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Passively viewing negatively valenced baby faces attenuates left amygdala activity in healthy females scoring high on 'Harm Avoidance'

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Running head: Harm Avoidance in healthy females

Abstract

The amygdalae play an important role in the evaluation and processing of emotionally salient visual stimuli. However, individual differences in personality traits, such as Harm Avoidance (HA), have been reported to influence emotional amygdalae responses. To trigger strong approach and withdrawal-related emotions in 'never depressed' young female subjects under fMRI, we presented them with blocks of happy 'healthy' baby faces and baby faces disfigured by severe dermatological conditions and we integrated the temperament dimension HA into our analysis. No other instructions were given than to watch the images attentively. Only in withdrawal-related emotional experience, we observed a negative correlation between HA and left amygdala activity, suggesting that during passive viewing females scoring higher on HA 'avoid' images with highly aversive content. When investigating the amygdala's emotional role in passive viewing paradigms, personality features such as HA should be taken into account.

Keywords: Approach and withdrawal-related emotions, Amygdala, fMRI, Healthy Females, Harm Avoidance

A number of studies, using a variety of task instructions, have investigated the role of the amygdalae in the evaluation of social cues and the processing of emotional stimuli such as 'emotional' facial expressions and gender, age, and differences in personality features have been reported to influence amygdala activity [1, 40]. When introducing individual information such as personality characteristics as covariate in the analysis of 'emotional' fMRI paradigms in healthy individuals, predominantly left sided amygdala activation has been reported [11]. Increased (left-sided) amygdala activation has also been reported in 'anxiety-prone' individuals (non-clinical subjects displaying high levels of anxiety-related traits) during the processing of emotion [5]. In addition, 'emotional' brain imaging research has already demonstrated the importance of the temperament dimension Harm Avoidance (HA) [29], extracted out of the Temperament and Character Inventory (TCI [12]). High scorers on HA show a tendency to respond more intensely to aversive stimuli compared to low HA scorers [24]. Subjects who score high on HA describe themselves as fearful, pessimistic, shy, and fatigued, and they have a tendency to respond intensely to signals of aversive stimuli, whereas those scoring low on HA characterize themselves as optimistic and outgoing risk-takers [12]. Amygdala 'hyperactivity' in affective disorders is commonly found and in depressed patients increases in amygdala activity have been reported to be lateralized to the left [14] (however, see [37]).

Paying special attention to the salient nature of the mood inducing stimuli, in this study we re-investigate the hypothesis that individual scores on the temperament dimension HA might influence the observation of predominantly left-sided amygdala processing. We have used an adapted paradigm with baby faces as visual 'emotional' stimuli to induce approach and withdrawal-related emotions. We included only female participants because women tend to rate their emotions more intensely and demonstrate greater facility at decoding non-verbal messages than men [19]. To avoid the ‘contamination’ of cognitive task performance and aiming for ‘spontaneous’ brain responses, the participants were only instructed to watch the images attentively.

Firstly, we hypothesized that passively viewing blocks of ‘healthy’ happy and sad looking ‘disfigured’ baby faces would result in strong approach- and withdrawal-related emotional experiences respectively. Secondly, based on a predominantly left-sided relation of amygdala responses to negatively valenced emotional stimuli and personality features such as HA found in the literature, we expected a positive correlation between HA and left amygdala activity. In approach-related emotional experiences, we did not expect that individual differences on HA would influence amygdala processing.

Twenty healthy right-handed female subjects were recruited for the fMRI study (mean age=26.6 years, *sd*=6.9). Three were mothers. Participants taking medication other than birth-control pills were excluded. Right-handedness was assessed by the van Strien questionnaire [39]. Female volunteers with a psychiatric disorder (Mini-International Neuropsychiatric Interview [33]) and/or a score higher than eight on the (21-item Beck Depression Inventory [2]) were excluded. All female volunteers from the imaging study were assessed using a Dutch version of the TCI [13]. The Institutional Ethical Review Board of our University Hospital (UZBrussel) approved of the study and all subjects gave written informed consent.

Baby face pictures from both genders were used (mean estimated age=5.5 months, *sd*=4.0). All babies were looking directly at the camera. Neutral pictures, matched for color and luminosity, were obtained on the basis of a set of baby face pictures by reduction of the image matrix and by smoothing the resulting pictures using CorelDRAW 11. See Fig 1A.

To prevent multiple exposures to the same faces, risking habituation to the stimuli, different but comparable groups of female volunteers provided the behavioral results. First, a group of 20 female volunteers (mean age=25.8 year, *sd*=5.9) evaluated the baby faces (90 color images of emotional baby faces: 40 positive, 40 negative and 10 neutral) with a paper and pencil version of the Self-Assessment Manikin (SAM), using a 9 point likert type scale for ratings of valence and arousal [7]. Second, to evaluate the influence of the pictures on emotional experience, three other independent, but comparable groups of 20 healthy female volunteers each (*n*=60; mean age=20.6 years, *sd*=0.9 years) rated their mood before and after passively viewing one category of baby faces per group. The subjects were given no instructions other than to watch the images attentively. Subjects were asked to rate their mood on a horizontal 100 mm visual analogue scales (VAS [22]), ranging from “totally not” to “very much”, in order to detect subtle changes in ‘feelings of happiness, sadness and disgust’.

The mean valence score was 1.83 (sd=0.42) for negative, 6.93 (sd=0.69) for positive, and 4.79 (sd=0.69) for neutral baby pictures. The mean arousal score was 7.29 (sd=1.08) for negative, 5.76 (sd=0.87) for positive and 1.54 (sd=0.51) for neutral baby pictures. Paired t–tests showed that the valence ratings for negative ($t(19)=15.45$, $p<0.01$) and for positive ($t(19)=10.72$, $p<0.01$) were significantly different from that for neutral baby faces. Paired t–tests showed that both negatively ($t(19)=19.96$, $p<0.01$) and positively ($t(19)=18.30$, $p<0.01$) valenced baby faces were evaluated as more arousing than the neutral baby faces. Valence and arousal correlated significantly ($p< 0.01$) for positive and negative baby faces (Pearson correlation coefficients of .55 and -.66, respectively).

After viewing the negative baby faces, subjects exhibited a significant increase of disgust ($t(19)=5.69$, $p<0.01$) and a decrease of happiness ($t(19)=5.03$, $p<0.01$). After viewing the positive baby faces, subjects showed a significant decrease of sadness ($t(19)=3.18$, $p<0.01$) and a marginal increase of happiness ($t(19)=1.90$, $p=0.07$). For the neutral pictures, no significant mood changes were found except for a reduced experience of happiness ($t(19)=2.48$, $p<0.05$). Univariate ANOVA’s between groups after mood induction showed significant differences in the measure of disgust ($F(2,57)=36.27$, $p<0.01$), sadness ($F(2,57)=5.69$, $p<0.01$) and happiness ($F(2,57)=13.98$, $p<0.01$). Post hoc analyses (LSD) revealed that the group viewing positive baby faces experienced significantly less sadness compared to the group viewing neutral pictures ($p<0.05$) and the group viewing negative baby faces reported significantly more disgust ($p<0.01$) and less happiness ($p<0.01$), compared to the group viewing the neutral pictures. See Table 1.

During fMRI scanning, stimuli, back-projected onto a flat screen, followed a blocked design with 36 sec (or 10 pictures) for each block. To control for carryover effects between conditions, the blocks were organized in a counterbalanced fashion (neutral-positive-negative-neutral-negative-positive-neutral-positive-negative-neutral-negative-positive-neutral). Images were displayed for 3.6 seconds and preceded by a short flash of a black crosshair centered on a white background, introduced for fixation purposes. To avoid habituation, each positively and negatively valenced but not neutral image was shown only once [33]. The subjects were given no instructions other than to watch the display attentively.

The brain imaging part of the study was carried out on a 1.5T MRI scanner (Philips Intera, Best, The Netherlands) equipped with a 6 channel sense head coil. We measured 156 consecutive FFE-EPI volumes (TR/TE=3000/35 msec, flip angle=90°, 18 slices, slice thickness/gap= 5.0/1.0 mm, size= 64x64, in plane resolution=3.75x3.75 mm, duration 7 min 48 sec) covering the whole brain. The fMRI data were analyzed with SPM5 software (Wellcome Department of Cognitive Neurology, London, UK). The fMRI time series was realigned to the first volume to correct for head movements. After the realignment step, normalization into the standard anatomical space (EPI MNI template) and smoothing with an 8 mm Gaussian kernel were performed. The anatomical scan was normalized to the standard anatomical space (T1 MNI template) to be used as anatomical underlay for the results. For each subject, we estimated condition effects using the general linear model [15]. We generated contrast (percentage signal change) maps and *t*-statistic maps corresponding to the contrasts negative versus neutral and positive versus neutral. Starting from the individual contrast maps we performed a 1-sample *t*-test for each contrast. The *t*-statistic maps of this random effects analysis were thresholded with *p* (uncorrected)<0.001. See Fig 1B and Table 2.

In a following step, ROI analyses were performed in Marsbar [8], using the AAL-atlas (Anatomical Automatic Labeling [38]) to define two mask-volumes which masked the whole brain with the exception of the left and right amygdala. To define our ROIs, we started from masked *t*-maps. To take inter-subject variability into account, we adjusted the threshold for the activation pixels for each subject using a technique that was introduced earlier by a number of other authors in order to improve the robustness of lateralization measures [18]. To reduce type I errors, only clusters containing 10 or more pixels were extracted to be used for further analysis. We calculated a mean maximum *t* defined as the mean of those 5% highest *t*-values for each left and right amygdala. The final ROIs contained the voxels in the masked maps with a *t*-value above 20% of the mean maximum *t*. This step resulted in individual contrast values for the three contrasts for the left and right amygdala separately. In starting from the individual contrast values and to provide statistical evidence whether individual particularities (HA) could affect left and right amygdala responses, the individual contrast values were further used in bivariate correlation analyses (SPSS 15, Chicago, IL) set at a two- tailed probability of $p<0.05$.

In evaluating the HA scores, due to three incomplete data sets, 17 TCI questionnaires were processed. The Kolmogorov-Smirnov normality test on HA ($D(17)=0.22$, $p<0.05$) failed to show normality. Logarithmic transformation did not result in data normality for HA ($D(17)=0.22$, $p<0.05$). Therefore, to examine the relationship between individual differences in HA and amygdala responses, we used non-parametric Spearman correlation analyses. When analyzing the positive versus neutral contrast, no significant correlations between individual scores on HA and amygdala activity emerged (left: $r_s=-.27$, $n=17$, $p=0.29$, right: $r_s=-.35$, $n=17$, $p=0.17$). When analyzing the negative versus neutral contrast, the right amygdala activity was not found to be correlated with individual scores on HA ($r_s=-.32$, $n=17$, $p=0.22$). In the same condition, Spearman correlation analysis revealed that the scores on the temperament factor Harm Avoidance correlated negatively with left amygdala activity ($r_s=-.57$, $n=17$, $p=0.02$). See Fig 2.

As predicted, our behavioral results showed that passively viewing blocks of positively valenced baby faces results in approach-related emotional experiences and that passively viewing blocks of negatively valenced baby faces elicits withdrawal-related emotional experiences (disgust). When viewing pictures of 'mutilation', women, especially, show marked psychophysiological reactions [31]. Our behavioral observations demonstrated that our negatively valenced baby faces were not evaluated as emotionally ambiguous stimuli (infants in distress might elicit approach-related behavior and the image of a crying child may invoke the desire to console rather than the desire to abandon [10]). Oster [27] also demonstrated that "infants with facial anomalies" were accurately scored on emotional facial expressiveness by healthy female raters.

In line with other 'passive viewing' functional brain imaging studies using visual emotional paradigms [25], we found predominantly bilateral posterior brain activity while the subjects were processing both blocks of baby faces. Occipital, fusiform and posterior temporal visual cortices play a critical role in the perceptual processing of socially and emotionally relevant visual stimuli [1, 20]. However, in disagreement with our initial hypothesis, in the withdrawal-related emotional experience we found a negative correlation between HA and left amygdala activity. Importantly, other authors who found significant positive correlations between left amygdala responses to negatively valenced stimuli and individual differences in state anxiety, disgust sensitivity or personality features such as HA, all used event-related designs in combination with some kind of cognitive/emotional reaction task [4, 24]. By introducing explicit cognitive loads, cortico-subcortical neuronal circuits are more strongly recruited, indicating that the modulation of attention to emotional visual stimuli appears to be under 'top-down control' [32]. As these 'top-down circuits' respond differently during the cognitive processing of aversive situations [5, 23], this circuit may be especially sensitive in women scoring high on HA. Therefore, our results could imply that aversive responses might have reduced attention processes in these women, in line with the specific affective information processing role for the left amygdala, which is sustained stimulus evaluation [17]. In women, left lateralized amygdala activation has predominantly been reported in emotional memory paradigms where one has to be focused on the given task [9]. By using a mental imagery paradigm, Schienle et al [34] found that after viewing images eliciting emotions of disgust female participants scoring high on disgust sensitivity displayed lower activation in the amygdalae. These authors suggest that this reduced response pattern reflects cognitive avoidance, which helps to control somatic arousal (see also [6]). Avoidance strategies to regulate emotional stress responses, while viewing aversive stimuli, have been reported in particular in 'anxious' subjects [33]. While predominantly the left amygdala is found to be modulated during emotional expectancies [4], fronto-cingulate cortical circuits are recruited when aversive stimuli are anticipated and emotional responses are potentially adapted to aversive events [26].

Because emotional valence and arousal may be controlled by different neural systems [16], and as our negatively and neutral valenced baby faces are not equal in arousal levels, this could have introduced a bias to our results. Although aversive stimuli are per definition withdrawal-related, it could be possible that highly empathic individuals might show approach-related tendencies when viewing 'disfigured' baby faces. Because we did not use any kind of manipulation check (such as eye movement monitoring), one could argue that female volunteers scoring higher on HA disengaged or anticipated, avoiding the intrinsically aversive nature of the negative stimuli. However, our random effect analysis showed strong visual involvement in the approach as well as in the withdrawal-related emotional experiences.

As the sample is relatively small, the interpretation of these results should be done cautiously. Due to the nature of this study, we can only draw conclusions regarding right-handed healthy young women and we cannot generalize our results to a broader population. Because “neutral” baby faces might not be perceived as emotionally neutral stimuli by young women, we preferred the use of face-like blurry images, matched for visual characteristics such as luminescence and colour, to the positive and negative baby faces. Our behavioural results confirmed the ‘neutral’ character in the valence and arousal scores of the ‘blurred’ baby images.

Nevertheless, the involvement of left amygdala in females susceptible to anxiety and depression is not unexpected and our observations could point to an underlying neurobiological vulnerability in this group. Our results indicate that personality features, such as HA, should be taken into account in paradigms investigating the amygdala’s role in emotional processing using passive viewing models to change a subjects’ mood in real time.

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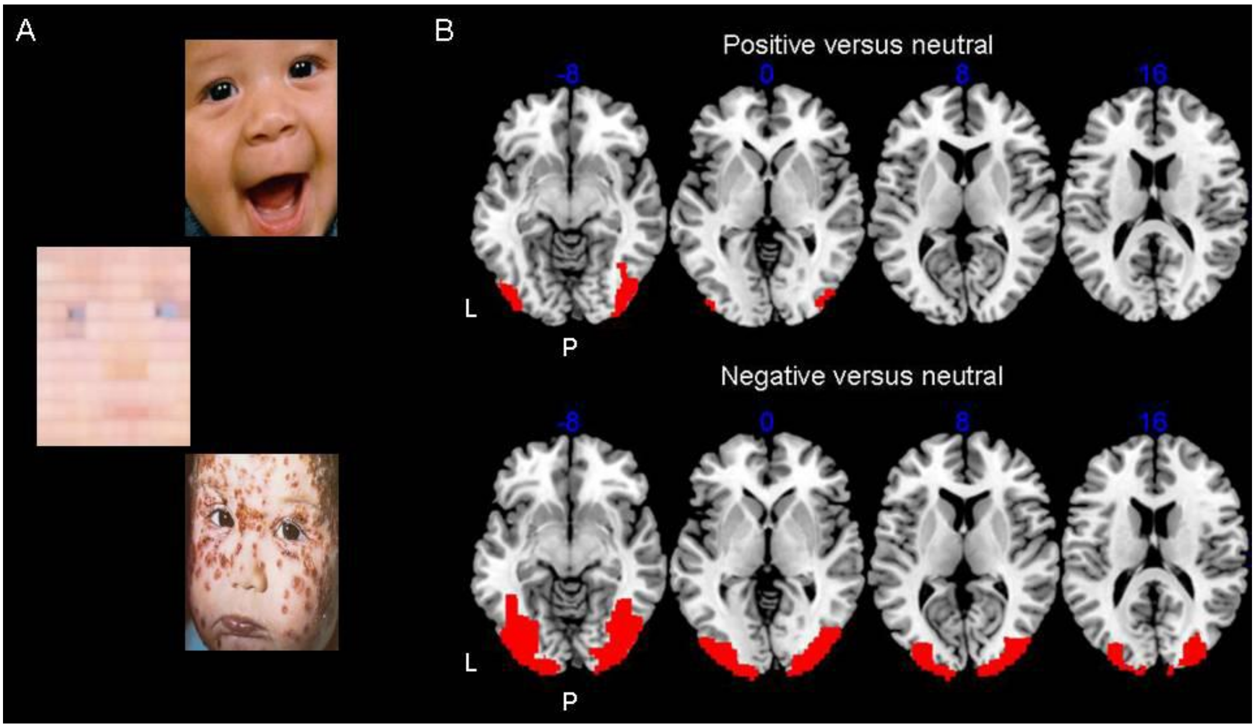

Fig 1: A) Example of a 'positive', a 'neutral' and a 'negative' visual stimulus. B) Axial view of whole brain activity found in the random effects analysis (T-contrast, $p<0.001$, uncorrected) for the group of young women overlaid on an anatomical T1-image for upper) the positive>neutral contrast and lower) the negative>neutral contrast. (L=left; P=posterior). The red areas represent the significantly activated clusters.

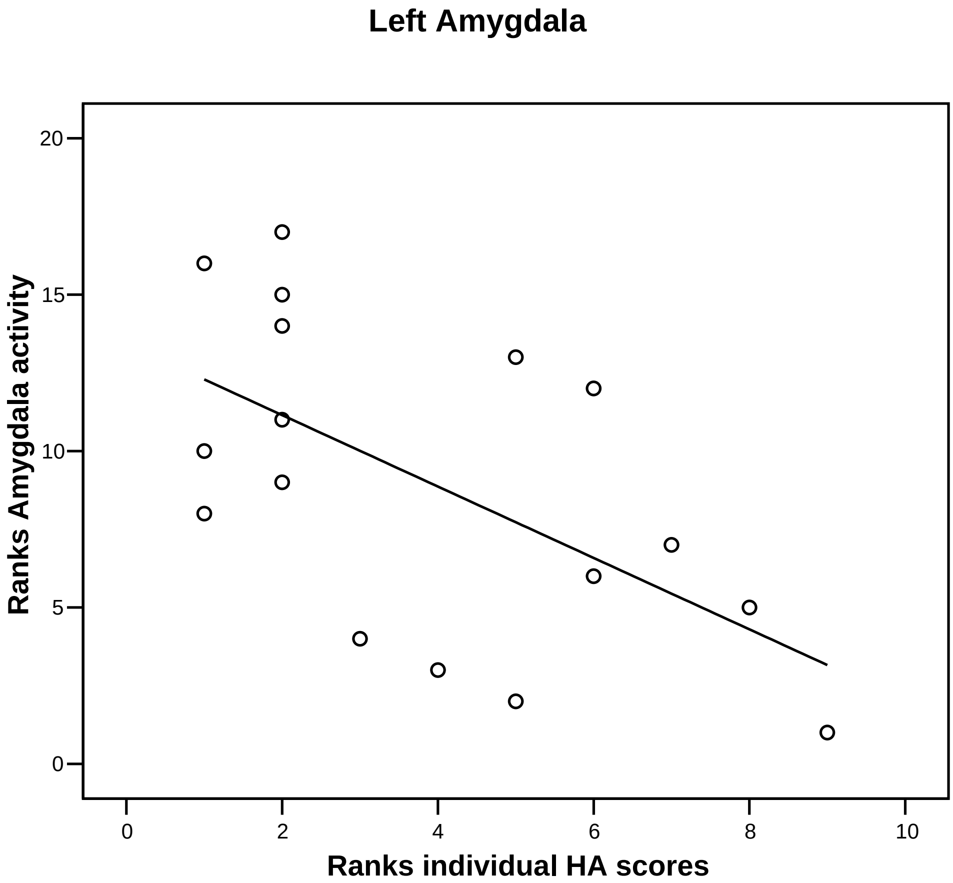

Fig 2: Scatter plot of the ranked order effect size in the left amygdala (Y) in the withdrawal-related emotional experience in combination with the ranked order of the individual scores on HA (X). The line represents the least squares fit to the data.

	Positive		Negative		Neutral	
	Pre	Post	Pre	Post	Pre	Post
Sadness	1.69 (1.48)	1.06 (.83)	2.09 (1.47)	2.44 (1.68)	2.24 (1.58)	2.42 (1.75)
Happiness	6.12 (1.63)	6.67 (1.61)	5.33 (2.10)	3.68 (1.96)	6.06 (1.48)	5.38 (1.78)
Disgust	.68 (.20)	.77 (.58)	1.18 (.99)	4.52 (2.47)	.92 (.86)	.97 (.96)

Table 1: Means and standard deviations of mood measures before and after viewing of positive, negative and neutral baby faces.

Voxel height threshold at P<0.001 significance uncorrected for multiple comparisons						
Cluster size	**Activation pattern**	**Anatomical region**	**Hemisphere**	**BA**	**Peak T value**	**Peak coordinates (x,y,z) (mm)**
T-contrast positive versus neutral						
4297	P>n	Fusiform gyrus/ Inferior occipital gyrus	Right	37/19	11.98	40 -54 -16
3813	P>n	Fusiform gyrus/ Inferior occipital gyrus	Left	19/37	9.29	-38 -80 -12
T-contrast negative versus neutral						
1053	N>n	Inferior occipital gyrus / Fusiform gyrus	Right	18/37/19	9.12	46 -80 -10
797	N>n	Inferior occipital gyrus	Left	18	6.63	-40 -52 -30

Table 2: Results of the random effects analysis for the contrasts positive versus neutral, negative versus neutral for all female volunteers. We listed only those clusters with a significance of p(uncorrected)<0.001 and a cluster size>100. For each cluster, we reported the T-value and MNI coordinates at the position of the maximum, the cluster size and the appropriate Brodmann area (BA). P:positive. N:negative. n:neutral.