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Cumulative activation during positive and negative events and state anxiety predicts subsequent inertia of amygdala reactivity

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Inertia, together with intensity and valence, is an important component of emotion. We tested whether positive and negative events generate lingering changes in subsequent brain responses to unrelated threat stimuli and investigated the impact of individual anxiety. We acquired fMRI data while participants watched positive or negative movie-clips and subsequently performed an unrelated task with fearful and neutral faces. We quantified changes in amygdala reactivity to fearful faces as a function of the valence of preceding movies and cumulative neural activity evoked during them. We demonstrate that amygdala responses to emotional movies spill over to subsequent processing of threat information in a valence-specific manner: negative movies enhance later amygdala activation whereas positive movies attenuate it. Critically, the magnitude of such changes is predicted by a measure of cumulative amygdala responses to the preceding positive or negative movies. These effects appear independent of overt attention, are regionally limited to amygdala, with no changes in functional connectivity. Finally, individuals with higher state anxiety displayed stronger modulation of amygdala reactivity by positive movies. These results suggest that intensity and valence of emotional events as well as anxiety levels promote local changes in amygdala sensitivity to threat, highlighting the importance of past experience in shaping future affective reactivity.

Keywords: emotional states; emotional inertia; positive emotions; mood; sensitization; desensitization; state anxiety; amygdala; fMRI

INTRODUCTION

Neuroscience research on emotions has generally focused on stimulus-locked responses in relation to perception, attention or memory. However, such approach does not fully capture the neural underpinnings of emotional states, which unfold in time beyond transient reactions to external stimuli. Understanding the dynamics of emotion and their prolonged impact on mental processes is crucial to understand how they shape adaptive behaviors in the short term (Gray, 2001), and also how they impact mental processes and behavior in the long term, and may potentially contribute to chronic anxiety or mood disorders (Nestler and Hyman, 2010).

In order to fully describe an emotion, it is important to quantify not only its intensity and valence, but also its dynamics over time (Davidson, 1998; Suls *et al.*, 1998; Kuppens *et al.*, 2010). Whereas the intensity and valence of transient emotional effects have been investigated extensively (Craig *et al.*, 2000; Anderson *et al.*, 2003; Small *et al.*, 2003), very little is known about the more prolonged temporal dynamics of emotional responses and the underlying neural substrates.

Temporal components characterizing the dynamics of affective responses are also a key aspect of inter-individual differences in emotional reactivity and regulation (Davidson, 1998; Schimmack *et al.*, 2000; Davidson, 2003). Such dynamics, referred to as affective chronometry, is an important constituent of 'affective style' and is thought to play a crucial role in determining vulnerability to psychopathology (Davidson, 2003). Neuroticism, for instance, has been associated with greater carryover of negative mood to subsequent occasions, as well as rapid positive affect decay and rapid negative affect rebound after positive mood induction (Suls *et al.*, 1998; Hemenover, 2003). Similarly, a phenomenon of emotion inertia has been proposed to favor the persistence of prior emotional state and/or promote resistance to change in current affective state (Suls *et al.*, 1998; Kuppens *et al.*, 2010). Higher levels of emotional inertia have been associated with higher levels of psychological maladjustment, ruminations and depression, suggesting that the protracted effects of inertia may have a profound impact on emotional life (Kuppens *et al.*, 2010; Koval *et al.*, 2012).

To identify the neural signature of affective features such as emotional inertia, it is necessary to consider modulations of brain activity over timescales longer than transient event-related responses lasting a few seconds, and to understand how 'acute' emotional events may induce a lingering sensitization or attenuation in affective reactivity. For instance, it is known that negative mood and anxiety level is associated with increased processing of negative information (so-called negativity bias, e.g. Mathews and MacLeod, 1985). At the brain level, exposure to unsolvable anagram tasks with the aim to induce negative emotions increases amygdala cerebral blood flow (Schneider *et al.*, 1996), a key region for processing threat (LeDoux, 2003), and also for reinforcement learning (Morrison and Salzman, 2010). More recently, it has been shown that short-term exposure to stressful situations (van Marle *et al.*, 2009) or negative semantic priming (Pichon *et al.*, 2012) also strongly increases subsequent amygdala reactivity to both emotional and neutral faces. On the other hand, influences of positive states are less well documented. It is generally considered that positive emotional experiences provide people with psychological resources that enable them to learn better (Nadler *et al.*, 2010), cope more effectively with psychological challenges or negative information (Isen, 1999; Mitchell and Phillips, 2007), but it is unknown whether these affects are accompanied by reduced

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amygdala reactivity to threat. A recent fMRI study looking at the impact of positive and negative movies on subsequent rest periods found differential patterns of activity in several regions associated with default mode and limbic networks, presumably reflecting post-emotion adjustment and regulation (Eryilmaz *et al.*, 2011). However, it is unresolved whether such changes in affective states may influence neural responses evoked by subsequent emotional events.

Here, we establish how negative, and also positive emotional states, induced by movie clips, influence brain reactivity to threat-related information in a subsequent visual attention task. Two different conditions alternated in short sessions, each consisting of a movie (positive, negative or neutral) followed by the attention task where subjects matched pairs of fearful and neutral faces or pairs of houses (Figure 1a). Movies are among the most effective emotion induction procedures, as convincingly evidenced by cinema and psychology research (Rottenberg *et al.*, 2007; Straube *et al.*, 2010). By manipulating attention toward or away from fearful faces, we could determine whether any change in emotional reactivity subsequent to the different movies was mediated or not by changes in attention (Vuilleumier *et al.*, 2001; Pichon *et al.*, 2012; Pourtois *et al.*, 2013). This paradigm thus enabled us to compare responses to threat cues when these were task-relevant or not, and across different emotional states. Importantly, we also tested whether any change in amygdala reactivity was causally related to the pattern of emotional response during the preceding movies. Finally, given evidence that anxiety level potentiates amygdala reactivity to threatening information (Bishop *et al.*, 2004; Cornwell *et al.*, 2011), we also tested whether any emotional inertia effects could be predicted by individual differences in anxiety levels.

METHODS

Participants

Twenty-five right-handed volunteers (13 females, mean age ± s.d. 23.2 ± 4.5) with no history of neurological and psychiatric disease were recruited. All provided written informed consent according to local ethics guidelines. After they had completed the fMRI experiment, they filled a questionnaire assessing state anxiety (Spielberger *et al.*, 1983). Trait anxiety was collected at least 1 day later, through an excel form sent to the subjects by email (Spielberger *et al.*, 1983). Participants' state anxiety scores ranged from 20 to 64 (mean ± s.d. 32 ± 11), and their trait anxiety scores ranged from 23 to 64 (37 ± 11). These scores are similar to the published norms for this age group (state 36 ± 10; trait: 36 ± 10) (Spielberger *et al.*, 1983). Cronbach reliability scores confirmed the internal consistency of the state ($\alpha = 0.95$, 20 items) and trait ($\alpha = 0.91$, 20 items) anxiety scales.

Stimuli and experimental procedure

During the fMRI experiment, participants performed two intermixed tasks arranged in 18 sessions. At the beginning of each session, subjects watched a positive, negative or neutral movie clip; this was immediately followed by an attention task with faces and houses. To keep the goal of the experiment as implicit as possible, participants were told that they would participate in two different studies performed in alternating sessions to make the experiment less repetitive. They were also instructed to get immersed in the movie as much as possible without being critical. We therefore collected ratings after the scanner session: participants indicated how much they had felt absorbed in each movie on a 10-point Likert scale (i.e. how much they felt emotionally immersed). In order to avoid explicit biases induced by the rating instruction (see Mitchell *et al.*, 2007), no mood ratings were collected during the scanning session. We used six movie clips per emotion context (negative, positive and neutral). The movies were selected from a standard database (Philippot, 1993); their pleasantness and

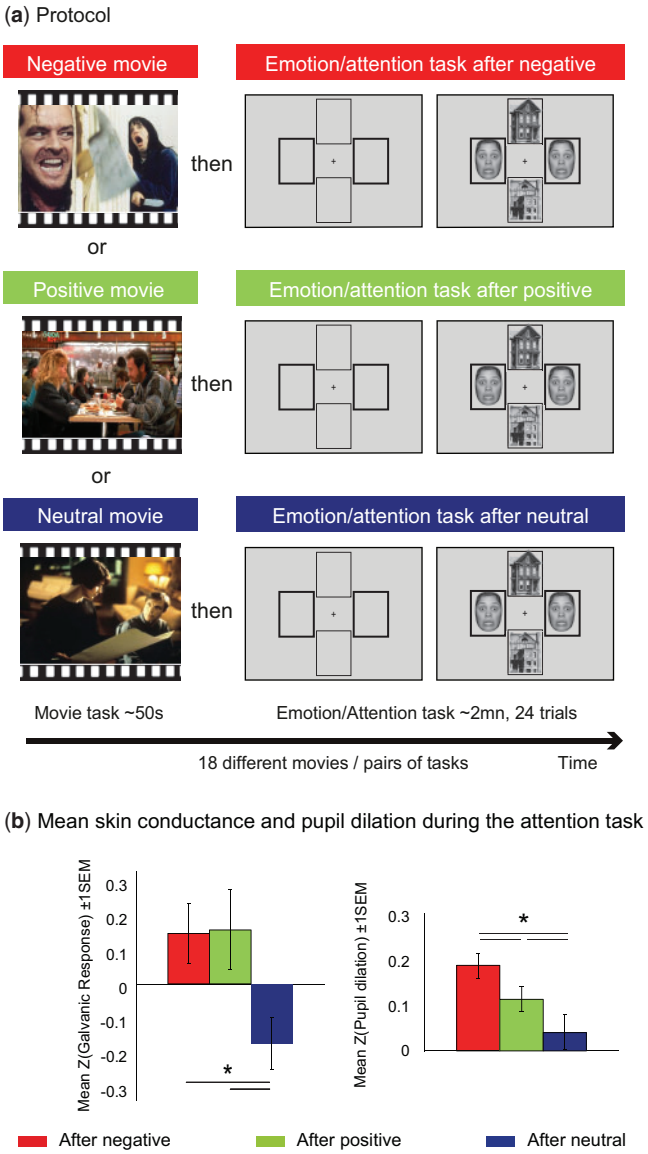

Fig. 1 Protocol and results. (a) The same visual attention task was performed after positive, negative or a neutral movie. (b) Peripheral physiological recordings confirmed that emotional movies increased peripheral arousal during the subsequent attention task (*$P < 0.05$).

emotionality ratings have been validated and reported in a previous study (Eryilmaz *et al.*, 2011). Examples of movies included *The Shining* (negative), *When Harry met Sally* (positive) or documentaries such as *Cosmos Mysteries* (neutral). The full list of movies is also described in Eryilmaz *et al.* (2011). We equated luminance across movies and Mood's median tests confirmed that audiovisual features were matched across contexts [luminance ($P = 0.13$), motion ($P = 0.69$), spatial frequency ($P = 1$), acoustic intensity and power ($P > 0.51$)].

Each session comprised a movie clip (~50 s), followed by a 0–10 s interval, and then a session of the attention task (92 s, comprising 24 trials per session). Movies were presented audio-visually. Emotional contexts were randomized and balanced every three sessions. Because we aimed at maximizing the influence of emotional context on the subsequent attention task, we used these individual absorption ratings to select the five (over six) most absorbing movie sessions within each context and the corresponding five (over six) subsequent sessions of the attention task. There are inevitably interindividual differences in the extent to which people felt absorbed by the movies, and it would be likely that low absorbing emotional movies produce less lingering effects

than highly absorbing movies. This was confirmed by comparing two models, one including all sessions and one discarding the least absorbing session per context. Both yielded very similar results, yet sensitivity to emotional effects was potentiated in the high-absorption model.

Attention task

The task was adapted from previous studies and has been shown to elicit robust response in the amygdala, fusiform face area (FFA), parahippocampal place area (PPA) and amygdala (Vuilleumier *et al.*, 2001; Pichon *et al.*, 2012). Each trial began with a black central fixation cross lasting 250 ms, followed by the four-picture display which lasted 250 ms (432 trials in total, 24 trials per session). Each display comprised two faces (both with either fearful or neutral expression) and two houses, arranged vertically and horizontally around a fixation cross. Subjects were asked to match (same/different judgment) the stimulus pair at pre-cued locations (thick placeholder frames around fixation), while ignoring the other stimulus category. The spatial arrangement of the display and the brief exposure time were specifically designed to make the task demanding in attention resources and ensured reliable central fixation, since eccentric eye movements toward one task-relevant stimulus would make the other less visible and would be counterproductive for matching performance (Duncan, 1980; Wojciulik *et al.*, 1998). The screen then returned to a white fixation-cross, and subjects had 2 s to indicate whether the attended pictures were identical or not, by using a response pad placed in the right hand. ITI were pseudo-randomly generated using a Poisson distribution with a mean of 3000 ms, lower and upper bounds of 2000 and 7000 ms, respectively. Depending on the session, subjects attended to either the vertical pictures only or to the horizontal pictures only. There were four task conditions: faces with fearful or neutral expression, presented at task-relevant or task-irrelevant locations. Each condition was analyzed as a function of the preceding emotional context (negative, positive or neutral movies), yielding 12 conditions. Stimuli pairs were repeated between contexts so the attention task sessions differed only by emotions in the preceding movie. Faces or houses appeared equally often in the vertically or horizontally paired position. Half of the pairs were composed of identical pictures and the other half consisted of different pictures. Within a pair of faces, we always used the same emotional expression (neutral or fearful). We controlled for face identities, so that for a given subject, the actors used to express fear always differed from the actors used for neutral expressions. New pairs were created for each subject and presented in random order. Over the whole experiment, a given pair of stimuli was therefore always seen 12 times, in two positions (vertical and horizontal), processed under both attentional contexts (attended and unattended) and all emotional context (positive, negative and neutral). Each picture subtended 4.4° of visual angle vertically and 3.8° horizontally. We used black-and-white pictures of houses ($n = 32$) and faces ($n = 32$ actors with two expressions, NimStim MacBrain set, www.macbrain.org).

Data acquisition

Gradient-echo T2*-weighted transverse echo-planar images (EPIs) with BOLD contrast and a high-resolution T1-weighted anatomical image were acquired with a 3 T Magnetom TIM Trio scanner (Siemens, Erlangen, Germany). Each volume contained 32 axial slices (TR/TE/Flip angle = 2100 ms/30 ms/80°, FOV = 205 mm, resolution = 64 × 64, voxels size 3 × 3 mm with 3.2 mm thickness). A shimming procedure minimized inhomogeneity of the static magnetic field. Image acquisition started after the recording of three dummy volumes to avoid T1 saturation. For each subject, we collected 1494 functional volumes for the movie and attention tasks. In addition, we collected 236 volumes for the localizer (see below) and a high-resolution T1-weighted anatomical image (TR/TI/TE/Flip angle = 1900 ms/900 ms/2.27 ms/9°, FOV = 256 mm, resolution = 256 × 256, slice thickness 1 mm, 192 sagittal slices).

Preprocessing of functional images

Image processing and analyses were carried out using SPM8 (Wellcome Department of Cognitive Neurology, London, UK). Functional images were realigned to the first volume by rigid body transformation, corrected for time differences, spatially normalized to the standard Montreal Neurological Institute EPI template, resampled to an isotropic voxel size of 2 mm and spatially smoothed with an isotropic 8 mm full-width at half-maximum Gaussian kernel.

fMRI general linear model analysis

At the individual level, we performed standard analyses using the general linear model (GLM) in SPM8. In the attention task, each session included four event types as described above. Because accuracy was high (84%) and did not differ between contexts, correct and incorrect responses were included in the same regressor, similarly to the methods used in previous publications (Vuilleumier *et al.*, 2001; Pichon *et al.*, 2012). For each condition, a covariate was calculated by convolving delta functions with a canonical hemodynamic response function (HRF). The length of each event encompassed the stimulation and the fixed response period similarly to models used in previous publications (Vuilleumier *et al.*, 2001; Pichon *et al.*, 2012). Movie sessions were modeled in a separate GLM (a single event per session covering the duration of the movie) to avoid contamination of the session mean during the subsequent attention task. Modeling the two tasks independently ensured that individual event regressors in the attention task were strictly comparable across emotional contexts (note that, regarding beta estimation, this is equivalent to modeling both tasks within the same GLM in separate sessions). The GLM models included the temporal derivatives of the scans realignment parameters. After model estimation, contrast images were calculated for each experimental condition (*vs* baseline) and entered in group-level statistics.

At the group level, whole-brain statistical maps were computed for the attention task from a random effect model, using a standard repeated-measure ANOVA (flexible factorial design) crossing the factors *context* (negative, positive and neutral), *emotion expression* of faces (threat and neutral) and *attention* (face at task-relevant or task-irrelevant locations). We applied non-sphericity correction to account for variance differences across conditions. A similar ANOVA was used for movies with a single factor *context* (negative, positive and neutral). Parametric maps were rendered on the T1-weighted average brain of the group.

Correction for multiple comparisons

All whole-brain statistical maps were corrected using small volume correction (SVC; $P < 0.05$ FWE, 2 × 2 × 2 mm box) based on amygdala, FFA and PPA peaks found in the localizer task (see below). SVC was applied on uncorrected contrast maps ($P < 0.05$). The same procedure was used for regression analyses with wavelet estimates (see below), except that we constrained our tests to those voxels activated by the main effect of threat in the attention task. Finally, we also examined possible context-dependent modulations in prefrontal regions known to be important in emotion regulation (Davidson, 1998; Phelps *et al.*, 2004; Etkin *et al.*, 2006) and sharing extensive connections with the amygdala (Ghashghaei *et al.*, 2006; Barbas *et al.*, 2010). We did so both in the standard GLM and in the psycho-physiological interaction (PPI) analysis described below. SVC was applied to statistical maps of the PPI analysis (*uncorrected at* $P < 0.05$) using predefined masks of ventromedial prefrontal areas,

created with the WFU pickatlas and comprising bilateral anterior cingulate cortices, plus medial orbital gyri and gyri recti.

PPIs analysis

To determine whether any change in amygdala reactivity following negative or positive movies reflected context-specific changes in functional connectivity between amygdala and other brain regions (e.g. prefrontal cortex), we performed a PPI analysis (Friston *et al.*, 1997) of the amygdala activation time-course during the attention task, testing for changes in inter-regional covariance as a function of the experimental context. First eigenvariate values were extracted for each participant from the amygdala peak (using a 4-mm sphere), as identified at the group level by contrasting trials with fearful *vs* neutral faces. The regressors were deconvolved to obtain an estimate of neural response, multiplied by the psychological context of interest (i.e. threat *vs* neutral trials), reconvolved using the canonical HRF to obtain a PPI regressor and entered in a GLM together with eight other regressors of no interest, including the time series of the seed region, the psychological factor convolved with the canonical HRF and six covariates modeling the temporal derivatives of the movement parameters. At the group level, we used two-sample *t*-tests to compare PPI estimates between the three emotional contexts.

Face localizer task

Subjects also performed a standard localizer task to identify amygdala, FFA (Kanwisher *et al.*, 1997) and PPA (Epstein *et al.*, 1999) independently of the main task. We used a 1-back task during blocked presentation of neutral faces, houses and scrambled images. We scanned 24 blocks, each containing 11 pictures presented for 600 ms, followed by a 500 ms ± 100 fixation. Subjects were required to press a button whenever a stimulus was presented twice in a row. The inter-block interval was 3 s and blocks were presented in random order. Reported peaks are: bilateral amygdala ([−24 −2 −26]; [18 −6 −20]) and bilateral FFA ([−44 −46 −24]; [42 −46 −26]) for the contrast faces > houses, bilateral PPA ([−24 −48 −14]; [30 −46 −10]) for the reverse contrast.

Correlation analysis with anxiety scores

For correlation analyses of amygdala responses with anxiety scores, we extracted beta weights using the contrast of matching threat > neutral faces in each context of the attention task at the left amygdala peak coordinates identified with the main effect of matching threat > neutral faces in the attention task (−26 −6 −8), and then extracted beta weights for the threat > neutral effect in each emotional context.

fMRI wavelet decomposition analysis

We used a wavelet decomposition procedure to obtain a quantitative measure of the cumulative amygdala signal power evoked by each movie in each participant. Wavelets offer an unbiased measure of fluctuations in brain activity arising in different frequency bands, without defining a priori discrete events during the movies or making a priori assumptions regarding their content. The wavelet transform complements GLM analysis by providing a compact time frequency representation of time-courses and, compared with conventional filtering, offers a powerful way of detrending the signal for its polynomial components (Bullmore *et al.*, 2004; Van De Ville *et al.*, 2006; Eryilmaz *et al.*, 2011). This has been exploited for better estimation of GLM parameters (Fadili and Bullmore, 2002) and also for functional connectivity in fMRI (Achard *et al.*, 2006; Eryilmaz *et al.*, 2011). Since the movie epochs were rather long, it was possible to examine both low and high frequency bands. Signal fluctuations in high frequency wavelet bands (>0.1 Hz) are likely to reflect transient neural activity, whereas signal in low frequency bands should reflect more sustained neural activity (Somerville *et al.*, 2013).

Time series were extracted for each subject and each amygdala using standard SPM routines (first *eigenvariate*) for the extraction of BOLD time series. To avoid selecting non-activated amygdala voxels, and activated non-amygdala voxels, we calculated the union between an anatomical mask of the amygdala (Eickhoff *et al.*, 2005) and the group-level amygdala cluster defined by contrasting emotional and neutral movies. Because the ROI was defined using an independent measure from the attention task, this analysis avoids any double dipping (see Kriegeskorte *et al.* 2009).

Next, a discrete wavelet-transform separated the signal into four different frequency bands similar to those used in a previous study (Eryilmaz *et al.*, 2011): (i) 0.12–0.24 Hz, (ii) 0.06–0.12 Hz, (iii) 0.03–0.06 Hz and (iv) 0.01–0.03 Hz, allowing us to quantify variations in activity from relatively slower to relatively faster changes. Because we aimed at comparing the impact of transient *vs* sustained activity during movie watching, we focused on the high (0.12–0.24 Hz) and low (0.01–0.03 Hz) frequency bands, which could then be correlated with amygdala reactivity during the subsequent independent attention task. We applied the orthogonal cubic B-spline wavelet transform in the temporal domain (Battle, 1987). Signal power in the selected frequency bands was estimated by calculating the quadratic mean (i.e. root mean square, RMS) of obtained wavelet coefficients and averaged across movies to obtain a single RMS score per context, amygdala and subject.

As expected, signal power in the lower frequency band correlated strongly with beta weights as estimated for the movie epochs using the standard GLM in SPM (where events were modeled using long BOLD responses), demonstrating the validity and sensitivity of the wavelet approach; whereas signal power in the higher frequency band did not correlate with this overall activity (see Supplementary Figure S1).

Finally, RMS scores in the high and low frequency bands were entered as covariates in group-level regression analyses, using the three context-specific contrast images comparing trials with fearful *vs* neutral faces in the attention task (for each amygdala side). For illustrative purposes, we plot the distribution of each regression's *t*-statistics in amygdala voxels identified using the previously described probability-based anatomical mask (Eickhoff *et al.*, 2005).

Somatovisceral data acquisition and processing

Pupil diameter and position were recorded during the entire scanning session, using MR-compatible eye-tracking system at a sampling rate of 60 Hz (Eye Track 6; Applied Science Laboratories, USA). Electrodermal activity was recorded continuously using a Biopac MP 150 Acquisition Unit (Santa Barbara, CA, USA) at a sampling rate of 200 Hz. Due to data loss ($n = 6$) or absence of electro-dermal signal ($n = 2$), pupil data were available for 19 subjects and skin conductance (SC) for 17 subjects.

We performed standard preprocessing for the pupillometric data. Blink artifacts were identified and removed by linear interpolation with the nearest neighboring valid data points. The rare trials with >25% of blink artifacts were not considered for analysis. For each subject, the SC and pupillometric time series were *z*-transformed to account for global between-subjects variance in signal amplitude. Both time series were temporally smoothed using a moving average (200 ms). To estimate whether emotional movies increased tonic arousal during the attention task, we averaged the data points over time and analyzed these values using repeated measures ANOVA with the factor *emotional context*. Whenever the ANOVA test was significant, three *post hoc* tests were performed between negative/positive and neutral contexts (unilateral *t*-tests) and between negative and positive contexts

(bilateral *t*-test). Results were Bonferroni-corrected. In these instances, we indicate the uncorrected *P*-value and state the Bonferroni-corrected that gave a family-wise error rate of 0.05.

RESULTS

SC and pupil dilation (PD) revealed a reliable impact of emotional conditions that outlasted the movies and persisted during the attention task (respectively, $F_{2,38} = 3.9$, $P < 0.05$, $F_{2,32} = 8.6$, $P < 0.001$, see Figure 1b). Indeed, both SC and PD were greater after negative ($t_{18} = 2.71$, $P = 0.007$ and $t_{16} = 3.77$, $P < 0.001$, $\alpha = 0.017$) or positive movies ($t_{18} = 2.33$, $P = 0.016$ and $t_{16} = 2.49$, $P = 0.012$, $\alpha = 0.017$) than after neutral movies. Finally, negative movies induced higher subsequent levels of PD than positive movies ($t_{16} = 2.7$, $P = 0.015$, $\alpha = 0.017$; for SC $P = 0.9$). During the movie period itself, the average PD was larger for negative movies when compared with neutral movies ($t_{16} = 3.96$, $P < 0.001$, $P > 0.175$ for positive > neutral movies). The average SC did not differ between negative, positive or neutral movies (all $P > 0.32$). Note that comparing the different emotional contexts during the attention task is less prone to non-specific confounds than during the movie periods, since the former involves the comparison of the exact same visual stimuli and more transient/phasic response evoked by them. In addition, average skin conductance during negative movies correlated with the power of right amygdala signals in low frequency bands ($r_{pearson} = 0.59$, $P = 0.008$), and with the power of left amygdala signals in high frequency bands ($r_{pearson} = 0.46$, $P = 0.044$) during the movie period (as determined by wavelet analyses, see below).

Accuracy and reaction times in the attention task showed no difference due to face expression or emotion context. This ensured that observed effects in the brain could not be explained by variations in performance, attentional effort or error processing. Only the attention factor influenced both measures, with higher accuracy for matching houses *vs* faces (91% *vs* 76%, $F_{1,25} = 111.2$, $P < 0.001$) and lower response speed (811 *vs* 895 ms, $F_{1,25} = 54.5$, $P < 0.001$).

During the movie period, fMRI demonstrated robust bilateral amygdala activation ($x\ y\ z = -24\ -2\ -26'$, $Z = 3.52$, $P < 0.001$ FWE and $x\ y\ z = 18\ -6\ -20$, $Z = 4.27$, $P < 0.001$ FWE) to both positive and negative movies (Figure 2a), consistent with a reliable emotional engagement of participants. Additional activations were also observed in widespread networks of visual, auditory and fronto-parietal cortices.

Next, we identified amygdala reactivity to fearful (*vs* neutral) faces during the attention task. Fearful faces produced activation in left amygdala, irrespective of attention focus ($x\ y\ z = -24\ -2\ -26$, $Z = 2.83$, $p = 0.002$ FWE, Supplementary Figure S2). In right amygdala, no suprathreshold voxels survived statistical correction ($P = 0.44$ FWE). This is consistent with the left amygdala activation observed in Vuilleumier *et al.* (2001) with a similar paradigm. A potential explanation for this asymmetric effect is that the repetition of stimuli through runs and contexts might have attenuated right amygdala reactivity, which is known to habituate more rapidly to emotional stimuli than left amygdala (Breiter *et al.*, 1996; Sergerie *et al.*, 2008).

More critically, we assessed how reactivity to fearful faces was influenced by the preceding movie. Remarkably, left amygdala activation to fearful faces (Figure 2b) was modulated by the previous emotional context. It was maximal after watching negative movies ($x\ y\ z = -24\ -2\ -26$, $Z = 2.49$, $P = 0.006$ FWE), intermediate in the neutral context ($x\ y\ z = -24\ -2\ -26$, $Z = 1.72$, $P = .044$ FWE) and no differential response to fear whatsoever was found in the positive context ($P = 0.46$ FWE). This difference between positive and negative contexts in left amygdala was formally confirmed by a significant context-by-threat interaction ($x\ y\ z = -24\ -2\ -26$, $Z = 1.76$, $P = 0.04$ FWE). This bias was specific to the left amygdala, and not found elsewhere in the brain, including in face-responsive cortices (see Figure 3). No significant attention-by-context interaction was observed in bilateral amygdala (all $P > 0.27$). Positive movies therefore induced a subsequent desensitization to threat in left amygdala, whereas negative movies produced the opposite effect.

Importantly, these changes were independent of whether attention was directed to faces or directed to houses (see also Vuilleumier *et al.*, 2001; Bentley *et al.*, 2003). Similar increases after negative movies and decreases after positive movies were found when fearful (*vs* neutral) faces were presented at task-relevant or task-irrelevant locations (see Figure 2b), indicating that the observed modulations by preceding movies were not indirectly caused by an impact of emotional state on attentional control (Compton, 2003; Bocanegra and Zeelenberg, 2011; Cohen *et al.*, 2011). In addition, attention to faces or to

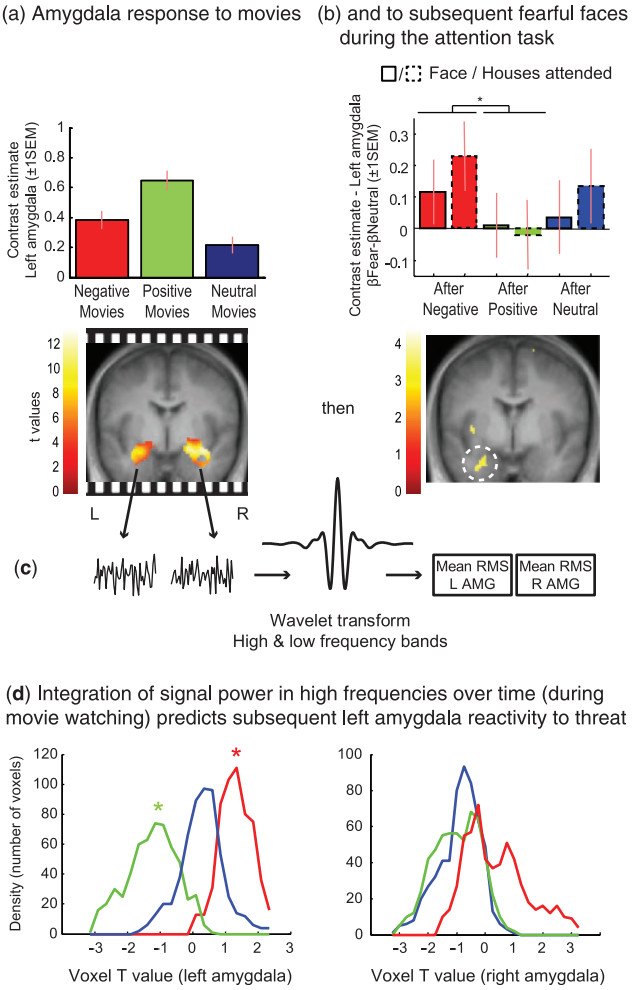

Fig. 2 Main fMRI results. (a) Greater responses in bilateral amygdala during emotional than neutral movies are shown by parameter estimates plotted (peak voxel) for each condition and group-level contrast map ($P < 0.001$ FWE). Parameter estimates were equivalent between left and right amygdala. (b) Left amygdala reactivity to fearful faces in the attention task was enhanced after negative movies but abolished after positive movies (session-by-threat interaction between the negative and positive contexts, $^*P < 0.05$ FWE). (c) Cumulative integration of amygdala activity during movies was computed for each individual using wavelet decomposition to isolate phasic (low frequency) and transient signals (high frequency), and quantified as the RMS of wavelet coefficients. (d) Distributions of correlation *t*-values (equivalent to Pearson *r*) across amygdala voxels obtained from the group-level regression of signal power in the high frequency band on activation maps comparing trials with fearful and neutral faces (irrespective of attention). Signal power in amygdala *during emotional movies* predicted the magnitude of change in response to fearful faces *during the attention task,* while movie valence predicted the direction of change ($^*P < 0.05$ FWE for the positive and negative contexts). Such correlations were not observed in low frequency bands (see Supplementary Figure S3).

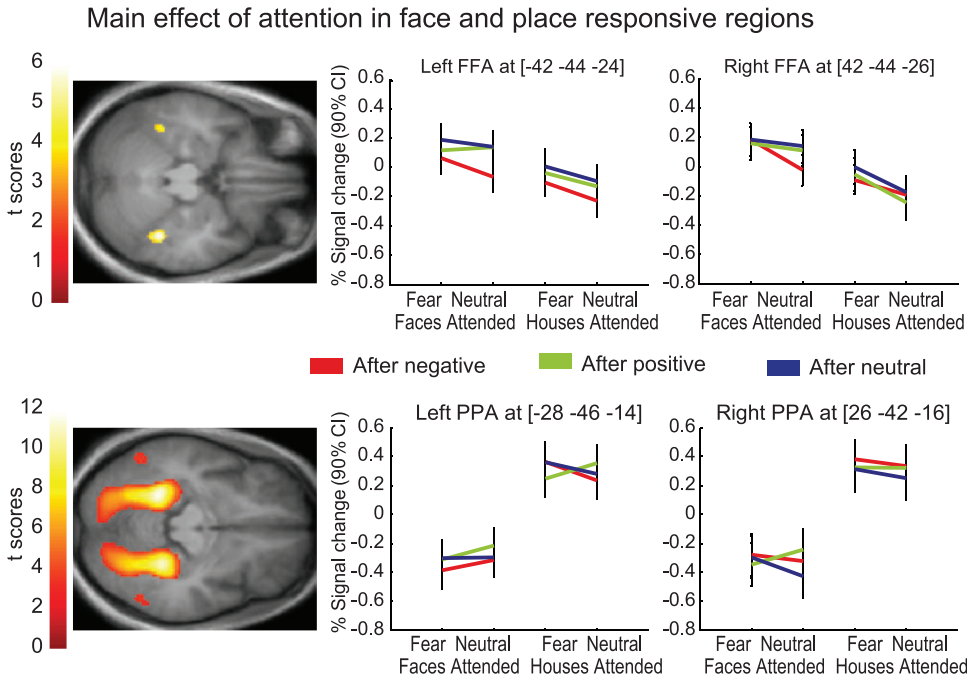

Fig. 3 Effect of focusing attention on faces or houses in face- and house-responsive visual regions. Mean group activation estimates ($P < 0.001$ FWE corrected, error bars correspond to 90% confidence interval, maps displayed at $P < 0.001$ uncorrected for display purpose). No significant attention-by-emotion interaction was observed in either region.

houses produced distinctive increases in BOLD signal in the FFA ($x\ y\ z = -44\ -46\ -24$, $Z = 4.06$, $P < 0.001$ FWE and $x\ y\ z = 42\ -46\ -26$, $Z = 5.58$, $P < 0.001$ FWE) and in the PPA ($x\ y\ z = -24\ -48\ -14$, $Z > 10$, $P < 0.001$ FWE and $x\ y\ z = 30\ -46\ -10$, $Z > 10$, $P < 0.001$ FWE) (Vuilleumier *et al.*, 2001; Bentley *et al.*, 2003).

We found no significant difference in these attentional modulations between positive and negative emotional contexts (i.e. no attention-by-context interaction [FFA: all $P > 0.074$, PPA: all $P > 0.14$], and no emotion-by-context interaction [FFA: all $P > 0.21$], PPA: all $P > 0.18$), again showing normal attentional control in all conditions (see Figure 3).

It could be argued that changes in amygdala response were mediated by exposure to movies with different content and in particular different amount, duration, expression and/or role of faces or people in the different movie conditions. Two results argue against such interpretation in terms of face habituation. On average, faces were present slightly longer in emotional (positive: 52 s, negative: 45 s) than in neutral movies (31 s), but face habituation effects would then predict that amygdala responses in the attention task should be maximal after the neutral movies, which was not the case. Second, if our results were due to face habituation, it would be difficult to explain why this effect was specific to amygdala and not observed in face-sensitive neurons in the fusiform gyrus (Grill-Spector *et al.*, 2006).

Could the changes in amygdala reactivity in different emotional states be caused by a modulation of regulatory signals from other brain areas controlling amygdala circuitry (e.g. medial prefrontal cortex, see Pezawas *et al.*, 2005; lateral prefrontal cortex, see Delgado *et al.*, 2008)? To address this possibility, we inspected potential context-dependent modulation of the response to fearful faces in other brain regions, but observed no other differences between emotional contexts ($P = 0.001$ uncorrected). We also specifically tested for changes in prefrontal regions (i.e. ventromedial, orbitofrontal and cingulate cortices) reputed critical for emotion regulation (Davidson, 1998; Phelps *et al.*, 2004; Etkin *et al.*, 2006; Ghashghaei *et al.*, 2006) and frequently activated during positive and negative mood states (Mitchell *et al.*, 2007). However, using predefined anatomical masks (see the 'methods' section), we observed no significant result in these regions, even at lower thresholds. Finally, to further address this issue, we performed a functional connectivity analysis allowing us to test for differential amygdala coupling in task periods following emotional *vs* neutral movies (psychophysiological interaction). Again, this analysis found no significant change in connectivity with key regions of the medial prefrontal cortex, or with any other brain regions when considering whole-brain results at uncorrected thresholds ($P = 0.001$).

We therefore asked whether the observed response biases might reflect local functional changes in amygdala induced by prior activation during movies. If so, the degree of amygdala engagement by previous emotional events in movies should determine the magnitude of subsequent biases in the attention task, while the valence of prior events might predict the direction of such biases. We first correlated beta estimates obtained for the whole movie period (in each emotion condition) with beta estimates corresponding to fearful face trials in the subsequent attention task, but observed no significant correlation. However, a single beta parameter estimated over the entire movie period might not accurately reflect meaningful emotion responses that could be evoked at various time points during the movies, possibly varying across individuals. We therefore reasoned that a more meaningful measure of emotional effects during the movies would be provided by a dynamic index of fluctuations in amygdala signals over time, which could potentially manifest at different frequency ranges (low/high). A first hypothesis could be that slow/tonic fluctuations in amygdala (i.e. low frequency signals) might drive subsequent sensitization or adaptation effects as a function of movie valence. An alternative hypothesis could be that because emotions might be elicited by particular events in the movie and amygdala neurons tend to habituate quickly (Breiter *et al.*, 1996), such sensitization effects might rather be determined by the cumulative sum of transient/phasic activations over time (i.e. high frequency signals). According to the latter hypothesis, we would thus predict that larger cumulative responses in amygdala (i.e. signal power over time) during negative movies should then lead

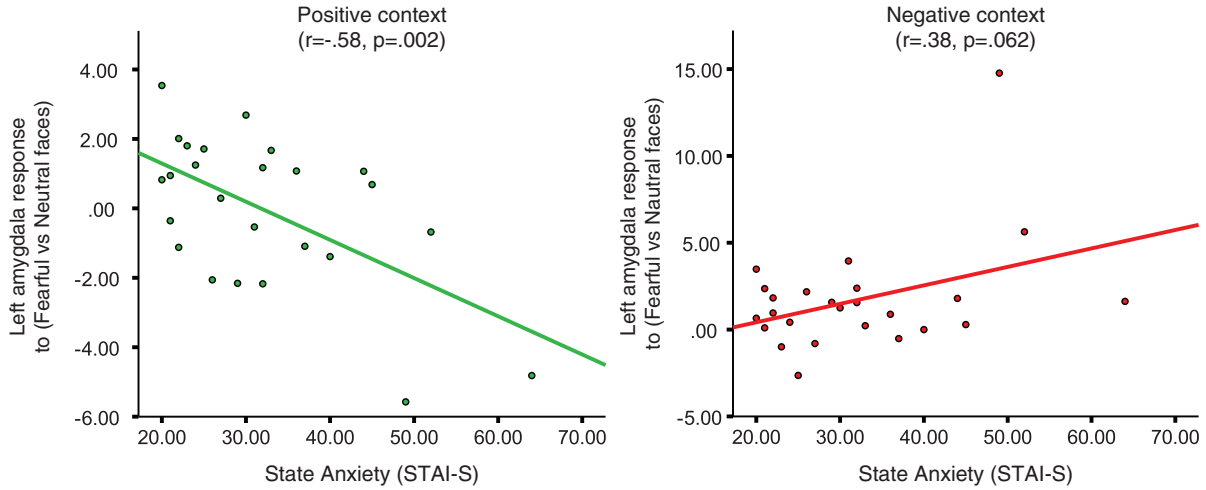

Fig. 4 State anxiety was inversely correlated with amygdala reactivity to threat in the positive context (attention task), suggesting that subjects, who were anxious at the time of the experiment were more likely to be permeable to emotional bias ($r_{pearson} = -0.58$, $P = 0.002$). Conversely, in the negative context, there was a trend toward increased sensitivity to threat which did not reach significance ($r_{pearson} = 0.38$, $p = 0.062$). No correlation was found in the neutral context ($P = 0.27$). Correlation in the positive context remained significant using a non-parametric test (see results).

to stronger increases in reactivity to threat, whereas higher response power during positive movies should lead to stronger attenuation.

To address this issue, we applied wavelet decomposition to isolate high- from low-frequency signals in the fMRI time series from each amygdala during each movie epoch, and then estimated signal power by computing the RMS of wavelet coefficients (see the 'Methods' section). Signal power was then used as a parametric covariate in whole-brain regression analyses (three emotion contexts × two amygdala sides) that compared activation with fearful (*vs* neutral) faces in the subsequent attention task (Figure 2c). Following positive emotions, we found a significant negative correlation in left amygdala between signal power during the movies and subsequent amygdala response to threat ($Z = 2.84$, $P = 0.045$ FWE; Figure 2d). Conversely, following negative emotions, left amygdala response to threat was positively correlated with signal power during movies; that is, stronger negative emotions predicted future enhancement of fear responses ($Z = 2.77$, $P = 0.048$ FWE). The negative correlation in the positive context was significantly different from the correlation at the same peak in the negative ($Z = 2.35$, $P = 0.0186$) and neutral contexts ($Z = 2.16$, $P = 0.0309$); tests adapted from Silver *et al.* (2004) using the cocor package available in the R software (Ihaka and Gentleman, 1996). We found no significant correlation for neutral movies ($Z = 1.76$, $P = 0.37$), or in any of the emotional context in the low frequency bands (see Supplementary Figure S3). Finally, we performed a control analysis now using the auditory cortex as a seed region. Contrary to what was observed in the high frequency band of the amygdala, no significant voxel was found in any context, neither in the left (all $p > 0.1$) or right hemisphere (all $p > 0.34$). The results demonstrate an emotional inertia of amygdala activity during the movies that influenced subsequent responses to fearful faces during the attention task. Thus, stronger transient amygdala responses during positive movies predicted greater reduction of fear responses in the subsequent attention task, while conversely stronger amygdala responses during negative movies predicted greater sensitization of subsequent fear responses.

Finally, we examined whether individual differences in anxiety might influence this inertia effect. People with higher state anxiety displayed stronger attenuation of amygdala response to threat after positive movies ($r_{pearson} = -0.58$, $P = 0.002$; Figure 4), and a trend toward stronger sensitization after negative movies which did not reach significance ($r_{pearson} = 0.38$, $P = 0.062$). Correlation in the positive context remained significant using non-parametric tests ($\rho_{spearman} = -0.44$, $P = 0.02$ for the positive context, $\rho = 0.14$, $P = 0.49$ for negative context). Trait anxiety scores were not significantly related to left amygdala reactivity to threat (although slopes were in the expected directions, positive context: $r_{pearson} = -0.3$, $P = 0.14$, negative context: $r_{pearson} = 0.19$, $P = 0.37$). This suggests that short-term state-anxiety favored emotion-induced changes in amygdala and increased its permeability to lingering biases in reactivity. In other words, state-anxiety promoted stronger emotional inertia. There was no such correlation whatsoever in the neutral context ($P = 0.27$).

DISCUSSION

Our finding that negative emotional state potentiates subsequent amygdala responses to threat reveals a lasting impact of negative affect, beyond transient events. Emotional history can thus exert prolonged effects on future response to new and unrelated emotional stimuli. These results may provide a potential substrate for the well-known 'negativity bias' in patients with mood and anxiety disorders, in whom persistent negative affect may lead to a tendency to over-react to and dwell on threat-related information (MacLeod *et al.*, 1986; Mathews, 1990; Fox, 1993; Mogg *et al.*, 2000; Williams *et al.*, 2005; Fox *et al.*, 2008; Disner *et al.*, 2011). It has been argued that such bias may play an important role in the maintenance and even possibly the etiology of anxiety (MacLeod *et al.*, 2002; Bishop, 2007). In contrast, positive emotional experiences induced the opposite bias and tempered subsequent amygdala responses to negative information, thereby showing how positive affect may promote resilience against fear-related stimuli. Importantly, our results suggest that these emotional biases emerge transiently and locally within the amygdala, unrelated to changes in regulatory influences from connected regions and independent of voluntary attention.

Such changes in amygdala reactivity appear very distinct from intentional regulation strategies usually studied in human neuroscience, such as emotion suppression, reappraisal or—conversely—enhancement (Ochsner *et al.*, 2012). For instance, instructions to deliberately prolong the emotional response to aversive pictures (Schaefer *et al.*, 2002) or to interpret neutral pictures as aversive (Ochsner *et al.*, 2009) both lead to increased amygdala responses, accompanied by modulations of prefrontal areas involved in cognitive and affective control. The effects we observed here may imply involuntary forms of regulation triggered

by recent emotional experiences (Bargh *et al.*, 2012; Pichon *et al.*, 2012), although we found no modulation of amygdala functional connectivity with prefrontal brain regions commonly associated with emotion regulation, in particular the medial orbitofrontal and anterior cingulate cortex (Davidson, 1998; Phelps *et al.*, 2004; Etkin *et al.*, 2006; Ghashghaei *et al.*, 2006). Similarly, no context-specific change was observed in these regions in the standard fMRI analysis. This lack of significant modulation of prefrontal activity by affective inertia does not constitute irrefutable evidence for an absence of effect and could result from a lack of power. On the other hand, this may accord with the lack of behavioral impact of our manipulation on the attention task performance. Accordingly, findings from studies using mood manipulation suggest that positive affect has most influence on explicit cognitive tasks that rely on the prefrontal cortex and high-level behaviors such as hypothesis testing, cognitive flexibility, rule selection and creativity (Gray, 2001; Nadler *et al.*, 2010).

Alternatively to prefrontally mediated changes, some regulation mechanisms may operate within the amygdala itself. For instance, repeated activation in response to positive or negative emotional events could trigger short-term plasticity in synaptic transmission within the amygdala (Pan and Zucker, 2009) leading to, respectively, subsequent desensitization or sensitization to negative information. The latter would accord with our findings that cumulative phasic amygdala activity in response to emotional events predicted changes in later response to threat. In primates, distinct neural populations encoding positive *vs* negative information have been isolated in the amygdala (Paton *et al.*, 2006; Belova *et al.*, 2008; Zhang *et al.*, 2013). In humans, several brain imaging studies have shown that amygdala responds to both positive and negative stimuli (Hamann and Mao, 2002; Hamann *et al.*, 2002, 2004; Killgore and Yurgelun-Todd, 2004; Fitzgerald *et al.*, 2006; Sergerie *et al.*, 2008; Ball *et al.*, 2009; Pichon and Kell, 2013). Differential recruitment of these populations during movies could support the opposite effects of positive *vs* negative emotions on subsequent amygdala reactivity (decreases *vs* increases) during the visual attention task.

Another possibility is that neuronal circuits within the amygdala might be modulated by opioid neurotransmission. Positive emotions induce the release of endogenous opioids in the amygdala (Koepp *et al.*, 2009) while negative affect such as sadness has the opposite effect (Zubieta *et al.*, 2003). Opioid agonists reduce the acquisition of conditioned fear (Davis, 1979), whereas blockade produces the reverse effect (Eippert *et al.*, 2008). Finally, activation of opioid receptors is also linked to hypoalgesia and reduction of amygdala response to noxious stimuli (Zubieta *et al.*, 2001; Wanigasekera *et al.*, 2012). Thus, opioid release in the amygdala in response to positive events during movies might provide a plausible neural mechanism for desensitization to subsequent negative information. Finally, it is known that acute stress can also trigger the release of glucocorticoid hormones (e.g. cortisol in humans) which then increases baseline neuronal activity in basolateral amygdala (Kavushansky *et al.*, 2006). However, given our experimental design, these hormonal changes are unlikely to drive the effects observed in our study because the kinetic of corticosteroid release (Joëls *et al.*, 2011) is much slower than the alternation between our positive, neutral and negative movies (presented one random order for every ~3 min). Hence, cortisol effects would have probably spread across different movie conditions.

The observation that past amygdala activity is important for shaping future emotional reactivity also provides novel neurobiological support to the notion that emotions have inertia (Davidson, 1998; Kuppens *et al.*, 2010). Emotional inertia is a fundamental property of emotion dynamics defined as the persistence of prior emotional state in time, and shown to have a profound impact on emotional life and psychopathology (Davidson, 2003; Kuppens *et al.*, 2010; Koval *et al.*, 2012). Although this concept has most often been invoked for describing variations in mood over longer period of time (days), our results for shorter time intervals seem compatible with this view. Higher levels of reactivity during negative or positive emotional episodes predicted stronger resistance to change and greater influence on subsequent response to fearful faces. This result is consistent with the literature on affective chronometry indicating that inter-individual differences in emotional reactivity may specifically implicate the temporal components of affective response and regulation (Davidson, 1998; Schimmack *et al.*, 2000; Davidson, 2003). This inertia is also reminiscent of anchoring effects (Tversky and Kahneman, 1974; Russell and Fehr, 1987), whereby some information encountered earlier distorts the evaluation of subsequent information. Emotional episodes experienced through movies may generate affective 'anchors' sensitizing or desensitizing amygdala reactivity to threat. Another implication is that affective state or recent experiences of subjects may affect whether amygdala activation is detected or not in typical fMRI studies.

We also observed that changes in amygdala reactivity were related to state anxiety, particularly in the positive context, indicating that current state anxiety or stress can modulate the permeability to positive and negative biases. Abundant literature on negativity biases has demonstrated that individuals high in state anxiety show increased threat detection sensitivity and increased difficulty to disengage attention from threat-related stimuli (e.g. Mathews and MacLeod, 1985; Mogg *et al.*, 1990; Fox *et al.*, 2001; Doty *et al.*, 2013). Similar permeability to negative biases has also been reported following acute social stress (Mogg *et al.*, 1990). Moreover, stronger permeability to mood-induced bias is also related to greater change in negative and positive psychological functioning in real life: participants showing stronger change in negative bias following negative mood induction were found to report higher state anxiety 3 weeks after the experiment, while greater change in positive bias following positive mood induction is associated with higher ratings in life satisfaction (Cavanagh *et al.*, 2011). At the brain level, subjects with high state-anxiety show stronger amygdala reactivity to fearful faces (Bishop *et al.*, 2004; Cornwell *et al.*, 2011) and weaker amygdala response to happy faces (Somerville *et al.*, 2004). Our results add to this by suggesting that individuals high in state anxiety benefit the most from positive emotional episodes since they showed the strongest attenuation in amygdala response. Similarly, participants with the highest trait anxiety benefit the most—in terms of state anxiety reduction—from a training to promote positive thinking (Yiend *et al.*, 2005).

Acute stress and anxiety states are known to be associated with alterations in brain plasticity, particularly in the amygdala, hippocampus and prefrontal cortex (McEwen *et al.*, 2012). In the short term, these changes may be adaptive, promoting increased vigilance and alertness in a threatening environment. However, in the long term, such response inertia may persist even after the danger has passed and thus become maladaptive, leading to chronic stress, pervasive negative biases, sustained physiological anomalies as well as perseverative patterns in affect-related cognitions or memories (Brosschot *et al.*, 2010). Likewise, high amygdala reactivity may be a predisposing factor influencing vulnerability to anxiety and stressors. In a recent study investigating brain responses to an economic game before and after exposure to military duties, Admon *et al.* (2013) found that stress vulnerability (assessed by post-exposure PTSD-related symptoms) corresponded to greater amygdala/hippocampus reactivity to risk both post- and pre-exposure, and to decreased nucleus accumbens reactivity to reward post-exposure. Dramatically, pre-exposure amygdala reactivity to risk was predictive of post-exposure PTSD symptom severity (Admon *et al.*, 2009, 2013).

In many studies, including ours, the link between state anxiety and negativity bias to threat is only correlational. Yet, it has been

demonstrated that emotional biases may themselves causally exacerbate anxiety vulnerability in stressful contexts. For instance, training or exposure studies have been used to induce experimentally interpretive biases favoring the threatening or non-threatening meanings of ambiguous information (MacLeod *et al.*, 2002; Wilson *et al.*, 2006). Negative training increased participant's anxiety reaction to a subsequent video stressor (Wilson *et al.*, 2006). Similarly, semantic priming with negative material increases pessimistic thinking (Mathews and Mackintosh, 2000) and amygdala response to fearful and neutral faces (Pichon *et al.*, 2012). In real life, emotion episodes (and their repetition or accumulation) may also produce lasting changes in subjective states and have significant impact on future cognitive and affective functioning. The present results extend this notion by demonstrating that both negative and positive experiences can modify later emotional reactivity, and that these changes may imply sensitization or desensitization of intrinsic amygdala processes.

How long may these effects last? Our data suggest that increased amygdala reactivity to negative information evolves during several minutes following exposure to arousing emotional episodes. A similar transfer has been reported following negative semantic priming (Pichon *et al.*, 2012) or during resting state following emotional movie clips (Eryilmaz *et al.*, 2011). In the former study, which used the same visual attention paradigm as here, exposure to negative words for 10 min also sensitized amygdala responses to fearful and neutral faces. Although our results did not show significant effects on behavior in the attention task itself, more potent, realistic or self-relevant emotional episodes might do so. Future studies are also needed to determine whether emotional events might influence amygdala reactivity over longer delays.

More generally, these results encourage future work toward better understanding the behavioral and neural consequences of positive psychology interventions that aim at facilitating positive emotions and positive interpretive bias. For instance, positive mood broadens attention and promotes orienting to positive stimuli (Wadlinger and Isaacowitz, 2006), consistent with the view that positive emotions broaden cognition (Fredrickson, 2004). Likewise, shift in attention to pleasant cues following positive mood induction resulted in more elevated life satisfaction 3 weeks after the experiment (Cavanagh *et al.*, 2011). Similarly, training-induced positive interpretation biases make participants interpret ambiguous situations in a more positive way, even 1 day after the training (Yiend *et al.*, 2005). Some evidence also indicates short-term benefits of positive training on state or trait anxiety (Yiend *et al.*, 2005; Salemink *et al.*, 2009).

Finally, the present data and methods may contribute to develop new ways of assessing emotion dynamics and plasticity in affective brain systems, as well as their modulation by therapeutic interventions or other factors, particularly in conditions associated with amygdala hyperactivity such as mood disorders or anxiety. They also underline the importance of considering model-free approaches to analyze long periods of fMRI data that are acquired in paradigms using ecologically valid situations, where no definite event occurrence can be defined a priori.

SUPPLEMENTARY DATA

Supplementary data are available at *SCAN* online.

CONFLICT OF INTEREST

None declared.

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