

Published in final edited form as:

Brain Cogn. 2008 October ; 68(1): 1–8. doi:10.1016/j.bandc.2008.01.008.

Pointing with the eyes: the role of gaze in communicating danger

Nouchine Hadjikhani^{1,2,3,*}, Rick Hoge^{1,2}, Josh Snyder¹, and Beatrice de Gelder^{1,4,*}

¹ Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Harvard Medical School, Charlestown, MA ² Division of Health Sciences and Technology, Harvard-MIT, Cambridge, MA ³ Brain Mind Institute, EPFL, Switzerland ⁴ Cognitive and affective neurosciences Laboratory, Tilburg University, PO Box 90153, Tilburg, The Netherlands

Abstract

Facial expression and direction of gaze are two important sources of social information and what message each conveys may ultimately depend on how the respective information interacts in the eye of the perceiver. Direct gaze signals an interaction with the observer but averted gaze amounts to “pointing with the eyes” and in combination with a fearful facial expression may signal the presence of environmental danger. We used fMRI to examine how gaze direction influences brain processing of facial expression of fear. The combination of fearful faces and averted gazes activated areas related to gaze shifting (STS, IPS) and in fear-processing areas (amygdala, hypothalamus, pallidum). Additional modulation of activation was observed in motion detection areas, in premotor areas and in the somatosensory cortex, bilaterally.

Our results indicate that the direction of gaze prompts a process whereby the brain combines the meaning of the facial expression with the information provided by gaze direction, and in the process computes the behavioral implications for the observer.

Keywords

face processing; gaze; emotion; fear recognition; action representation

Introduction

Facial expression and direction of gaze are significant components of the information provided by a face. In the course of development, detection of gaze orientation plays an important role. Human and nonhuman primates interact with their caregivers and learn from observing the direction of gaze what objects to avoid. In primates, fear can be communicated through the mechanism of joint attention: young rhesus monkeys, initially unafraid of snakes, show fear after witnessing the fearful reaction of their parents to a snake (toy or real), suggesting that they are able to couple their parents’ fearful expression and their direction of gaze to learn that snakes are dangerous (Mineka, Davidson, Cook, & Keir, 1984).

*To whom correspondence should be addressed. Email: nouchine@nmr.mgh.harvard.edu.
Nouchine Hadjikhani, M.D. Athinoula A. Martinos Center for Biomedical Imaging, 149 13th Street, Charlestown, MA 02129, Tel: 617 724 5625, Fax: 530 309 4973

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Until recently, studies of gaze processing have used neutral faces, and investigated the attentional cues provided by gaze direction. Direction of gaze influences the level of activity in areas involved in processing faces, including the fusiform gyrus, the superior temporal sulcus and the intraparietal sulcus (George, Driver, & Dolan, 2001; Hoffman & Haxby, 2000; Pelphrey, Singerman, Allison, & McCarthy, 2003). But gaze direction may play a more complex role when it belongs to a face expressing a specific emotion (Adams, Gordon, Baird, Ambady, & Kleck, 2003; Adams & Kleck, 2003; Klucharev & Sams, 2004; Mathews, Fox, Yiend, & Calder, 2003; Sato, Yoshikawa, Kochiyama, & Matsumura, 2004); but see (Hietanen & Leppanen, 2003). A fearful facial expression with an observer-averted gaze is automatically recognized (Anderson, Christoff, Panitz, De Rosa, & Gabrieli, 2003) as possibly indicating environmental threat (“there is a danger located where I am looking at”) and as requiring an adaptive response (“you need to avoid it”).

Several recent studies indicate gaze direction influences other brain areas besides the ones specifically associated with face recognition. To account for this, several groups have developed a distributed representation model of face perception (Bruce & Young, 1986; de Gelder, Frissen, Barton, & Hadjikhani, 2003; Haxby, Hoffman, & Gobbini, 2000; Haxby et al., 1994; Haxby et al., 1996; Hoffman & Haxby, 2000), in which different areas of the brain respond to different attributes of a face, such as identity (fusiform gyrus, inferior occipital gyrus), gaze direction and recognition of action (superior temporal sulcus), and expression and/or emotion (orbitofrontal cortex, amygdala, anterior cingulate cortex, premotor cortex).

It is well known that the sight of a fearful face expression provides a very strong signal, however, a fearful face can be either empathy-evoking to the observer or threat-related, depending on its gaze direction. Facial expression of fear can be ambiguous because it may be unclear whether the emphasis is on communicating an experienced emotion to the observer and possibly provoking empathy, or on providing a danger signal to an observer with the goal of preparing him to act. To date there have only been very few studies that have manipulated separately the facial expression and the direction of gaze (Adams & Kleck, 2005; Ganel, Goshen-Gottstein, & Goodale, 2005). Two previous studies used behavioral measures (Adams & Kleck, 2003) and event-related brain imaging (Adams et al., 2003) to investigate the combined effect of gaze and facial expression. The behavioral study revealed a shorter reaction time for fearful faces looking away compared with fearful faces looking at the observer. The brain imaging study revealed increased amygdala activation for stimuli consisting of angry faces with an averted gaze and fearful faces with a direct gaze, that were ambiguous in terms of their significance as threat to the observer. No other areas were reported.

It is reasonable to expect that different brain networks are involved as a function of the direction of gaze a facial expression. To address this issue, we manipulated direction of gaze in fearful faces. Our goal was to test a single very specific prediction related to the combined perception of fear and averted gaze and its impact on action readiness. Our hypothesis was that a fearful face expression with averted gaze signals a danger in the environment and may trigger activity in brain areas involved in characteristic adaptive action associated with fear such as preparing to flight. If fearful faces with averted gaze do indeed signal danger in the environment (threat-related), then they should prompt more premotor and motor activity than faces with directed gaze where the emphasis is more on communicating the emotion and triggering empathy in the observer (empathy-evoking). We tested the hypothesis that threat-related fearful face would modulate activation in areas involved in stimulus detection, in fear processing, and in preparation for action. We did not use neutral faces in this study, because in the context of an emotional expression study, neutral faces suffer from carry-over effects and acquire an unintended emotional significance. To specifically address our hypothesis related to fear processing we limited our paradigm to fearful expression of emotion.

Materials and Methods

Stimuli were taken from the NimStim Emotional Face Stimuli database (<http://www.macbrain.org/faces/index.htm#faces.>), a set of over 600 face images, consisting of 16 expressions posed by 45 professional actors. All expressions have been validated, and only faces that received more than 90% agreement in the validation were used. Eight fearful faces (four females) were selected. We used Adobe Photoshop 8.0 to alter gaze direction towards the left and the right and downwards (Figure 1). Grayscale stimuli were shown in an AB-blocked presentation of 8 cycles of 24 seconds. Blocks of averted and direct gaze alternated every 24 seconds. Within each block, images were presented in a random order every 1.5 seconds for 300 ms with a 1200 ms blank-screen interval between stimuli. A fixation cross was present on the screen between the stimuli.

Subjects viewed images passively and were instructed to observe the images attentively and maintain fixation. No other task was required, because of possible interference with recognition of the emotion (Lange et al., 2003).

Imaging

Structural and functional MR images of brain activity of 8 participants (3 males, age 29 ± 6 years) were collected in a 3T high-speed echoplanar imaging device (Allegra, Siemens) using a phased-array head coil. Participants all had normal or corrected-to-normal vision. Informed written consent was obtained before the scanning session, and the Massachusetts General Hospital Human Studies Committee under Protocol #2002P-000228 approved all procedures. Structural images were collected with the following parameters: sagittal MPRAGE: 128 slices, 1.33mm isotropic voxels, repetition time (TR) = 2730 ms, echo time (TE) 3.44ms, flip angle 7° . Functional image volumes consisted of 40 contiguous 3 mm thick slices covering the entire brain (TR = 3,000ms, 3.125 mm by 3.125 mm in plane resolution, 128 images per slice, TE=30ms, flip angle 90° , matrix=64×64).

Image statistics

Image analysis was conducted using the NeuroLens analysis package (Hoge & Lissot, 2004) (<http://www.neurolens.org>, version 1.3). All functional EPI and structural scans were first converted from DICOM to MINC format using NeuroLens. Functional image series were motion corrected to the third frame in each series within NeuroLens using a hardware-accelerated module based on source code from AFNI's 3dvolreg module (Cox & Jesmanowicz, 1999). Next, each image series was spatially smoothed in 3D with a 6 mm FWHM 3D Gaussian kernel. Intensity normalization was also applied to set the mean intra cranial signal of each EPI series to a standard value of 10,000. The signal at each voxel in the motion-corrected, smoothed, and intensity normalized image series was then fit with a linear model consisting of a regressor representing the periods of gaze diversion, plus four regressors containing the terms of a third order polynomial to represent the baseline EPI signal (in this case corresponding to direct gaze) plus low frequency signal drift. Volumes containing the estimated effect size and associated standard error for the primary contrast (gaze diversion vs. direct gaze) at each voxel were then registered to a standard space based on the MNI Talairach template (Collins, Neelin, Peters, & Evans, 1994). This spatial normalization was performed in NeuroLens by fitting the third frame of each individual's EPI series to an EPI target brain and applying the resultant transformation to the computed effect size and standard error volumes for that individual. The EPI template was generated by registering whole-brain EPI scans from forty subjects (using the same pulse sequence and parameters as the present study) to the MNI standard space and averaging. The spatially normalized effect size and standard error volumes were input to a mixed effect group analysis in NeuroLens based on the method described by Worsley et al in

(Worsley et al., 2002). This procedure combines fixed and estimated random effects variance in proportions required to achieve a user-specified number of degrees of freedom (in this case 100). The modeled group effect size and standard error were then divided to produce a volumetric map of T statistic with 100 degrees of freedom. Based on this T statistic volume, a map of p-values was computed based on the T value at each voxel. The computed significance values were displayed as the negative base ten logarithm of each voxel's p value, which produces a low background value while highlighting areas of elevated significance. The map of $-\log(p)$ was then thresholded using an amplitude cutoff of 2.0 (corresponding to $p=0.01$), and a cluster size threshold of 0.16 ml, which requires that 20 contiguous voxels must all exceed the specified amplitude threshold to be included. This size threshold, plus restriction of the search volume to the intracranial space, reduces the effective p value for the minimal accepted cluster to less than 10^{-5} . The thresholded p map was then sampled on the cortical surface of an individual subject using the inverse coordinate transformation between this individual's native space and the group Talairach space. Cortical surface files were generated using FreeSurfer (Dale, Fischl, & Sereno, 1999; Fischl & Dale, 2000; Fischl, Sereno, & Dale, 1999) (<http://surfer.nmr.mgh.harvard.edu>) and loaded in NeuroLens, which was then used to interpolate the values in the group T Statistic volume (transformed to the individual's space) at the vertex locations of the cortical surface.

Results and discussion

Fearful faces with the gaze averted compared with the same faces directly gazing at the observer increased activation in areas belonging to face and emotion processing networks. Areas of increased BOLD signal were found in gaze processing areas (superior temporal sulcus, intraparietal sulcus); in face areas (fusiform gyrus, inferior occipital gyrus); in areas involved in rapid stimulus detection (left amygdala, visual area MT+); in areas involved in fear processing (left amygdala, hypothalamus, pallidum, dorsomedian nucleus of the thalamus); and in areas involved in motor preparation (premotor and motor cortices, superior parietal lobule) (Figure 2, 3 and 5; Table 1).

The reverse comparison (fearful direct > fearful averted) resulted in activation in the posterior occipital cortex, in the foveal representation of extrastriate areas (Figure 4).

Gaze and face processing network

As expected, faces with diverted gaze – indicating a potential danger by “pointing with the eyes” – activated areas that have been previously involved in gaze perception, including the superior temporal sulcus, and the intraparietal sulcus (Grosbras, Laird, & Paus, 2005; Hoffman & Haxby, 2000; Pelphrey et al., 2003; Pelphrey, Viola, & McCarthy, 2004; Puce, Allison, Bentin, Gore, & McCarthy, 1998; Wicker, Michel, Henaff, & Decety, 1998). Modulation by gaze was also found in areas involved in face processing (fusiform gyrus, inferior occipital gyrus) as had already been shown in studies using neutral faces with shifting gaze (George et al., 2001; Hoffman & Haxby, 2000; Pageler et al., 2003).

Stimulus detection and emotional network

Activity in the stimulus detection system (amygdala; area MT+) supports the model developed by several investigators (Adolphs, 2002; de Gelder, Vroomen, Pourtois, & Weiskrantz, 1999; LeDoux, 1992; Morris, Ohman, & Dolan, 1998) according to which a rapid system based on coarse visual analysis sustains orientation towards novel stimuli and detection of potentially dangerous signals.

The amygdala is a brain structure essential to the perception of fear (Amaral, 2003; LeDoux, 2003), and activation in the amygdala is reliably produced by presentation of biologically

relevant sensory stimuli, and stimuli that predict threat (Whalen, 1998). We observed left but not right amygdala activation, consistent with the findings of Morris et al (1998) who demonstrated left amygdala activation for consciously recognized stimuli, and right amygdala involvement for unseen stimuli. Laterality effects in the amygdala have however not been consistently obtained so far (Zald, 2003). Left amygdala activation for ambiguous threat-related stimuli was observed previously (Adams et al., 2003). However, in that study (which only reported results for the amygdala), activation was more important for fearful faces looking directly at the observer and was interpreted as being a result of threat ambiguity, while we observed here clear amygdala activation for fearful faces gazing away.

The discrepancies between these two studies may reflect several differences between the studies. First, there is a difference in the stimuli used. Adams et al. study used several exemplars from diverse emotion libraries (the Montreal Set of Facial Display of Emotions (Beaupre, Cheung, & Hess); the classical Ekman faces (Ekman & Friesen, 1976); custom-made stimuli Young Adult Facial Display made by (Adams & Kleck); a set from (Kirouac & Dore) in which gaze was displaced laterally. In our study, we used validated facial expression from the NimStim database and selected the intense fear expressions on which there was more than 90% agreement; in addition gaze was displaced laterally and towards the ground as if indicating the presence of a danger (snake, spider) coming from the floor. It is therefore possible that our averted stimuli felt more like indicating the presence of an environmental danger. In addition, one needs to note that looking down increases the amount of sclera visible over the iris, which has been shown to trigger amygdala response to fear even subliminally (Whalen et al., 2004). The second difference between our study and that of Adams et al. (2003) is to be found in the experimental design: we used a block-design in our experiment, whereas they used an event-related design; it is possible that response to and processing demands associated with threat-related ambiguity is reduced by cue redundancy. In addition, we used rapid presentation of faces (300ms) compared to 2.5 seconds in the Adams et al study. One may speculate that longer exposure durations trigger more in depth processing demands and increase sensitivity to ambiguity, whereas perhaps initial responding is more cued only highly salient threat cues. This, exposure duration may be very relevant issue in explaining these differences. A third point is to be found in recent data from Graham and Labar (Graham & LaBar, 2007) who reported that when the emotional expression is very intense and easily recognizable it is processed more quickly than gaze direction such that all emotional expressions tend to be processed faster when coupled with direct gaze. However, they also reported that when gaze direction is processed more quickly than expression, the two interact (i.e., the influence of gaze on emotion varies as a function of the type of emotion displayed), which explains conditions under which emotions like fear and sadness are processed more efficiently when combined with averted gaze. In our study, because we used very intense, extremely recognizable expressions (ones with 90% agreement) it is possible that fear combined with direct gaze might be actually more readily and efficiently processed than fear combined with averted gaze. If this is the case, then the findings of the current study are not necessarily in conflict with the previous findings. In other words, both studies then would be reporting more activation for those pairings that require longer to process. We note also that in their behavioral study, Adams and Kleck (Adams & Kleck, 2003) reported data that are compatible with our imaging data, namely a decreased reaction time to stimuli of fearful faces with averted gaze compared with fearful faces with direct gaze, that can be interpreted as an amygdala-mediated response. Overall though, it remains difficult to postulate a direct link between behavioral and brain activation data also when the influence of task and stimulus presentation is not fully controlled.

Activations in the other areas involved in fear detection are consistent with previous studies. Concomitant activation of the left amygdala and the left pallidum for fearful faces has been reported previously. The hypothalamus receives direct connections from the central nucleus of the amygdala (LeDoux, 2000) and is responsible for the behavioral manifestations of fear

such as tachycardia, increased galvanic skin response, paleness, pupil dilation and blood pressure elevation. The dorsomedial thalamus receives input from the amygdala and is a key structure for visual input into the prefrontal cortex (Jones, 1981; J. E. Krettek & J. L. Price, 1977; J.E. Krettek & J.L. Price, 1977). It belongs to the circuitry activated by fear-inducing stimuli (Sewards & Sewards, 2002), and in the animal model activated neurons were recorded in stimuli such as predator exposure (Canteras, Chiavegatto, Valle, & Swanson, 1997).

Activity in the somatosensory cortex is consistent with the importance given to this structure in the somatic marker hypothesis, whereby feedback from the autonomic, musculoskeletal and endocrine system to the somatosensory areas plays a crucial role in emotion perception (Damasio, 1996) and was shown to be active together with the left amygdala in a paradigm of visual fear acquisition in healthy controls (Birbaumer et al., 2005).

Taken together, we found that important elements of the fear network were positively modulated when a fearful face gazing towards an unseen danger was compared to a fearful face looking directly at the observer. This implies that the brain's perception of fear itself can be modulated by gaze direction.

Premotor and motor network

Activation in the premotor cortices together with the caudate nucleus may be related to a preparatory defense response (Fischer, Andersson, Furmark, Wik, & Fredrikson, 2002; Knight, Cheng, Smith, Stein, & Helmstetter, 2004), and are consistent with the results of our previous study, where we found premotor and motor activation when comparing bodies expressing fear with bodies performing neutral actions (de Gelder, Snyder, Greve, Gerard, & Hadjikhani, 2004).

Conclusion

The network of areas observed in the present study of combined fear and gaze direction resembles closely those found in our previous studies looking at brain activation elicited by viewing fearful bodies (de Gelder et al., 2004; Hadjikhani et al., 2004). Observing fearful faces “pointing to a danger” with their eyes compared with fearful faces looking at the observer modulates cortical and subcortical areas sustaining detection and rapid orientation, as well as fear perception and preparation for action. A fearful expression in somebody looking away may signal imminent danger for both the actor and the observer, and consequently it will activate a circuit leading to an adaptive fear response to danger.

Our findings indicate that viewing facial expressions may trigger an active process of gaze interpretation allowing the brain to elaborate not only the meaning of the facial expression, but also what the implications are for the observer.

Acknowledgements

This research was supported by NIH grant RO1 NS44824-01 and Swiss National Foundation grant PPOOB—110741 to Nouchine Hadjikhani. We thank Reginald Adams and an anonymous reviewer for their comments on our manuscript.

References

- Adams RB Jr, Gordon HL, Baird AA, Ambady N, Kleck RE. Effects of gaze on amygdala sensitivity to anger and fear faces. *Science* 2003;300(5625):1536. [PubMed: 12791983]
- Adams RB Jr, Kleck RE. Young Adult Facial Display.
- Adams RB Jr, Kleck RE. Perceived gaze direction and the processing of facial displays of emotion. *Psychol Sci* 2003;14(6):644–647. [PubMed: 14629700]

- Adams RB Jr, Kleck RE. Effects of direct and averted gaze on the perception of facially communicated emotion. *Emotion* 2005;5(1):3–11. [PubMed: 15755215]
- Adolphs R. Recognizing emotion from facial expressions: psychological and neurological mechanisms. *Behav Cognit Neurosci Rev* 2002;1:21–61. [PubMed: 17715585]
- Amaral DG. The amygdala, social behavior, and danger detection. *Ann N Y Acad Sci* 2003;1000:337–347. [PubMed: 14766647]
- Anderson AK, Christoff K, Panitz D, De Rosa E, Gabrieli JD. Neural correlates of the automatic processing of threat facial signals. *J Neurosci* 2003;23(13):5627–5633. [PubMed: 12843265]
- Beaupre, MG.; Cheung, N.; Hess, U. Montreal Set of facial Displays of Emotion.
- Birbaumer N, Veit R, Lotze M, Erb M, Hermann C, Grodd W, et al. Deficient fear conditioning in psychopathy: a functional magnetic resonance imaging study. *Arch Gen Psychiatry* 2005;62(7):799–805. [PubMed: 15997022]
- Bruce V, Young AW. Understanding face recognition. *British Journal of Psychology* 1986;77:305–327. [PubMed: 3756376]
- Canteras NS, Chiavegatto S, Valle LE, Swanson LW. Severe reduction of rat defensive behavior to a predator by discrete hypothalamic chemical lesions. *Brain Res Bull* 1997;44(3):297–305. [PubMed: 9323445]
- Collins DL, Neelin P, Peters TM, Evans AC. Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space. *J Comput Assist Tomogr* 1994;18(2):192–205. [PubMed: 8126267]
- Cox RW, Jesmanowicz A. Real-time 3D image registration for functional MRI. *Magn Reson Med* 1999;42(6):1014–1018. [PubMed: 10571921]
- Dale AM, Fischl B, Sereno MI. Cortical surface-based analysis. I. Segmentation and surface reconstruction. *Neuroimage* 1999;9(2):179–194. [PubMed: 9931268]
- Damasio AR. The somatic marker hypothesis and the possible functions of the prefrontal cortex. *Philos Trans R Soc Lond B Biol Sci* 1996;351(1346):1413–1420. [PubMed: 8941953]
- de Gelder B, Frissen I, Barton J, Hadjikhani N. A modulatory role for facial expressions in prosopagnosia. *Proc Natl Acad Sci U S A* 2003;100(22):13105–13110. [PubMed: 14561892]
- de Gelder B, Snyder J, Greve D, Gerard G, Hadjikhani N. Fear fosters flight. A mechanism for fear contagion when perceiving emotion expressed by a whole body. *Proc Natl Acad Sci U S A* 2004;101(47):16701–16706. [PubMed: 15546983]
- de Gelder B, Vroomen J, Pourtois G, Weiskrantz L. Non-conscious recognition of affect in the absence of striate cortex. *Neuroreport* 1999;10(18):3759–3763. [PubMed: 10716205]
- Ekman, P.; Friesen, WV. Pictures of facial affects. Palo Alto: Consulting Psychologists Press; 1976.
- Fischer H, Andersson JL, Furmark T, Wik G, Fredrikson M. Right-sided human prefrontal brain activation during acquisition of conditioned fear. *Emotion* 2002;2(3):233–241. [PubMed: 12899356]
- Fischl B, Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proc Natl Acad Sci U S A* 2000;97(20):11050–11055. [PubMed: 10984517]
- Fischl B, Sereno MI, Dale AM. Cortical surface-based analysis II: Inflation, flattening, and a surface-based coordinate system. *NeuroImage* 1999;9:195–207. [PubMed: 9931269]
- Ganel T, Goshen-Gottstein Y, Goodale MA. Interactions between the processing of gaze direction and facial expression. *Vision Res* 2005;45(9):1191–1200. [PubMed: 15707927]
- George N, Driver J, Dolan RJ. Seen gaze-direction modulates fusiform activity and its coupling with other brain areas during face processing. *Neuroimage* 2001;13(6 Pt 1):1102–1112. [PubMed: 11352615]
- Graham R, LaBar K. Facial expression and gaze interaction. *Emotion*. 2007in press
- Grosbras MH, Laird AR, Paus T. Cortical regions involved in eye movements, shifts of attention, and gaze perception. *Hum Brain Mapp* 2005;25(1):140–154. [PubMed: 15846814]
- Hadjikhani N, Joseph RM, Snyder J, Chabris CF, Clark J, Steele S, et al. Activation of the fusiform gyrus when individuals with autism spectrum disorder view faces. *NeuroImage* 2004;22(3):1141–1150. [PubMed: 15219586]
- Haxby JV, Hoffman EA, Gobbini MI. The distributed human neural system for face perception. *Trends Cogn Sci* 2000;4(6):223–233. [PubMed: 10827445]

- Haxby JV, Horwitz B, Ungerleider LG, Maisog JM, Pietrini P, Grady CL. The functional organization of human extrastriate cortex: a PET-rCBF study of selective attention to faces and locations. *J Neurosci* 1994;14(11 Pt 1):6336–6353. [PubMed: 7965040]
- Haxby JV, Ungerleider LG, Horwitz B, Maisog JM, Rapoport SI, Grady CL. Face encoding and recognition in the human brain. *Proc Natl Acad Sci U S A* 1996;93(2):922–927. [PubMed: 8570661]
- Hietanen JK, Leppanen JM. Does facial expression affect attention orienting by gaze direction cues? *J Exp Psychol Hum Percept Perform* 2003;29(6):1228–1243. [PubMed: 14640840]
- Hoffman EA, Haxby JV. Distinct representations of eye gaze and identity in the distributed human neural system for face perception. *Nat Neurosci* 2000;3(1):80–84. [PubMed: 10607399]
- Hoge, R.; Lissot, A. NeuroLens: an integrated visualization and analysis platform for functional and structural neuroimaging. Paper presented at the Proceedings of the International Society for Magnetic Resonance in Medicine; Kyoto, Japan. 2004.
- Jones EG. Functional subdivision and synaptic organization of the mammalian thalamus. *Int Rev Physiol* 1981;25:173–245. [PubMed: 6110641]
- Kirouac, G.; Dore, FY. Set of facial emotions.
- Klucharev V, Sams M. Interaction of gaze direction and facial expressions processing: ERP study. *Neuroreport* 2004;15(4):621–625. [PubMed: 15094464]
- Knight DC, Cheng DT, Smith CN, Stein EA, Helmstetter FJ. Neural substrates mediating human delay and trace fear conditioning. *J Neurosci* 2004;24(1):218–228. [PubMed: 14715954]
- Krettek JE, Price JL. Projections from the amygdaloid complex to the cerebral cortex and thalamus in the rat and cat. *J Comp Neurol* 1977;172(4):687–722. [PubMed: 838895]
- Krettek JE, Price JL. The cortical projections of the mediodorsal nucleus and adjacent thalamic nuclei in the rat. *J Comp Neurol* 1977;171(2):157–191. [PubMed: 64477]
- Lange K, Williams LM, Young AW, Bullmore ET, Brammer MJ, Williams SC, et al. Task instructions modulate neural responses to fearful facial expressions. *Biol Psychiatry* 2003;53(3):226–232. [PubMed: 12559655]
- LeDoux J. Brain mechanisms of emotion and emotional learning. *Curr Opin Neurobiol* 1992;2(2):191–197. [PubMed: 1638153]
- LeDoux J. Emotion circuits in the brain. *Annu Rev Neurosci* 2000;23:155–184. [PubMed: 10845062]
- LeDoux J. The emotional brain, fear, and the amygdala. *Cell Mol Neurobiol* 2003;23(4–5):727–738. [PubMed: 14514027]
- Mathews A, Fox E, Yiend J, Calder A. The face of fear: Effects of eye gaze and emotion on visual attention. *Visual Cognition* 2003;10(7):823–835. [PubMed: 17453064]
- Mineka S, Davidson M, Cook M, Keir R. Observational conditioning of snake fear in rhesus monkeys. *J Abnorm Psychol* 1984;93(4):355–372. [PubMed: 6542574]
- Morris JS, Ohman A, Dolan RJ. Conscious and unconscious emotional learning in the human amygdala. *Nature* 1998;393(6684):467–470. [PubMed: 9624001]
- Pageler NM, Menon V, Merin NM, Eliez S, Brown WE, Reiss AL. Effect of head orientation on gaze processing in fusiform gyrus and superior temporal sulcus. *Neuroimage* 2003;20(1):318–329. [PubMed: 14527592]
- Pelphrey KA, Singerman JD, Allison T, McCarthy G. Brain activation evoked by perception of gaze shifts: the influence of context. *Neuropsychologia* 2003;41(2):156–170. [PubMed: 12459214]
- Pelphrey KA, Viola RJ, McCarthy G. When strangers pass: processing of mutual and averted social gaze in the superior temporal sulcus. *Psychol Sci* 2004;15(9):598–603. [PubMed: 15327630]
- Puce A, Allison T, Bentin S, Gore JC, McCarthy G. Temporal cortex activation in humans viewing eye and mouth movements. *J Neurosci* 1998;18(6):2188–2199. [PubMed: 9482803]
- Sato W, Yoshikawa S, Kochiyama T, Matsumura M. The amygdala processes the emotional significance of facial expressions: an fMRI investigation using the interaction between expression and face direction. *Neuroimage* 2004;22(2):1006–1013. [PubMed: 15193632]
- Sewards TV, Sewards MA. Fear and power-dominance drive motivation: neural representations and pathways mediating sensory and mnemonic inputs, and outputs to premotor structures. *Neurosci Biobehav Rev* 2002;26(5):553–579. [PubMed: 12367590]

- Whalen PJ. Fear, Vigilance, and Ambiguity: Initial Neuroimaging Studies of the Human Amygdala. *Current Directions in Psychological Science* 1998;7(6):177–188.
- Whalen PJ, Kagan J, Cook RG, Davis FC, Kim H, Polis S, et al. Human amygdala responsivity to masked fearful eye whites. *Science* 2004;306(5704):2061. [PubMed: 15604401]
- Wicker B, Michel F, Henaff MA, Decety J. Brain regions involved in the perception of gaze: a PET study. *Neuroimage* 1998;8(2):221–227. [PubMed: 9740764]
- Worsley KJ, Liao CH, Aston J, Petre V, Duncan GH, Morales F, et al. A general statistical analysis for fMRI data. *Neuroimage* 2002;15(1):1–15. [PubMed: 11771969]
- Zald DH. The human amygdala and the emotional evaluation of sensory stimuli. *Brain Res Brain Res Rev* 2003;41(1):88–123. [PubMed: 12505650]

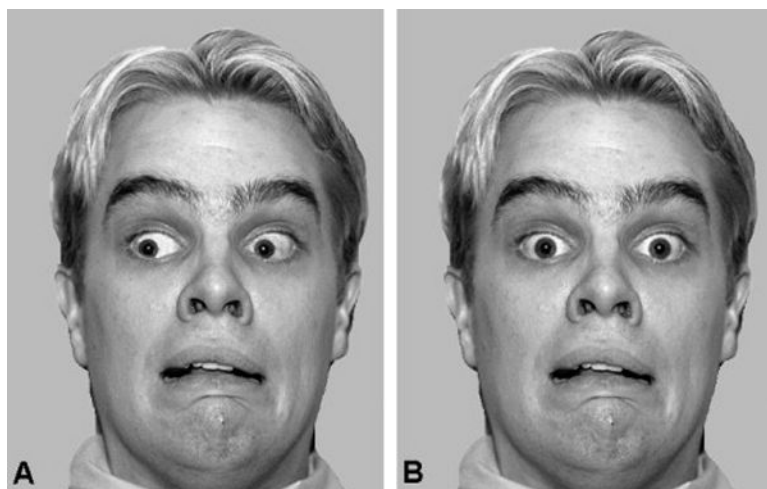


Figure 1. example of the stimuli used in this experiment. Panel A shows the actor looking with averted gaze and a fearful expression, and panel B shows the same actor looking directly at the observer. The left stimulus was generated by moving the direction of the eyes with Photoshop 8.0.

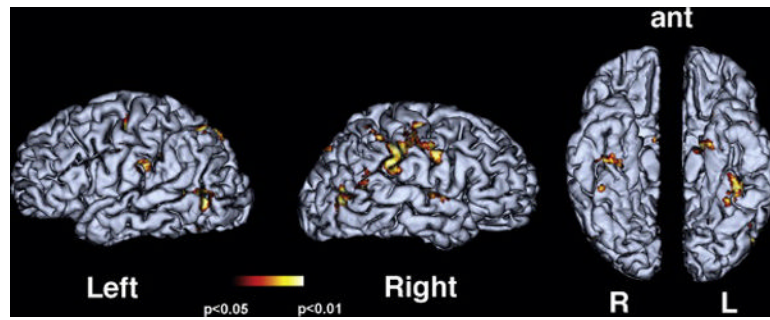


Figure 2.

Regions involved in the visual analysis of facial expressions of fear with averted vs. direct gaze. Lateral and ventral views of a 3D reconstruction of a single subject brain, with a projection of group data activation. Areas that were activated in the mixed-effect group average by faces with a fearful expression and an averted gaze are displayed in red to white ($p < 0.05$). Activation for averted fear was found in areas involved with gaze detection (STS, IPS), with face identification (fusiform gyrus, inferior occipital gyrus), with action representation (superior parietal lobule, premotor and motor cortices) as well as in visual area MT and in the somatosensory cortex.

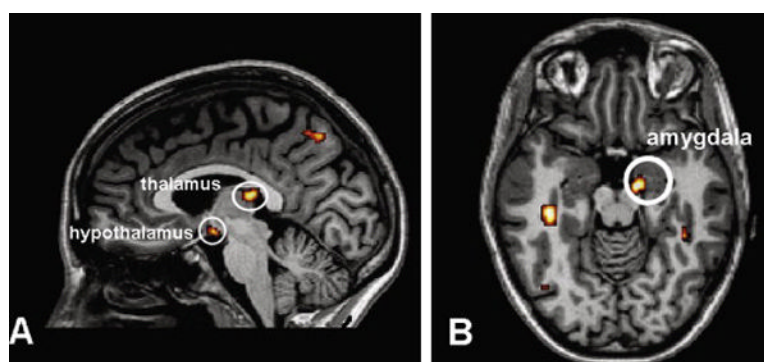


Figure 3.

Sagittal (panel A) and horizontal slices (panels B) showing subcortical regions involved in the visual analysis of facial expressions of fear with averted vs. direct gaze. Areas that were activated in the mixed-effect group average by faces with a fearful expression and an averted gaze are displayed in red to white ($p < 0.05$) on one individual MP-RAGE. A signal of danger in a fearful face gazing away, the hypothalamus and the thalamus DM (panel A) as well as the amygdala (panel B).

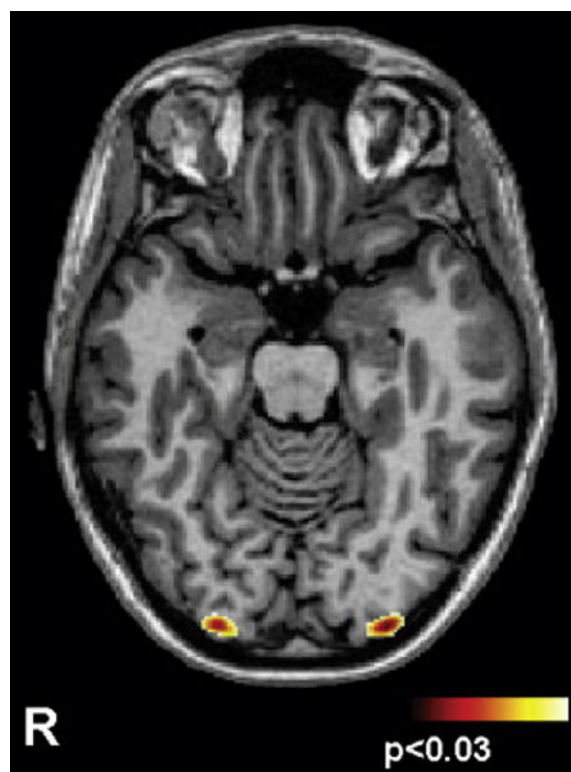


Figure 4. Horizontal slices showing visual cortex activation for direct vs averted fearful face. Activation was not found in other parts of the cortex.

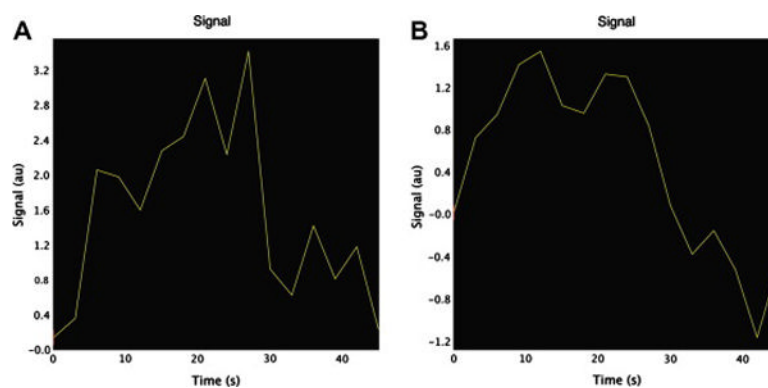


Figure 5.
Time course of activation in the amygdala (left panel) and the STS (right panel).

Table 1
Areas activated for fearful faces gazing away
20 voxels min

	Tscore	HEMI	MNI coordinates			# of voxels
			X	Y	Z	
Gaze processing						
Superior temporal sulcus	3.75	rh	48	-54	14	1272
	4.37	lh	-50	-64	10	1093
Intraparietal sulcus	3.20	rh	24	-78	44	619
	3.91	Lh	-18	-64	58	1983
Face identification						
Fusiform gyrus	2.64	rh	-42	-42	-20	204
	3.73	lh	34	-24	-32	370
Inferior occipital gyrus	3.74	rh	47	-54	13	1272
	4.37	lh	-50	-64	10	1093
Fear processing						
Amygdala	2.35	lh	-12	-11	-26	22
Hypothalamus	2.79		18	-12	34	35
Pallidum	2.80	rh	18	-3	-12	35
Stimulus detection						
Amygdala	2.35	lh	-12	-11	-26	22
MT	4.37	lh	-50	-64	10	1093
	3.75	rh	48	-54	14	1272
Thalamus DM	2.64	rh	2	-19	14	35
Motor preparation						
Premotor/motor cortex	4.12	lh	-24	-11	54	978
	2.94	rh	62	7	38	209
Caudate	2.60	lh	-18	26	6	53
Other						
Somatosensory cortex	4.12	lh	-70	-20	36	490
	2.92	rh	54	-15	60	99
Anterior fusiform	3.73	rh	34	-24	-32	370
	3.49	Lh	-26	-20	-34	115

Table 2
Areas activated for fearful faces gazing at the observer

	Tscore	HEMI	MINI coordinates			# of voxels
Visual areas			X	Y	Z	
Visual cortex	4.46	rh	30	-104	17	1493
	3.93	lh	-38	-106	-2	1383