

A 7 Tesla fMRI Study of Amygdala Responses to Fearful Faces

Wietske van der Zwaag · Sandra E. Da Costa ·
Nicole R. Zürcher · Reginald B. Adams Jr. ·
Nouchine Hadjikhani

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Abstract The amygdalae are involved in the perception of emotions such as happiness, anger and fear. Because of their proximity to the sinuses, the image signal intensity in T2* weighted fMRI data is often affected by signal loss due to through-slice dephasing, especially at high field strength. In this study, the feasibility of fMRI in the amygdalae at 7 Tesla was investigated. A paradigm based on the presentation of fearful faces was used for stimulation. Previously, opposite effects have been found for presentation of averted and direct gaze fearful faces. Here, we show that (1) sufficiently high temporal SNR values are reached in the amygdalae for detection of small BOLD signal changes and (2) that the BOLD signal in the amygdalae for presentation of a direct or averted gaze in a fearful face depends on stimulus duration.

Keywords Amygdala · fMRI · 7 Tesla · Fear · Face perception

W. van der Zwaag
Department of Radiology, University of Lausanne, Lausanne,
Switzerland

S. E. Da Costa · N. R. Zürcher · N. Hadjikhani
Brain Mind Institute, EPFL, Lausanne, Switzerland

R. B. Adams Jr.
Department of Psychology, The Pennsylvania State University,
University Park, USA

N. Hadjikhani
MGH/HMS/HST Martinos Center for Biomedical Imaging,
Boston, USA

N. Hadjikhani (✉)
GRHAD, Station 19, 1015 Lausanne, Switzerland
e-mail: nouchine@nmr.mgh.harvard.edu

Introduction

As the BOLD signal is based on the susceptibility difference between deoxyhaemoglobin and surrounding tissue, BOLD-based fMRI sees a significant signal increase with field strength (van der Zwaag et al. 2009; Yacoub et al. 2001). This signal increase is typically traded for higher spatial resolution or shorter scan times. As fMRI studies of the amygdala generally report small signal changes (Norbury et al. 2010), the use of ultra-high field could be advantageous. Unfortunately, the amygdalae are in a brain region which can be severely affected by through-slice dephasing and susceptibility induced distortions in gradient echo EPI (Merboldt et al. 2001), which also increase with field strength. Therefore, the use of relatively small voxel size to limit the susceptibility-induced distortions and a thin slice thickness in combination with careful slice positioning to avoid through-slice dephasing become even more important at higher fields. As the main magnetic field gradients are found in the cranio-caudal and anterior–posterior directions, a pseudo-coronal slice orientation is generally found to be optimal (Merboldt et al. 2001; Robinson et al. 2004).

A fearful face signals to the viewer the presence of a threat, thus inducing fear, although the exact mechanisms remain to be determined. Amygdala activation is known to be modulated by the perception of fearful faces (Ohrmann et al. 2007) and the relevance thereof for the observer (Cristinzio et al. 2010). Relevance can be changed by modifying the gaze direction of the presented face. Studies using similar stimuli of fearful faces (Adams et al. 2003; Hadjikhani et al. 2008; N'Diaye et al. 2009) have reported opposite results. While Adams et al. reported signal increases in the amygdalae for direct versus averted fearful faces (Adams et al. 2003), others reported BOLD signal

increases for presentations of averted vs direct fearful faces (Hadjikhani et al. 2008; N'Diaye et al. 2009). However, these studies used different cohorts of subjects, different sets of stimuli and different presentation parameters, all of which can modulate the amygdale response. A recent study, using a between subject design, suggested that this apparent discrepancy is due to stimulus duration (Adams et al. 2011). Here, the same fearful faces are presented a within subjects design during two separate runs in a single scanning session at 7 Tesla, varying only the stimulus presentation time.

Methods

Eighteen healthy volunteers (10 males, mean age 24 years) passively observed fearful faces with direct or averted gaze in a short (300, 1,200 ms ISI) or a long (1,500, 0 ms ISI) presentation paradigm. Stimuli were identical to those previously used by Hadjikhani et al. (2008), taken from the NimStim Emotional Face Stimuli database. 24 s blocks of averted (4 blocks left/4 blocks right) and direct gaze were presented in a pseudo random order during two runs of 384 s each. All procedures were approved by Lausanne University ethical committee and all subjects provided written consent.

Data were acquired on a 7 Tesla scanner (Siemens, Germany) with eight channel rf-coil (Rapid Biomedical, Germany). A multi-slice EPI sequence (Speck et al. 2008) with sinusoidal read-out, to limit the helium boil-off, was used for functional acquisition (40 1.5 mm thick slices, oriented 30° from AC-PC, TR = 3,000 ms, TE = 21 ms, flip 60°, FOV 160 mm², matrix 64 × 64, 2.5 × 2.5 × 1.5 mm). Slices were positioned at an approximately 30° angle from the AC-PC line (Robinson et al. 2004), while ensuring that the eyes and mobile parts of the brainstem were not included in the imaging slab to avoid motion-induced Nyquist ghosting (Fig. 1b). The relatively thin slice thickness was chosen to further reduce through-slice signal dephasing in the medial part of the amygdalae.

A single full brain EPI volume (100 slices, TR = 6,000 ms) was acquired to aid co-registration with the anatomical images acquired with MP2RAGE ((Marques et al. 2010), TR = 6.9 ms, TE = 2.82 ms, TR = 5,000 ms, TI₁/TI₂ = 700/2,500 ms, flip 4°/5°, FOV 256 mm², matrix size 256 × 240).

Images were analyzed using mixed-effect with FSL FEAT (www.fmrib.ox.ac.uk/fsl), after motion correction, spatial smoothing (FWHM = 6.0 mm, to ensure equal smoothness after spatial normalisation), high pass temporal filtering ($\sigma = 50$ s) and co-registration to the MNI brain with FLIRT.

Temporal SNR, tSNR, maps were obtained per subject by dividing the mean of each voxel timecourse by its temporal standard deviation after motion correction, smoothing and temporal filtering.

Results and Discussion

tSNR was, on average over an amygdala ROI taken from the Harvard–Oxford atlas, 116 ± 7 (mean \pm stderr); high enough to detect the small BOLD signal changes expected in the amygdalae. $90 \pm 2\%$ of the amygdalae ROI fell in areas with tSNR > 50. A tSNR map from a representative subject is shown in Fig. 1b.

Bilateral amygdala activation (maximum at: MNI 24, -4, -20: $Z = 2.28$ and -22, -7, -18: $Z = 2.36$) was found for short duration averted versus direct presentations (Fig. 2a), in agreement with the signal changes reported by Hadjikhani et al. (2008) for the left amygdale and as reported for dynamic stimuli in (N'Diaye et al. 2009). This effect was reversed, however, in the same subject cohort, for long duration direct versus averted presentations (maximum at: MNI 15, -9, -19: $Z = 2.76$ and -17, -18, -20: $Z = 3.06$, Fig. 2b), in accordance with results from Adams et al. (2003) in the left amygdala. A direct comparison revealed a significant difference for the influence of gaze in short versus long presentations, (maximum at: MNI 15, -9, -19: $Z = 3.15$ and -15, -8, -19: $Z = 3.06$) with greater response to averted minus direct for short presentations and to direct minus averted for long presentations (Fig. 2c). That activation is found bilaterally in this study as opposed to previous reports (Adams et al. 2011; Adams et al. 2003; Hadjikhani et al. 2008) is likely due to the higher BOLD sensitivity at 7 Tesla or the more liberal threshold. The maximum z-score for both short and long duration stimuli is slightly higher in the left amygdala, in agreement with previous work. Bilateral activation has previously been reported for related emotional fMRI tasks (N'Diaye et al. 2009).

An ISI was introduced in the short-presentation protocol to allow block timing and the number of presented stimuli to be the same between the two protocols, hence ISIs varied across duration conditions. However, the within-run BOLD contrasts always used the same ISI for both averted and direct gaze, and thus processing during ISI was not thought to influence the results; although further testing, with stimulus durations constant and varying ISI, would be needed to confirm this.

Areas involved in joint attention included in the images (frontal operculum, inferior parietal cortex and insula) showed higher activation for averted gaze regardless of stimulus duration.

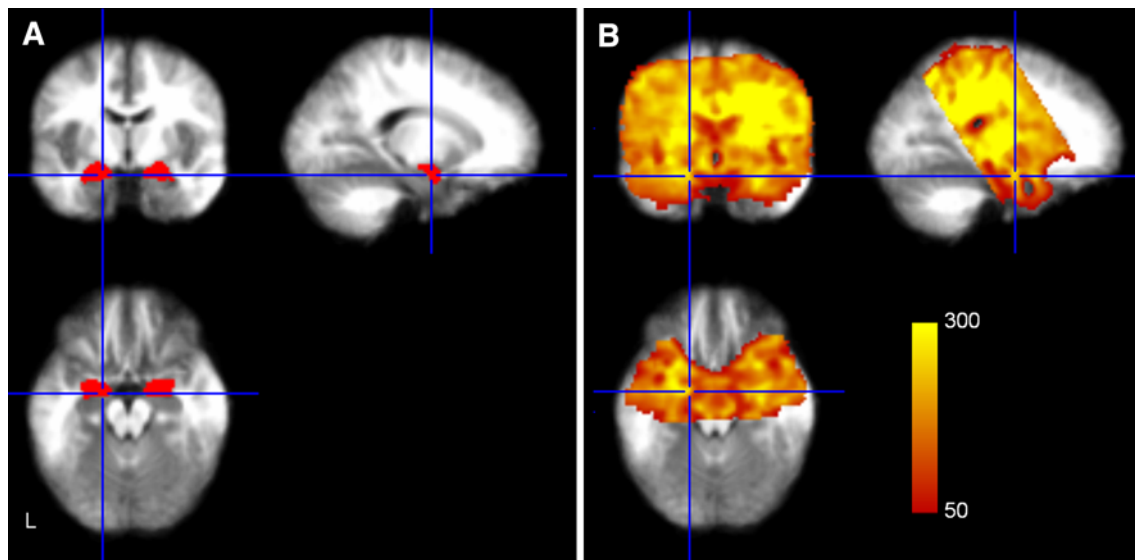


Fig. 1 **a** Amygdalae from the Harvard–Oxford subcortical atlas. **b** Temporal SNR map from a representative subject for the area of the fMRI acquisition volume. Shown tSNR values range from 50 to 300.

Crosshair lines are positioned at -18 , -5 , -17 in MNI space. Note that tSNR in the medial part of the amygdala is lower than in the lateral region due to through-slice dephasing

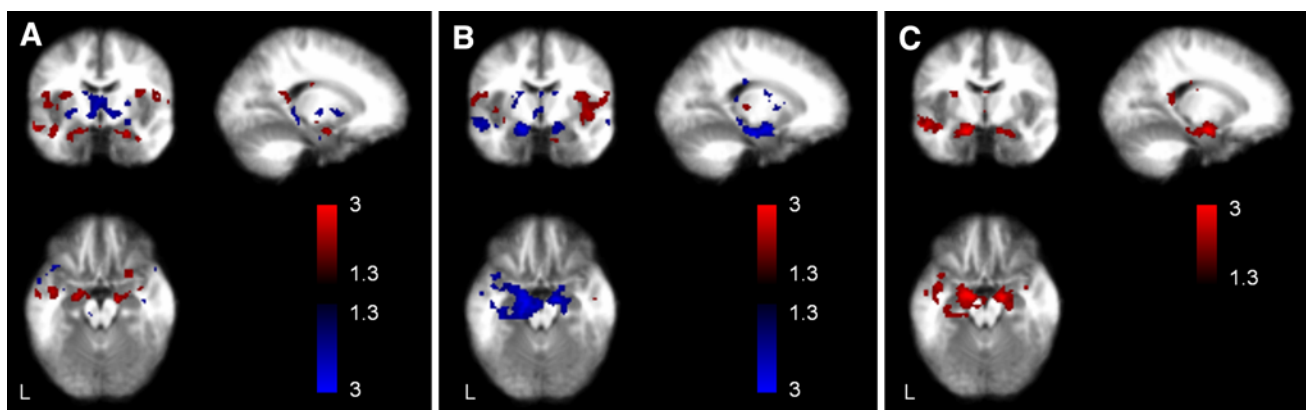


Fig. 2 **a** Group activation map (z scores, threshold 1.3 or $p < 0.05$) for the short duration fearful gaze, averted versus direct: increased BOLD signal in the amygdalae. Planes correspond to $x = -18$, $y = -5$, $z = -17$ in MNI space, as in Fig. 1. **b** Same for long

duration fearful gaze, averted versus direct: decreased BOLD signal in the amygdalae. **c** Duration effect: significant duration effects found in both amygdalae

Threat and gaze are thought to affect different amygdaloid nuclei (Hoffman et al. 2007), which in this study could not be separated. In future studies, the high spatial resolution available at 7T in single subject studies, could be employed to further disentangle threat, gaze and stimulus duration effects.

These data help reconcile findings from previous studies, and show that stimulus duration can considerably influence the amygdala's response to threat. We interpret these data as being the result of variations in stimulus appraisal: the short percept (300 ms) of a fearful face looking away rapidly orients the viewer to the presence of a potential danger (Hadjikhani et al. 2008)—however, when more time is given to process the stimulus ($\geq 1,500$ ms),

the ambiguity surrounding the source of threat associated with direct gaze fear becomes prominent and alerting (Adams et al. 2003).

Conclusion

These data show that, provided an appropriate slice orientation is used in combination with a thin slice thickness, fMRI at ultra-high field can be used to detect BOLD signal from the amygdalae. Such acquisitions allowed a comparison of BOLD responses to averted and direct gaze fearful faces with a relatively short or long duration in a single session, confirming that the inversion of the detected

BOLD responses is due only to the duration of the presented stimulus.

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