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Effect of direct eye contact in women with PTSD related to interpersonal trauma: Psychophysiological interaction analysis of connectivity of an innate alarm system

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ABSTRACT

In healthy individuals, direct eye contact is thought to modulate a cortical route eliciting social cognitive processes via activation of a fast subcortical pathway. This study aimed to examine functional brain connectivity during direct eye contact in women with posttraumatic stress disorder (PTSD) related to childhood abuse as compared with healthy controls. We conducted psychophysiological interaction (PPI) analyses in Statistical Parametric Mapping-8 (SPM8) using the superior colliculus (SC) and locus coeruleus (LC) as seed regions while 16 healthy subjects and 16 patients with a primary diagnosis of PTSD related to childhood maltreatment viewed a functional magnetic resonance imaging (fMRI) paradigm involving direct (D) versus averted (A) gaze (happy, sad, neutral). The PTSD group showed a significantly enhanced connectivity between the SC and the anterior cingulate, and between the LC and the thalamus, caudate, putamen, insula, cingulate gyrus, and amygdala, as compared with healthy individuals. Symptom severity scores on the Clinician-Administered PTSD Scale (CAPS) showed significant positive correlations with superior colliculus connectivity with the perigenual and posterior cingulate, insula, and sublenticular extended amygdala. Functional connectivity data suggest increased recruitment of brain regions involved in emotion processing during direct gaze in PTSD in association with the fast subcortical pathway. The interpretation of eye contact as a signal of threat may require more emotion regulatory capacities in patients with PTSD.

1. Introduction

In healthy individuals, direct eye contact is thought to activate a fast subcortical pathway which then modulates a cortical route eliciting higher social cognitive processes (Senju and Johnson, 2009). In a previous study (Steuwe et al., 2014), we examined the neurobiological effects of mutual eye-to-eye contact in healthy controls as compared with individuals with posttraumatic stress disorder (PTSD) related to childhood maltreatment. Irrespective of the displayed emotion, individuals with PTSD showed increased activation in the superior colliculus (SC) and locus ceruleus (LC). Our findings suggest that direct gaze leads to a sustained activation of a subcortical route of eye contact processing in individuals with PTSD which has been suggested to function as an innate alarm system. A study by Georgetown University MedicalCenter (2009) supports the view of the subcortical route of direct gaze processing being an innate alarm system 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, and activation of brain structures involved in such defensive responses during direct eye gaze may help to explain why individuals with PTSD often perceive eye contact as threatening (Krill and McKinnon, 2010; Wilkinson, 2010) and why they exhibit abnormal neural responses during social cognitive processing (for review, see Lanius et al., 2011).

A cortical network involving the right posterior superior temporal sulcus, with components of both ventral and dorsal

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

Variable	Full sample $N=32$	Controls $n=16$	PTSD $n=16$	Statistical values
Demographic				
Mean (S.D.) age	32.06 (12.03)	30.56 (12.61)	33.56 (11.63)	$t_{(30)}=-0.70$, $p=0.490$
% Employed (full or part time)	84.38	100	68.75	$\chi^2_{(\text{d.f.}=1)}=5.93$, $p=0.015$
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)	$t_{(30)}=-4.17$, $p<0.001$
M (S.D.) on CTQ-EA	11.53 (7.23)	5.94 (1.61)	17.13 (6.23)	$t_{(30)}=-6.96$, $p<0.001$
Mean (S.D.) on CTQ-SA	10.22 (6.91)	5.00 (0)	15.44 (6.36)	$t_{(30)}=-6.56$, $p<0.001$
Mean (S.D.) on CTQ-PN	8.81 (4.43)	5.56 (1.37)	12.06 (4.02)	$t_{(30)}=-6.12$, $p<0.001$
Mean (S.D.) on CTQ-EN	12.00 (6.33)	7.50 (1.37)	16.50 (5.98)	$t_{(30)}=-5.73$, $p<0.001$

Diagnostic and Statistical Manual of Mental Disorders (4th ed.) disorders 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.

frontoparietal attentional networks, has been proposed to be engaged during eye gaze in healthy subjects (Nummenmaa et al., 2010). To our knowledge, however, no studies have examined functional connectivity during eye gaze in PTSD to date. The objective of the current investigation is therefore to examine whole brain connectivity in PTSD and healthy individuals during direct (D) versus averted (A) gaze using the SC or LC as seed regions for the subcortical pathway. We hypothesized altered patterns of connectivity involving brain regions involved in emotion processing and regulation during direct gaze in persons with PTSD compared with controls. More specifically, we expected to see altered neural activation within brain regions involved in higher order social cognitive and emotion-regulatory processes in healthy individuals compared with PTSD subjects.

2. Methods

2.1. Participants

The sample consisted of 32 female participants: 16 healthy comparison subjects and 16 patients with a primary diagnosis of PTSD as previously described (Steuwe et al., 2014). Demographics, clinical severity, and comorbidity characterizing the present sample are presented in Table 1. Healthy comparison subjects and PTSD subjects did not differ in age. However, significantly more control subjects were currently employed. Trauma history was assessed via the Childhood Trauma Questionnaire – Short Form (Bernstein et al., 2003) and the Clinician-Administered PTSD Scale (CAPS) (Blake et al., 1995). All subjects experienced PTSD related to a traumatic history of childhood abuse and scored above the common cut-off of 50. The Structured Clinical Interview for DSM-IV Axis I Disorders – Research Version (First et al., 1996) was administered to ascertain Axis I comorbidities in subjects with PTSD and control participants. Present and lifetime Axis I disorders are depicted in Table 1. 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 injury or metallic implantations (to account for imaging requirements) were excluded. Among the PTSD subjects, 68.8% ($n=11$) were receiving psychotherapy at the time of assessment for this study. All subjects refrained from taking medications for at least 1 month before participation in the study. 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.

2.2. Stimuli

Stimuli and course of events were modeled from the paradigm developed by Schrammel et al. (2009) and consisted of three-dimensional dynamic animations of four virtual characters moving across a computer screen. The stimulus material consisted of video sequences displaying a virtual character that moves across the screen and then either turns towards the observer directly or at 30° to the left or right, the latter usually giving the impression that the character is looking at someone or something else (Fig. 1). For the purpose of this analysis, incongruent data were eliminated from the analysis and data were pooled across emotions to study the main effect of gaze direction.

2.3. 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 tri-dimensional T1-weighted anatomical image of the whole head with 1-mm isotropic resolution (Magnetization Prepared Rapid Gradient Echo (MP RAGE), repetition time (TR)/echo time (TE)/inversion time (TI)=2300 ms/2.98 ms/900 ms, flip angle=9°, field of view (FOV) (x, y, z)=256 mm × 240 mm × 192 mm, acc. factor=4, and total acqusition 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 commisures mid-sagittally and as the source image for interindividual spatial normalization. A set of 64 contiguous, 2-mm-thick imaging planes for functional magnetic resonance imaging (fMRI)/blood-oxygen-level-dependent (BOLD) were prescribed parallel to the anterior and posterior commissures (AC–PC) plane.

BOLD fMRI images were acquired with the manufacturer's standard gradient echo EPI (Echo Planar Imaging) pulse sequence (single-shot blipped EPI) using an interleaved slice acquisition order and tri-dimensional Prospective Acquisition Correction (3D-PACE). 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, and 178 measurements.

2.4. Connectivity analyses

This is a re-analysis of a previously published study (Steuwe et al., 2014). Whereas the previous report compared BOLD response between groups during