPPLEMENTARY DATA

Supplementary data are available at *SCAN* Online.

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### Conflict of Interest

None declared.

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