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Amygdala reactivity and connectivity during social and non-social aversive stimulation in social anxiety disorder

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ABSTRACT

Social anxiety disorder (SAD) is characterized by exaggerated amygdala reactivity in response to symptom provocation, but it is unclear if such hyper-reactivity is elicited by disorder-specific challenges only or characterizes reactions to aversive stimuli in general. Here, using functional magnetic resonance imaging in 14 patients with SAD, as compared to 12 healthy controls, we found that amygdala hyper-reactivity is confined to disorder-relevant social stimulation. SAD patients displayed increased amygdala reactivity to fearful as compared to neutral facial pictures, but not in response to generally aversive but mainly non-social stimulation when compared to neutral pictorial stimuli taken from the International Affective Picture System. The increased amygdala reactivity was not mediated by an altered prefrontal inhibition among SAD patients as compared to controls, suggesting increased bottom-up processes rather than attenuated top-down control. In conclusion, the enhanced amygdala reactivity in SAD seems specific to socially relevant stimuli rather than aversive stimuli in general.

1. Introduction

Social anxiety disorder (SAD) affects around 12% of the population in Western societies (Kessler et al., 2005), compromises quality of life (Stein and Stein, 2008), imposes high societal costs (Grant et al., 2005; Stein et al., 2005) and enhances the risk for depression (Beesdo et al., 2007). Core symptoms of SAD include excessive fear of being judged by others or scrutinized in social situations such as public speaking. The excessive concern of being negatively evaluated leads to profound anxiety in social situations or their avoidance (American Psychiatric Association, 2013).

The neurobiological underpinnings of SAD include an exaggerated amygdala response to disorder-relevant stimulation including harsh or fearful faces (Blair et al., 2008; Etkin and Wager, 2007; Freitas-Ferrari et al., 2010; Brühl et al., 2014; Gentili et al., 2016; Stein et al., 2002) when compared to healthy controls, which is seen also during emotion processing (e.g. Klumpp et al., 2010; Phan et al., 2013). Further, studies have compared amygdala activation in response to generally aversive pictures/scenes in SAD patients vs. other anxiety disorders and healthy controls (Shah et al., 2009; Buff et al., 2016; Weidt et al., 2016) but none of these studies included comparisons of amygdala reactivity across social and non-social stimulation. The only study to date that has investigated responses to both harsh faces and aversive scenes in SAD patients reported that both categories increased amygdala reactivity, but to an equal degree as in healthy controls (Goldin et al., 2009). However, the critical three-way interaction between stimulus (faces vs. scenes), valence (negative vs. neutral) and group (SAD vs. healthy controls) was not reported. Thus, it is not clear if amygdala hyper-reactivity in SAD is generalized, characterizing exaggerated reactions to aversive stimulation at large, or if it is specific for social stimuli like faces, targeting the symptom dimensions of social anxiety.

Here, we performed a functional magnetic resonance imaging (fMRI) study in patients with SAD and healthy controls to evaluate the neural effects of social and non-social aversive stimuli. Fearful facial emotional expressions known to elicit exaggerated amygdala reactivity in SAD patients (Phan et al., 2006; Prater et al., 2013) were contrasted

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against aversive but mainly non-social scenes (Shah et al., 2009), and both types of aversive stimuli were compared to their neutral counterparts. This approach enables to test whether social and non-social stimuli affect the two groups differently, addressing if SAD patients react with heightened amygdala response to the social stimuli specifically. Moreover, because the ventromedial prefrontal cortex (vmPFC) is suggested to be critical for the regulation of amygdala activity in humans (see e.g. Motzkin et al., 2015), enhanced amygdala responsivity could mirror an intrinsically hyper-reactive amygdala complex or be a marker of attenuated prefrontal top-down inhibition. While it has been argued that anxiety disorders are characterized by a lack of modulation of the amygdala from the vmPFC (e.g. Kim et al., 2011), it is not known if this is a general mode of brain action or confined to disorder-specific stimuli discriminating between affected and non-affected individuals. Thus, we also examined if the connectivity between the amygdala and the vmPFC differs between SAD patients and healthy controls during social and non-social stimulation.

2. Methods

2.1. Participants

Fourteen patients who met the DSM-IV criteria (American Psychiatric Association, 2000) for SAD (Mean age = 32.4, SD = 8.8 years) were enrolled in the study along with 12 healthy controls (HC) (Mean age = 28.0, SD = 8.2 years). All participants were right-handed men and a subset of the data has previously been reported in Frick et al. (2013). The two groups were not statistically different in terms of their age ($t(24) = 1.28$, $p = 0.21$) or educational level ($\chi^2(1) = 0.097$, $p = 0.76$). SAD patients were recruited through newspaper advertisements and HC participants were recruited through public billboards at a local hospital. All participants underwent the Structured Clinical Interview for DSM-IV Disorders (SCID) (First et al., 1997) administered by a master student, under supervision, at the Department of Psychology, Uppsala. Patients were initially screened with the Social Phobia Screening Questionnaire (Furmark et al., 1999) and interviewed with SCID only if they fulfilled the screening criteria for SAD. The Liebowitz Social Anxiety Scale self-report measure (LSAS-SR) (Fresco et al., 2001) was additionally administered to evaluate the self-experienced severity of social anxiety in the SAD group (Mean = 72.1, SD = 25.7). All patients met the DSM-IV criteria for SAD as primary diagnosis. Two of these patients had subthreshold obsessive-compulsive disorder and one had comorbid specific phobia. One individual received pharmacological treatment (venlafaxine).

The criteria for exclusion of the SAD group were: recently started or ongoing psychological treatment; primary diagnosis other than SAD; current drug or alcohol abuse and other psychiatric or organic disorders that could affect the results (e.g. schizophrenia). Participants from the HC group did not fulfil any of the DSM-IV axis I disorders, nor did they have a history of any psychiatric disorder.

The research was approved beforehand by the Ethical Committee at the Karolinska Institute, Stockholm. All participants provided their written informed consent before their actual participation in the research. The pre-research clinical assessments did not reveal any compromised ability to provide informed consent.

2.2. MR image acquisition

A Siemens Avanto 1.5 T whole-body MR-scanner with a 12-channel matrix head coil was employed to acquire both structural and functional images. For structural images, 176 slices were collected using a 3D magnetization-prepared rapid acquisition gradient echo sequence, repetition time 2300 ms, inversion time 1100 ms, echo time 3.93 ms, slice thickness 1 mm, field of view 256 × 256 mm, matrix 256 × 256. Functional scans were acquired using a T2*-weighted gradient echo planar imaging sequence, 30 interleaved coronal slices, repetition time 3000 ms, echo time 50 ms, slice thickness 5 mm, gap between slices 0.5 mm, field of view 220 mm, matrix 64 × 64, inplane voxel dimension 3.4 × 3.4 mm.

2.3. fMRI paradigms

All participants underwent two standard emotional paradigms – emotional faces and emotional scenes paradigms, in that order, during functional MRI. Participants viewed the stimuli in both paradigms projected on a screen through a mirror on top of the head coil.

2.3.1. Emotional face paradigm

The emotional face paradigm consisted of alternating blocks of neutral and fearful faces interspersed with blocks showing a fixation cross. Photographs of faces from the Ekman and Friesen (1976) face collection were used as stimuli. Every participant started with the neutral face block. Three neutral face blocks and three fearful face blocks were presented. Both blocks consisted of 15 faces presented for 2 s each followed by a fixation cross for 400 ms (block duration of 36 s in total). In between the face blocks, an 18-second-long rest block with white fixation cross on a black background was presented. As in other similar studies (e.g. Blair et al., 2008; Stein et al., 2002) the task also required subjects to identify the sex of the face by pressing buttons with their right index and middle fingers in order to make sure that the participants were attentive to the task during the entire paradigm. The total duration of the paradigm was 5 min and 42 s.

2.3.2. Emotional scenes paradigm

The emotional scenes paradigm consisted of alternating blocks of neutral and aversive, but mainly non-social scenes interspersed with blocks showing a black screen. Photographic stimuli for this paradigm were derived from the well standardized International Affective Picture System (IAPS) (Lang et al., 2008). Every participant started with the neutral block. Both blocks consisted of 5 scenes presented for 3.9 s, each followed by a black screen for another 3.9 s (block duration of 39 s in total). In between the blocks with scenes, a 21-second-long rest block with white fixation cross on a black background was presented. During presentation of each scene, participants responded through a button press if the scene was unpleasant (middle finger) or not (index finger). The total duration of the paradigm was 8 min and 35 s. The following IAPS slides were used: aversive- 1300, 3000, 3010, 3015, 3051, 3053, 3060, 3062, 3063, 3064, 3080, 3120, 3130, 3150, 3170, 3266, 3400, 9040, 9252, 9253, 9405, 9410, 9420, 9570, 9921; neutral- 2440, 2480, 2518, 2570, 2580, 2620, 2840, 2850, 2870, 2880, 2890, 5731, 7140, 7180, 7205, 7215, 7234, 7235, 7490, 7491, 7500, 7700, 9210, 9360, 9700.

2.4. Behavioral and demographic analyses

All behavioral and demographic data were analyzed using IBM SPSS Statistics 22 software. Data on valence, arousal, accuracy and reaction times were analyzed using between-group t-tests with the alpha level set to $p < 0.05$.

2.5. Functional magnetic resonance imaging analyses

The functional magnetic resonance imaging analyses were performed by using Statistical Parametric Mapping Software 12 (SPM12; Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab R2017a (MathWorks, Natick, MA, USA). The first three volumes for each participant were discarded to allow for T1 equilibration effects. Standard image pre-processing steps were done: (1) realignment of functional volumes to mean volume in order to correct for motion, (2) co-registration of structural and functional images, (3) normalizing functional images to Montreal Neurological Institute (MNI) standard space and re-slicing to 3 mm isotropic voxels

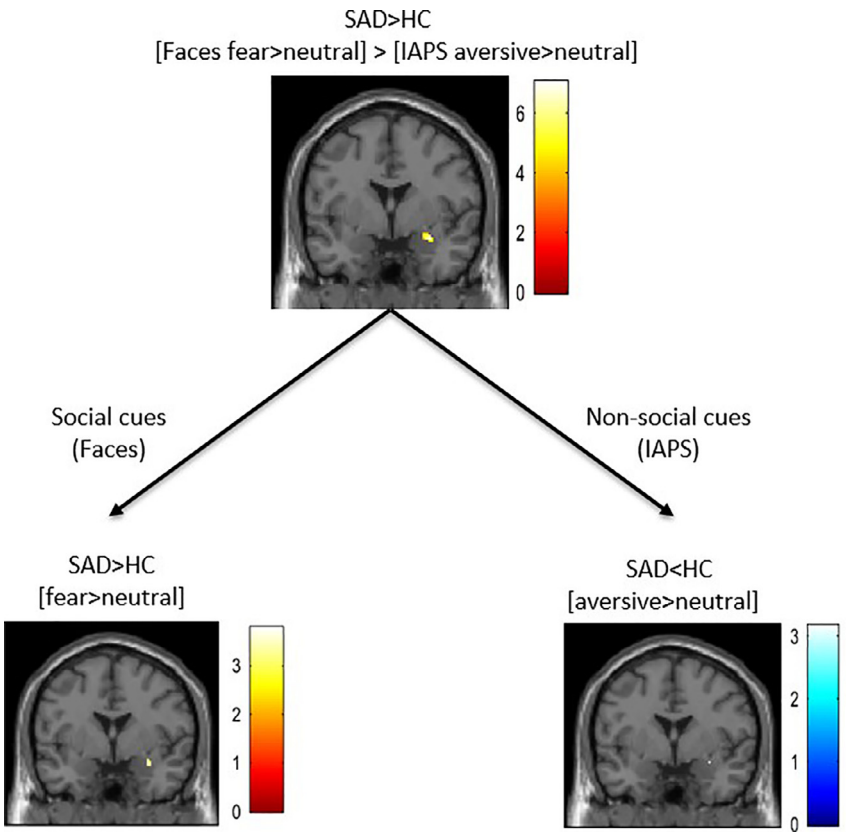

Fig. 1. Significant 3-way interaction indicating heightened right amygdala reactivity in patients with social anxiety disorder (SAD) as compared to healthy controls (HC) to fearful (vs. neutral) faces contrasted against aversive (vs. neutral) IAPS scenes (top row). Follow-up analyses revealed higher amygdala reactivity in SAD than HC individuals to fearful (vs. neutral) faces (bottom left) but lower corresponding reactivity to aversive (vs. neutral) IAPS scenes (bottom right). Images are oriented with right to the right.

and (4) smoothing of functional images with an 8-mm 3D Gaussian kernel (full width, half maximum). Quality assurance by visual inspection indicated adequate image quality and that the preprocessing steps were successful. Between-volume (relative) movement and rotation during fMRI scanning was less than 3 mm and 3 degrees for all participants and scans.

The blood oxygenation level-dependent (BOLD) signal was modelled with the general linear model at each voxel using the SPM canonical hemodynamic response function and a 128-s high-pass filter. Neutral and fearful face-blocks and neutral and aversive scenes (IAPS) were included as regressors in two separate first level models together with six realignment parameters from the respective motion correction step. From these models, difference images depicting brain reactivity to fearful minus neutral faces and aversive minus neutral IAPS scenes, as well as their difference (faces minus scenes) were calculated with the SPM Imcalc function. These difference images were then entered into group level analyses. Our main aim was to perform a three-way interaction analysis with the factors group (SAD and HC) × stimulus (faces and IAPS scenes) × valence (fearful/aversive and neutral). This allowed us to study potential differences in brain reactivity between social vs. non-social fear and aversive vs. neutral stimuli between SAD and HC groups.

The statistical threshold for significance was set at $p < 0.05$ family-wise-error-corrected (*FWE*). Starting with the three-way contrast, the bilateral amygdala was chosen as the a priori anatomical region of interest (ROI), based on earlier findings of increased reactivity to threat, its reliable activation in response to emotionally valenced pictures (e.g. Yoon et al., 2007) and its exaggerated activity in SAD patients (Brühl et al., 2014; Freitas-Ferrari et al., 2010; Gentili et al., 2016). The amygdala was defined using the Automated Anatomical Labeling (AAL) library from the Wake Forest University Pickatlas (Maldjian et al., 2003). Additionally, for significant clusters found in the three-way interaction, correlational analyses were performed in IBM SPSS Statistics 22 to test the relation between brain reactivity and social anxiety symptom severity (LSAS-SR). The AAL atlas was also used to map voxel coordinates to brain regions. All coordinates are reported in MNI standard space.

Additionally, because of the central role of vmPFC in regulating amygdala activity (see e.g. Motzkin et al., 2015), we performed connectivity analyses using the Generalized Form of Context-Dependent Psychophysiological Interactions (gPPI) (McLaren et al., 2012), with the amygdala cluster reflecting group differences in the three-way interaction chosen as the seed region. In a priori analyses, we used an inclusive mask of the vmPFC to examine its functional connectivity with our primary seed region. We used the same mask specifications as in our previous paper (Agren, et al., 2012), i.e., based on Phelps et al. (2004) and Milad et al. (2007), vmPFC was defined as a 10-mm spherical ROI centered on the MNI coordinates *x,y,z* = 4, 32, -5. In addition to ROI analyses, whole brain reactivity and connectivity analyses were also conducted.

3. Results

Accuracy (% correct) during the sex-identification task was M = 97.9 (SD = 1.1) for the SAD patients and M= 96.9 (SD = 2.9) for the HC group. Reaction time for neutral faces was M = 706.9 ms (SD =125.5) for the SAD patients and M = 668.2 ms (SD = 89.7) for the HC group. Reaction time for fearful faces was M = 690.1 ms (SD =139.7) for the SAD patients and M = 671.7 ms (SD = 111.1) for the HC group. No significant differences between SAD and HC groups were found in reaction times or accuracy scores during the sex-identification task (both p's > 0.3). Aversive relative to the neutral scenes were perceived as more arousing and negative in both groups and there were no significant differences between HC and SAD in arousal or valence ratings during neutral or aversive IAPS scenes (all p's > .05).

We found a significant 3-way interaction in the right amygdala (peak voxel co-ordinate *x, y, z* [30, 0,-16], $Z = 5.15$, $pFWE < 0.0001$, 248 mm^3) indicating higher amygdala reactivity in SAD patients than in

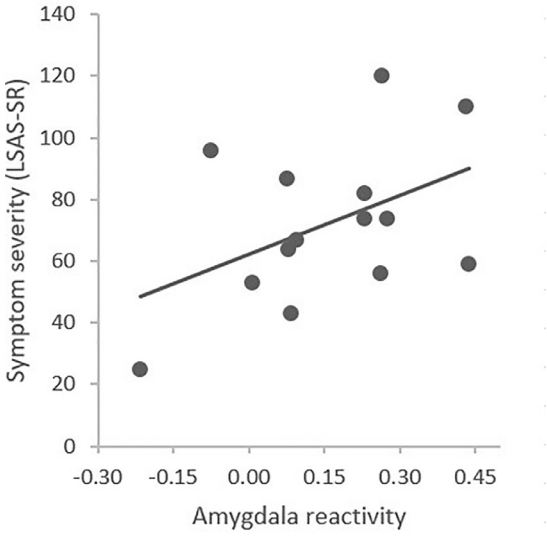

Fig. 2. Scatter plot and linear fit line illustrating the positive correlation between amygdala reactivity to fearful (>neutral) faces vs. aversive (>neutral) scenes and social anxiety symptom severity measured with the Liebowitz Social Anxiety Scale Self-Report questionnaire (LSAS-SR) in patients with social anxiety disorder.

healthy controls when viewing fearful (vs. neutral) faces in contrast to aversive (vs. neutral) IAPS scenes (Fig. 1, top row). Reactivity (fearful [>neutral] faces vs. aversive [>neutral] scenes) in this amygdala cluster correlated positively ($r(12) = 0.46$, $p < 0.05$) with social anxiety symptom severity as measured with LSAS-SR within the SAD group (Fig. 2).

Follow up analyses revealed that SAD patients relative to controls had higher amygdala reactivity to fearful (vs. neutral) faces (*x, y, z* [30, 0, -16], $Z = 3.32$, $pFWE = 0.005$, 104 mm^3) (Fig. 1 bottom left) and lower amygdala reactivity to aversive (vs. neutral) IAPS scenes (*x, y, z* [32, –2, –14], $Z = 2.87$, $pFWE = 0.017$, 24 mm^3) (Fig. 1, bottom right). Symptom severity was not significantly related to amygdala reactivity to fearful (>neutral) faces or aversive (>neutral) scenes (both $p >$ 0.10).

There were no significant group differences in amygdala connectivity to fearful (>neutral) faces or aversive (>neutral) scenes or to the interaction between stimulus (faces and scenes) and valence (fearful/aversive and neutral), neither in the whole-brain nor in the vmPFC ROI analyses.

4. Discussion

Here, using fearful facial emotional expressions to elicit socially induced amygdala activation, we found that exaggerated amygdala reactivity in patients with SAD is specific for social stimuli, because generally aversive but mainly non-social stimuli (IAPS scenes) did not elicit elevated amygdala reactivity in patients relative to healthy controls. It should be noted that the comparison is conservative, as some IAPS scenes included humans. However, these scenes depicted injured faces, which downplays the social dimension and most likely elicit reactions associated with blood and injury rather than social fears. Furthermore, a positive correlation between symptom severity (LSAS-SR) and heightened amygdala responses, supports the claim that there is a linear relation between amygdala responsivity and symptom severity. In addition, as there were no amygdala-vmPFC connectivity differences between patients and healthy controls, enhanced amygdala reactivity suggests increased bottom-up processes rather than attenuated top-down control in patients.

Increased amygdala reactivity is a hallmark of most anxiety disorders (Fredrikson and Faria, 2013; Shin and Lieberzon, 2010), and both pharmacological and psychological treatments reduce amygdala reactivity (Clark and Beck, 2010; Furmark et al., 2002, 2005, 2008; Gingnell et al., 2016; Rauch et al., 2003). Our findings support diagnostic specificity of increased amygdala reactivity, because it was elicited by disorder-relevant social stimulation only, and not by aversive conditions in general. The present data replicate a relatively large and mainly consistent body of literature indicating that emotional faces with negative expressions elicit enhanced amygdala reactivity in SAD, as many (e.g. Stein et al., 2002; Phan et al., 2006; Prater et al., 2013), but not all (e.g. Furmark et al., 2009) studies have reported heightened reactivity in SAD patients compared to healthy individuals. Regarding general aversive stimulation, there are conflicting findings because Shah and co-workers (2009) found higher amygdala reactivity in SAD patients than healthy controls when viewing generally aversive versus neutral IAPS scenes, but they did not include a purely social stimulation condition. This leaves open the possibility that although aversive stimulation in general might elicit enhanced amygdala reactivity, the effect of socially relevant facial stimulation might be more pronounced in patients. On the other hand, Gaebler et al. (2014) reported no differences between SAD patients and controls in amygdala activation using the IAPS. We failed to observe enhanced IAPS-induced reactivity among patients which is in line with Gaebler et al. (2014) but inconsistent with Shah et al. (2009). This may reflect cohort differences, as the studies differ in respect to inclusion and exclusion criteria. Also, differences in the stimuli used, with socially relevant scenes presented more frequently in Shah et al. (2009), may account for reactivity differences. Further, Weidt et al. (2016) compared patients with either obsessive–compulsive disorder (OCD) or SAD using generally aversive but non-social stimuli and reported that the two patient groups combined displayed increased amygdala reactivity, but also that OCD superseded SAD in this respect. They did not report any findings contrasting only SAD and HC for general aversive scenes, suggesting that amygdala hyper-reactivity mainly characterized OCD patients. Buff et al. (2016) compared amygdala reactivity in patients with SAD, generalized anxiety disorder, and panic disorder and healthy controls, noting increased amygdala reactivity to threat-inducing as compared to neutral IAPS pictures, but no group differences in the amygdala.

With regard to other anxiety and stress-related disorders, Michalowski et al. (2015), using EEG derived measures of brain activity, reported that enhanced event-related potentials in specific phobia were restricted to phobia-relevant rather than generally aversive stimuli. Consistently, Wright et al. (2003) did not find differences in amygdala reactivity between patients with specific animal phobia and healthy controls when exposed to disorder-irrelevant human fearful facial pictures. In contrast, patients with posttraumatic stress disorder (PTSD) may exhibit a generally heightened amygdala reactivity because both disorder-specific and non-specific aversive stimulation, including subliminal presentations, have been reported to elicit increased amygdala activity in comparison to healthy controls (Brunetti et al., 2010).

It is worth noting that the whole-brain analysis did not reveal any significant difference between SAD and HC. While this may be due to low statistical power it might also reflect that SAD is a relatively circumscribed disorder and that the difference in reactivity between SAD patients and HC group is confined mostly to areas in the brain devoted to emotional processing and foremost to the amygdala.

There are several limitations of this study that should be noted. First, sample sizes are small possibly reducing statistical power. However, as we found enhanced reactivity to one (faces) but not another (IAPS scenes) stimulus class, power issues must be related to one stimulus category in order to explain findings. This seems unlikely as we, in essence, replicated the often reported (Stein et al., 2002; Phan et al., 2006; Prater et al., 2013) finding of enhanced amygdala reactivity to negative faces in SAD. Second, the positive relation of symptom severity to amygdala response to the [fearful (>neutral) faces vs. aversive (>neutral) scenes] but not to the fearful (>neutral) faces alone, was a bit surprising and may have been related to differences in

task instructions between the two paradigms. Potential order effects cannot be excluded as the social stimuli were presented before the non-social, although it is unlikely that this would affect the two groups differently. Third, we included only male subjects, which may limit the generalizability of our findings. Fourth, we focused on the amygdala only, given its importance for and involvement in anxiety, but other limbic or paralimbic regions might be relevant (Amir et al., 2005) and considered in future research. Lastly, ratings of emotional arousal and valence were collected only for the IAPS images, not the faces, precluding us from determining that the differential neural response (social vs. non-social in SAD vs. controls) also corresponds to a differential emotional response at the subjective/behavioral level.

In conclusion, we demonstrate exaggerated amygdala reactivity in patients with SAD specifically to disorder-relevant social stimuli rather than to aversive stimuli in general, and a dose-response relation between symptom severity and amygdala reactivity to social cues. We did not find any amygdala-prefrontal connectivity differentiating patients from controls in either task. Thus, amygdala reactivity to facial emotional expressions seem to reflect bottom-up rather than top-down processes, and may serve as a biomarker for social anxiety and treatment evaluation.

Declarations of interest

None.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2018.08.012.

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