International Journal of Psychophysiology xxx (2013) xxx–xxx

Contents lists available at SciVerse ScienceDirect

International Journal of Psychophysiology

journal homepage: www.elsevier.com/locate/ijpsycho

Amygdala responses to valence and its interaction by arousal revealed by MEG

Charalampos Styliadis [a], Andreas A. Ioannides [b], Panagiotis D. Bamidis [a,*], Christos Papadelis [c]

[a] Laboratory of Medical Informatics, School of Medicine, Aristotle University of Thessaloniki, P.O. Box 323, 54124 Thessaloniki, Greece
[b] Laboratory for Human Brain Dynamics, AAI Scientific Cultural Services Ltd., Office 501, Galaxias Building Block A, 33 Arch. Makarios III Avenue, 1065 Nicosia, Cyprus
[c] Department of Neurology, Boston Children's Hospital, Harvard Medical School, 9 Hope Av., Waltham, MA 02453, USA

ARTICLE INFO

Article history:
Received 23 November 2012
Received in revised form 17 April 2013
Accepted 10 May 2013
Available online xxxx

Keywords:
Magnetoencephalography (MEG)
Arousal
Valence
Interaction
Synthetic Aperture Magnetometry (SAM)
Emotion
Affective pictures

ABSTRACT

It is widely accepted that the amygdala plays a crucial role in the processing of emotions. The precise nature of its involvement is however unclear. We hypothesized that ambivalent findings from neuroimaging studies that report amygdala's activity in emotions, are due to distinct functional specificity of amygdala's sub-divisions and specifically to differential reactivity to arousal and valence. The goal of the present study is to characterize the amygdala response to affective stimuli by disentangling the contributions of arousal and valence. Our hypothesis was prompted by recent reports claiming anatomical sub-divisions of amygdala based on cytoarchitecture and the functional maps obtained from diverse behavioral, emotional, and physiological stimulation. We measured magnetoencephalography (MEG) recordings from 12 healthy individuals passively exposed to affective stimuli from the International Affective Picture System (IAPS) collection using a 2 (Valence levels) × 2 (Arousal levels) design. Source power was estimated using a beamformer technique with the activations referring to the amygdala sub-divisions defined through probabilistic cytoarchitectonic maps. Right laterobasal amygdala activity was found to mediate negative valence (elicited by unpleasant stimuli) while left centromedial activity was characterized by an interaction of valence by arousal (arousing pleasant stimuli). We did not find a main effect for amygdala activations in any of its sub-divisions for arousal modulation. To the best of our knowledge, our findings from non-invasive MEG data indicate for the first time, a distinct functional specificity of amygdala anatomical sub-divisions in the emotional processing.

1. Introduction

Functional neuroimaging studies have so far distinguished the major participating sources for emotional processing to deep brain structures (amygdala, thalamus, insula, anterior cingulate cortex, cerebellum) and fairly superficial cortical areas (prefrontal cortex, operculum, temporal and visual cortices) (Davidson and Irwin, 1999; Phan et al., 2002; Wager et al., 2003). The last are more accessible by non-invasive electrophysiological recordings in contrast to the deep brain structures that are more difficult to detect. Up to date research claims that these brain cortical and subcortical structures contribute to the processing of emotions through interactions that form widespread cortico-limbic networks. It is still under debate though, at least for some of these structures (i.e. amygdala), which are the factors in internal or external stimuli (perceptual features, duration, positive or negative qualities, emotional dimensions) that engage them in functioning with others so as to perform emotional processing.

Neuroimaging studies on healthy participants have complemented the findings from research on laboratory animals (LeDoux, 2000; Zikopoulos and Barbas, 2012) and clinical data from humans (Adolphs and Spezio, 2006; J.E. Kim et al., 2012), thus cementing the human amygdala's critical role in the processing of emotionally significant information. Most work to date has assessed amygdala function within the framework of its role in the rapid and automatic detection of threatening stimuli (Adolphs et al., 1999), though other researchers proposed a more general role for this structure in processing unpleasant stimuli (Davis, 1992; Adolphs et al., 1994; LeDoux, 1996; Morris et al., 1996; Phan et al., 2002; Cornwell et al., 2008). Subsequent research on the human amygdala suggested an even less specific role as it was demonstrated that the human amygdala responds to both unpleasant and pleasant stimuli (Beauregard et al., 2001; Garavan et al., 2001; Hamann and Mao, 2002; Murphy et al., 2003; Wager et al., 2003; Ferretti et al., 2005; Fitzgerald et al., 2006; Kensinger and Schacter, 2006). These findings formulated the most recent model, which calls for the human amygdala involvement in evaluating stimulus salience, regardless of their valence, acting as a signaling detector that initiates appropriate behavioral responses (Sander et al., 2003). An up to date

* Corresponding author. Tel.: +30 2310999310; fax: +30 2310999263.
E-mail addresses: styliadis@hotmail.com (C. Styliadis), a.ioannides@aaiscs.com (A.A. Ioannides), bamidis@med.auth.gr (P.D. Bamidis), christos.papadelis@childrens.harvard.edu (C. Papadelis).

0167-8760/$ – see front matter © 2013 The Authors. Published by Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.ijpsycho.2013.05.006

review (Armony, 2012) concludes that the amygdala elicits consistent and strong responses to unexpected, novel stimuli thus acting as a detector of novelty for stimuli with potential biological significance. When these stimuli cease to carry biological or behavioral relevant information, then the amygdala rapidly habituates.

Recent studies on rodents and non-human primates have shown that the amygdala is not a single but rather a complex structure, the functional diversity of which is reflected on an anatomical basis as well (McDonald, 1998, 2003; Emery and Amaral, 2000; LeDoux, 2000; Phelps and LeDoux, 2005; Hoffman et al., 2007). Similar to that of animals, the human amygdala is divided anatomically into three major sub-divisions, namely the laterobasal (LB), the centromedial (CM) and the superficial (SF) amygdala (Amunts et al., 2005). One important notion is that there is a controversy on how the amygdala complex should be sub-divided as well as how these sub-divisions relate to other brain areas. This is partly due to the fact that the amygdaloid complex is actually a conglomeration of at least 13 nuclei of even more sub-nuclei (Sah et al., 2003), which are separated in terms of the trajectory of fibers, chemical signature and histological appearance (LeDoux, 2007). Currently, the functional neuroimaging spatial resolution in humans does not allow one to separate these individual nuclei within the amygdala. Thus, the microlevel focus on amygdala evident in rodent and non-human primate studies is not achieved in human neuroimaging studies. However, the resolution is high enough to demonstrate structural (Sheline et al., 1998) and functional (Morris et al., 2001; Kim et al., 2003; Whalen et al., 2004) distinctions for the amygdala. It is a common practice in neuroimaging studies to group these 13 nuclei into the LB, CM and SF sub-divisions (Whalen and Phelps, 2009). For instance, LB consists of the lateral, basolateral, basomedial and paralaminar nuclei, CM consists of the central and medial nuclei and SF comprises the anterior amygdaloid area, the ventral and posterior cortical nuclei (Amunts et al., 2005). This approach has eventually allowed assessment of amygdala's sub-division differences. Novel neuroimaging work on the human amygdala sub-divisions suggests that they play pivotal roles in mediating diverse behavioral, emotional, and physiological responses (Ball et al., 2007).

The functional role of the anatomical sub-divisions of human amygdala in emotional processing has received little attention so far in neuroimaging studies. Animal studies distinguish activations from the amygdala to contributions from its different sub-divisions. In contrast, the majority of imaging studies on the human amygdala have treated the amygdala as a single homogenous structure (Sergerie et al., 2008). In addition, previous work did not control for the different effects of valence, arousal and their interaction. As a consequence, previous studies characterize the activity elicited by various stimuli at the level of the entire amygdala complex rather than at the level of its sub-divisions, and they do not address its functional specificity. The few exceptions we are aware of include functional magnetic resonance imaging (fMRI) studies that identified distinct activity in dorsal and ventral areas of the amygdala (Morris et al., 2001; Kim et al., 2003; Whalen et al., 2004). A more recent study (Ball et al., 2007) examined specific functional differences among the LB, CM and SF sub-divisions using probabilistic cytoarchitectonic maps (PCMs) (Amunts et al., 2005).

The goal of the present study is to better characterize the amygdala response to affective stimuli by assessing the differentiated functional role of its sub-divisions in the emotional processing. Thus, we focused on the central nervous system (CNS). IAPS stimuli are known to affect the autonomic nervous system (ANS). The interested reader can find more details on the affective ANS reactions to briefly presented IAPS elsewhere (Bradley and Lang, 2000; Codispoti et al., 2001). Our motivation is to build upon the novel work of Ball et al. (2007) who found distinct signal changes in different amygdala sub-divisions in response to auditory emotional stimuli. We hypothesized that the distinct sub-divisions of amygdala exhibit unique functional roles for different aspects of the emotional processing (valence and/or arousal). An orthogonal design was employed that also considered valence by arousal interaction. In emotion research, it is recognized that the interactions between valence and arousal play an important role, but the underlying technical complications have often been difficult to handle. Recently, amygdala responses to emotional stimuli as a result of interactions between orthogonal valence and arousal were examined in Winston et al. (2005) and Lewis et al. (2007). These studies brought forward important confounds on the interpretation of previous results and challenged the functional role of the amygdala as a mere intensity detector. Here, four stimuli sets that were used in a pseudo-random fashion, manipulated the level of arousal independently for pleasant and unpleasant pictures. Whole head MEG signals were recorded from healthy individuals exposed to the affective visual stimuli. MEG is a non-invasive neuroimaging technique that measures the tiny magnetic activity generated by the human brain within millisecond time resolution (Cohen, 1972; Hamalainen et al., 1993). Although it is traditionally thought that the localization accuracy of MEG is limited for deep sources, like amygdala, recent phantom (Papadelis and Ioannides, 2007; Papadelis et al., 2007) as well as human studies have challenged this view (Papadelis et al., 2012) providing strong evidence that MEG is able to localize deep thalamic activity with an accuracy of 10–15 mm. In line with this, many MEG studies on emotions have indicated that deep sources such as amygdala can be localized accurately despite relatively low signal strength using various source analysis methods (Ioannides et al., 1995, 2000; Streit et al., 2003; Cornwell et al., 2008; Rudrauf et al., 2008; Bayle et al., 2009; Luo et al., 2007, 2010; Liu and Ioannides, 2010). Only in the last study (Liu and Ioannides, 2010) an attempt was made to identify from which sub-division of the amygdala the identified activation was generated. Therefore, in this study, emphasis is placed on understanding the functions of the individual amygdala sub-divisions by unmasking their contributions to the processing of valence, arousal or their interaction effect.

2. Materials and methods

2.1. Subjects

Twelve healthy volunteers of normal or corrected-to-normal visual acuity (7 males, mean age 30.8 ± 5.3, range 23 to 40 years, 5 females mean age 27.8 ± 5.3, range 21 to 35 years) participated in the experiment. All subjects were aware of the type and modality of the stimuli and gave written informed consent to participate in the study, which was approved by the host's ethics committee. To ensure the effectiveness of the erotic stimuli, we included only subjects who identified themselves as heterosexual.

Subjects with a history of psychiatric, neurological or other serious physical illness, drug or alcohol abuse, regular consumption of medication as well as existence of metal implants in their body were excluded. Each subject refrained from any alcohol and caffeine consumption the day before and on the day of the experiment and slept adequately and comfortably the night before the measurements. All subjects understood that they could terminate the experiment at any time without explanation. MEG data from two (2) male subjects were not further analyzed due to heavy artifact contamination.

2.2. Affective stimuli

Subjects passively viewed pictorial stimuli from the International Affective Picture System (IAPS) collection (Lang et al., 2008) on a homogenous black background. IAPS is a set of standard photographic picture stimuli, calibrated for affective response, characterized primarily along normative ratings of valence and arousal that span the affective space. The valence and arousal dimensions of the selected stimuli were orthogonally manipulated, since recent research suggests that these two dimensions may interact (Cuthbert et al., 2000) (Fig. 1).

Please cite this article as: Styliadis, C., et al., Amygdala responses to valence and its interaction by arousal revealed by MEG, International Journal of Psychophysiology (2013), http://dx.doi.org/10.1016/j.ijpsycho.2013.05.006

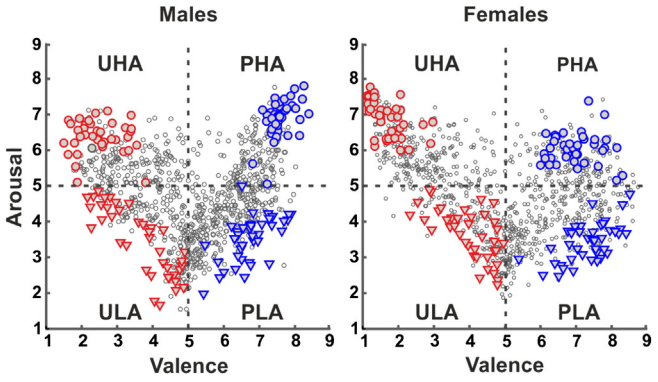

Fig. 1. Distribution of the selected visual stimuli in terms of valence and arousal. Normative valence is shown on the x axis, and normative arousal is shown on the y axis.

Four (4) stimuli categories that manipulated the level of arousal within pleasant and unpleasant pictures (Cuthbert et al., 1996) were used; i) pleasant and high arousing (PHA), e.g. erotica, sports, ii) pleasant and low arousing (PLA), e.g. scenes of nature, neutral faces, iii) unpleasant and high arousing (UHA), e.g. human violence, angry faces, attack and mutilation and iv) unpleasant and low arousing (ULA), e.g. pollution, illness and household objects. Thus, clear distinctions between arousal and valence contribution to neuronal activations were established (Lang et al., 1997; Bradley and Lang, 1994). Stimulus categories were based on the ratings by male and female subjects provided in the IAPS database. The stimuli selection was in accordance to a previous study of our group (Lithari et al., 2010).

Although men and women generally rate IAPS stimuli differently (Lang et al., 1997), the IAPS collection does not have enough pictures matched on valence and arousal ratings for both males and females. Effectiveness of the stimuli was achieved by using different sets of pictures for men and women (common pictures were used when available) but of similar affective context. Thus, we used the gender-specific ratings provided by the IAPS collection (Lang et al., 2008) following the spirit of previous studies (Bernat et al., 2006; Anonkin et al., 2006) that dealt only with male or female subjects. This limitation has been discussed in previous studies (Cuthbert et al., 2000; Rozenkrants and Polich, 2008). In the latter study, no gender differences were obtained besides the interactions with the electrode factor, despite the sample sizes for each group (16 per gender) being adequate. Thus, similar affective processing occurred for IAPS stimuli across genders. In our design, we accepted the notion that different cues raise emotion in males and females. Despite specific sex differences, men and women are quite similar in their affective reactions to a variety of pictures depicting life's pleasant and unpleasant events (Bradley et al., 2001). We managed to control the affective meaning of these cues in terms of arousal and valence. This design allowed us to ensure that men and women will prompt similar responding. Although gender differences have not been examined herein because of the limited size of our subject pool, sex differences on amygdala (Hamann et al., 2004; Cahill, 2006) and its sub-divisions (H.J. Kim et al., 2012) have been previously discussed by other groups.

Sex differences in valence and arousal ratings and complexity (picture's histogram entropy), overall Apparent Contrast (AC = standard deviation of luminance matrix/mean of luminance matrix) (Delplanque et al., 2007), as well as AC for each color level were kept minimal ($p > 0.05$). After the experiment, the presented stimuli were rated by the subjects on a 9-point scale using the Self-Assessment Manikins model (Bradley and Lang, 1994) (see Table 1). The decision that subjects should not rate the stimuli during scanning was made so as not to confound subjective evaluations of the stimuli with the affective reactions that the stimuli may induce. Passive viewing of affective stimuli has been demonstrated to produce emotional responses (Lang et al., 1998; Lithari et al., 2010). Differences of the subjects' ratings compared to the normative IAPS ratings were found to be minimal ($p > 0.05$) (Table 1).

Table 1
Mean valence and arousal ratings (standard deviations in parentheses) for the stimuli selection.

		Normative IAPS ratings	Subjects' ratings
Males			
Valence	Pleasant	7.18(±0.66)	6.97(±0.61)
	Unpleasant	3.05(±0.96)	3.45(±1.30)
Arousal	High arousing	6.64(±0.56)	6.52(±0.83)
	Low arousing	3.51(±0.80)	4.21(±0.91)
Females			
Valence	Pleasant	7.15(±0.67)	7.05(±0.59)
	Unpleasant	2.83(±1.29)	3.07(±1.51)
Arousal	High arousing	6.46(±0.62)	6.81(±1.36)
	Low arousing	3.56(±0.65)	4.12(±0.67)

2.3. Experimental paradigm

The experiment was performed at the Laboratory for Human Brain Dynamics (1998–2009), Brain Science Institute (BSI), RIKEN, Japan. Stimuli were controlled by the Presentation software (0.60 06.10.03) from Neurobehavioral Systems. The affective visual stimuli were back-projected onto a 10 inch screen, 55 cm from the subject's visual field, at a visual angle of 4° horizontally and vertically via a DLP projector with a 96 Hz refresh rate (HL8000Dsx+, NEC Viewtechnology Ltd., Tokyo, Japan) located outside the Magnetically Shielded Room (MSR). The task was performed in dim light of the MSR.

We used a random design of two runs each of 80 trials (20 stimuli per category). The stimuli in both runs were presented in a mixed fashion to prevent habituation, limit anticipation and to assess various affective state measures. The experiment started with the presentation of a fixation cross centered on the screen, at 40 × 40 pixel resolution for a pseudo-randomized interval of 1.5 ± 0.2 s (see Fig. 2). Trials began with the presentation of a single stimulus centered on the screen, at 400 × 400 pixel resolution for 1 s along with the fixation cross. Each single epoch consisted of a 0.5 s pre-stimulus and a 2 s post-stimulus period. The duration of the stimuli was long enough to engage processes that have a relatively fast time constant, therefore eliciting responses in the neural substrates. In addition, its short duration is unlikely to produce considerable variability in subjects' responses.

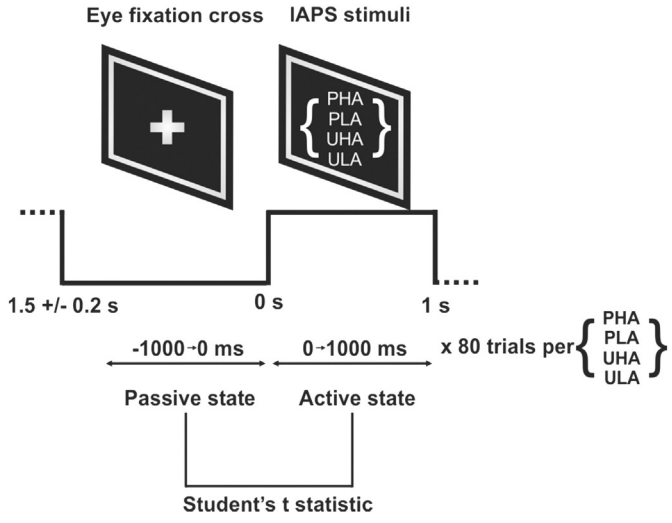

Fig. 2. Sequence of events in the visual affective task. The participants passively viewed each stimulus from PHA, UHA, PLA, and ULA presented in a pseudo-random order for 1000 ms followed by a 1500 ± 200 ms inter-stimulus. The latencies of the stimuli and the inter-stimuli formed the active and passive states.

Each run lasted 220 s resulting in a total duration of 440 s (Fig. 2). Subjects were instructed to fixate on the cross, to stay still and not to blink during the recordings.

2.4. Coregistration

The subjects' heads were scanned with a high-resolution anatomical MRI (1.5 T MRI, Model ExcelArt, Toshiba Medical Systems) using a T1-weighted volume acquisition sequence resulting in a voxel-size of $1 \times 1 \times 1$ mm^3. The coordinates of MEG sensors were determined relative to the individual subject MRI for each run by the localization of fiduciary coils and an in-house co-registration procedure (Hironaga et al., 2002). Before the MEG experiment, three head coils were fitted to the nasion, the left and right pre-auricular points and defined a coil-based coordinate system. Two extra coils were also attached to the right and left forehead for better precision.

The surface of the head and face, with all five coils, was digitalized using a 3D camera system (VIVID 9i 3D Digitizer, Konica Minolta Holdings, Inc., Tokyo, Japan) and the scalp with a 3D digitizer (FASTTRAK, Polhemus, Colchester, VT, USA). The combination of the head and face surface details was used to reconstruct each subject's head shape as accurately as possible. The digitized head shape was fitted to the subject's MRI to get a transformation matrix between the coils (fiduciary and extra) and the MRI coordinate system. The relative positions of the five coils were found by measuring the generated magnetic field. The two extra coils were then removed. The three fiduciary coils were activated at the beginning and end of each experimental run and so the precise position of the brain relative to the sensors for each run was known. Coregistration results were manually checked and regarded as accurate if the mean distance between the surface of the head and face derived from the 3D camera, the 3D digitizer and the anatomical scan was less than 2 mm. Finally, subjects' realistic geometry head models were reconstructed from T1-weighted MRIs.

2.5. MEG recordings and signal processing

The MEG data were recorded at a sampling rate of 1250 Hz using a 151-channel CTF whole head MEG system in a shielded environment. The CTF MEG system is equipped with synthetic 3rd gradient balancing, an active noise cancelation technique that uses a set of reference channels to subtract background interference. At the beginning and end of each measurement, the subject's head position was registered with localization coils that were placed at the nasion and the bilateral preauricular points. Electrooculography (EOG) and Electrocardiography (ECG) were simultaneously recorded through auxiliary channels with the use of four and five Ag/AgCl electrodes respectively. The DC (direct current) offset was removed. The recorded MEG signal was visually inspected for possible artifacts and bad channels inferring noise (100 mV, >5pT between minimum and maximum) were removed. Markers in the MEG data were synchronized to the onset of each visual stimulus. This was established by luminance detection via an optical sensor of a white pixel, at 20×20 pixel resolution which was synchronized to the onset of each stimulus.

2.6. MEG sensor level analysis

The processed signal was filtered by high-pass filtering at 2 Hz, low-pass filtering at 30 Hz, power-line notch filtering at 50 Hz and its harmonics. The filtered signal was segmented into trials, each one lasting 600 ms, beginning 100 ms before and ending 500 ms after the onset of each stimulus. The epochs were separated according to the four conditions' events (PHA, PLA, UHA, ULA), and the average baseline level in the prestimulus period (−100 to 0 ms) was removed. The resulting single trial signal was averaged for each stimulus condition producing one average trace for each condition in the time interval from −100 to 500 ms. For each subject, the global field power (GFP) was estimated from the average signal of each experimental condition. GFP is a simple and well-established quantifier of scalp field strength (Lehmann and Skrandies, 1980, 1984). It is estimated as the square root of the sum of squares of the magnetic measurements over the sensors for each data point in the filtered and averaged epoch:

$$\mathrm{GFP} = (1/\mathrm{N}) * \mathrm{SQRT}(\mathrm{Sx}^{\wedge}2) \quad (1)$$

where N is the number of sensors which measure the fields and Sx is the mean magnetic field of all sensors. A repeated-measures analysis of variance (ANOVA) with valence (pleasant/unpleasant) and arousal (high/low) as the within-subjects factors was used for the statistical analysis of the main effects and their interaction. A threshold of $p < 0.001$ was regarded as significant.

2.7. MEG source level analysis

Source activity was estimated by using the Synthetic Aperture Magnetometry (SAM) which is based on the beamformer approach (Robinson and Vrba, 1999). SAM requires no a priori estimates of numbers or approximate locations of sources. It uses the second-order covariance between channels rather than single-channel averages and thus is sensitive to spatially correlated activity (Vrba and Robinson, 2001). SAM detects dipole sources and therefore is less sensitive to artifacts that do not look like dipoles (Vrba and Robinson, 2001).

SAM makes use of the spatial and temporal correlations of the MEG sensor array to achieve three-dimensional source estimation during task in the following way. For a given location in the brain, SAM first derives a spatial filter for each voxel of the image to retain the theoretical signal, while suppressing the interference of unwanted signals from other locations (Robinson and Vrba, 1999; Taniguchi et al., 2000). The source power at that location is then estimated from the unaveraged signals. For this purpose, we used the processed signals previously described (see Section 2.5) which were then only notch filtered. The task-related power change is represented by a pseudo-t value, which is a measurement of the source power difference between the active and control time windows normalized by the noise variance. The active state was defined as the 1 s time window following the stimuli's onset, and the control state as the 1 s time window preceding the stimuli's onset. A multiple local-sphere model served as head model. Brain activity ranging from 2 to 30 Hz entered the analysis.

Source power difference was calculated between active and control states for each $2 \times 2 \times 2$ mm cubic volume element within the conducting volumes. Pseudo-t statistical parametric images were computed on a voxel-by-voxel basis from the difference in source power between states for the PHA, PLA, UHA and ULA conditions. The resultant volumetric maps were overlaid on the individual subject's structural MRI. Details of the calculation of SAM pseudo-T source image statistics are described in detail in a number of sources (Robinson and Vrba, 1999; Singh et al., 2002, 2003; Cheyne et al., 2006; Hillebrand et al., 2005). SAM images from the two runs were averaged to generate a single SAM image per subject per condition (Singh et al., 2002, 2003). Previous studies from our group (Papadelis and Ioannides, 2007; Papadelis et al., 2009) have shown that MEG can localize with SAM analysis relatively deep sources that correspond in terms of localization difficulty to amygdala (i.e. dipolar source PhS3 in Papadelis et al., 2009), with an accuracy of approximately 7 mm, when the signal to noise ratio (SNR) is high enough. In our previous phantom studies, a higher number of trials (360) were collected in order to achieve this localization accuracy compared to here (80 for each main effect). However, the phantom study examined very weak transient signals and SAM analysis was performed by using short time windows (20 ms) having lower signal power. Here, we used much larger time windows (1000 ms) in order to perform the SAM analysis. We thus

Please cite this article as: Styliadis, C., et al., Amygdala responses to valence and its interaction by arousal revealed by MEG, International Journal of Psychophysiology (2013), http://dx.doi.org/10.1016/j.ijpsycho.2013.05.006

expect the signal power of our recordings to be at least equal or even higher with the one achieved in our phantom studies, providing a similar accuracy of few mm for relatively deep sources that correspond in terms of localization difficulty to amygdala.

2.8. Group level analysis of MEG source activity

The resulting SAM images were normalized into the Montreal Neurological Institute (MNI) space. Then, these were entered into second level analyses. A factorial design computed repeated ANOVA measures having stimulus valence (pleasant/unpleasant) and arousal (high/low) as the within-subjects factors. Finally, the mean activation across subjects for valence, arousal and their interaction was assessed. Statistical maps for the effects of valence and arousal had 32 degrees of freedom with a confidence level set at $p < 0.001$ (uncorrected), unless indicated otherwise. To minimize false-positive activations, we only accepted activations with an extent exceeding thirty (30) contiguous voxels.

2.9. Probabilistic maps

Sites and volumes of significant activation were identified using probabilistic cytoarchitectonic maps (PCMs) (Amunts et al., 1999, 2000, 2005; Caspers et al., 2006; Scheperjans et al., 2008; Kurth et al., 2010) based on histological analysis of ten (10) human post-mortem brains. These probabilistic maps provide information about the location and inter-individual variability of brain areas in MNI standard reference space. This approach aids in assigning the activation sites to histologically defined brain regions, even if these regions are not conspicuous in structural images. For instance, the amygdala appears as a relatively uniform gray matter region when employing only the structural anatomic maps.

The probabilistic maps are freely available through the anatomy toolbox (Eickhoff et al., 2005), (http://www.fz-juelich.de/inm/inm-1/DE/Forschung/_docs/SPMAnatomyToolbox/SPMAnatomyToolbox_node.html). This toolbox provided the anatomical probabilities of our functional maps. We assigned a cytoarchitectonic identity to our activation sites based on these probabilities. The assignment algorithm used (Eickhoff et al., 2006), is based on the assignment of each voxel to the most probable cytoarchitectonic area at the position under investigation.

We used the same threshold (80%) as in the fMRI studies of Ball et al. (2007, 2009); in the latter two studies cytoarchitectonic probabilistic maps were used to define the sub-divisions of the amygdala. Ball et al. (2007) were the first to demonstrate functional distinctions of the amygdala sub-divisions (LB, CM, SF) in the human brain, supporting the use of PCMs to guide interpretations of functional neuroimaging data. The probability limit for assignment was set to ≥80%. We considered the quite high (≥80%) probability limit as a prerequisite for the anatomical assignment in order to increase the robustness against localization errors.

After the closure of the BSI MEG laboratory the data were anonymized and transferred under a material transfer agreement to the Laboratory for Human Brain Dynamics, at AAI Scientific Cultural Services Ltd., in Nicosia, Cyprus for follow up research and data analysis.

3. Results

3.1. Valence effect

Fig. 3 shows the GFP of grand-average ERFs for 2–30 Hz elicited by pleasant and unpleasant stimuli. We found differences in the GFP between pleasant and unpleasant pictures at around 25 ms (latency: 23.2 ms; F: 22.35, p: 0.0009).

Fig. 4 presents the localization results for the valence effect. The effect of pleasant pictures (PHA + PLA > UHA + ULA), ($p < 0.001$, uncorrected) was localized in the right middle frontal gyrus (BA 6) and the right primary visual cortex (V1, BA 17), (see Table 2/Fig. 4A). The effect of unpleasant pictures (UHA + ULA > PHA + PLA), ($p < 0.001$, uncorrected) showed a pattern of neural responses in the amygdala (LB), the putamen, the broca area/ventrolateral prefrontal (VLPFC) gyrus (BA 45) and the dorsomedial thalamus (Th-prefrontal) all in the right hemisphere (see Table 2/Fig. 4B). The probability limit for assignment to amygdala (LB) was 90%. Table 2 presents the anatomical location of the maxima of statistical significant differences for all contrasts in the MNI coordinate system and their corresponding statistical value.

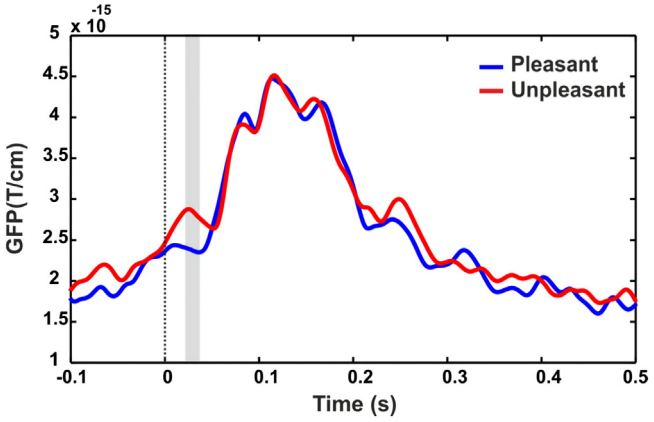

Fig. 3. Whole-head MEG GFP activity for valence. Stimulus onset is at 0 s. Waveforms for pleasant and unpleasant stimuli are in blue and red color respectively. Statistical significance is reported across a confidence level of $p < 0.001$ (gray-colored shadow); minimum is 6 contiguous samples (4.8 ms). The difference between valence levels is at 23.2 ms.

3.2. Arousal effect

Fig. 5 shows the GFP of grand-average ERFs for 2–30 Hz elicited by stimuli of high and low arousal. We found differences in the GFP between high and low arousal pictures at around 250 ms (latency: 224 ms; F: 22.21, p: 0.001).

Fig. 6 presents the localization results of the arousal effect. High arousal (PHA + UHA > PLA + ULA), ($p < 0.005$, uncorrected) was correlated to activity in the right anterior cingulated cortex (ACC) only (see Table 2/Fig. 6A). Low arousal (PLA + ULA > PHA + UHA) ($p < 0.001$, uncorrected) was correlated to activity in the right inferior parietal lobule (IPF (PFop)) and right temporal pole (TP). In addition, there was activation in the left superior parietal lobule (SPL (7A), SPL (5 L)), see Table 2/Fig. 6B).

3.3. Arousal by valence interaction

Fig. 7 shows the differences derived by the GFP of grand-average ERFs for 2–30 Hz elicited by arousal's interaction to valence. We found differences at around 300 ms (265 ms, $F = 21.95$, $p = 0.001$; 298 ms, $F = 25.85$, $p = 0.0007$). Specifically, we found stronger responses for pleasant than unpleasant pictures when arousal was high at 265 ms as well as larger activations for unpleasant than pleasant pictures when arousal was low at 298 ms.

Fig. 8 presents the localization results of the interaction effect (valence by arousal). The interaction effect of valence and arousal (PHA + ULA vs UHA + PLA) ($p < 0.001$, uncorrected) revealed activation in the left amygdala (CM), see Table 2/Fig. 8A. This is the neural area where the arousal effect was larger for pleasant than for unpleasant pictures. The contrast PHA > ULA revealed that these effects were mainly due to the PHA pictures. The probability limit for assignment to amygdala (CM) was 80%. The reverse contrast (i.e. UHA + PLA > PHA + ULA) ($p < 0.001$, uncorrected) revealed activation

Please cite this article as: Styliadis, C., et al., Amygdala responses to valence and its interaction by arousal revealed by MEG, International Journal of Psychophysiology (2013), http://dx.doi.org/10.1016/j.ijpsycho.2013.05.006

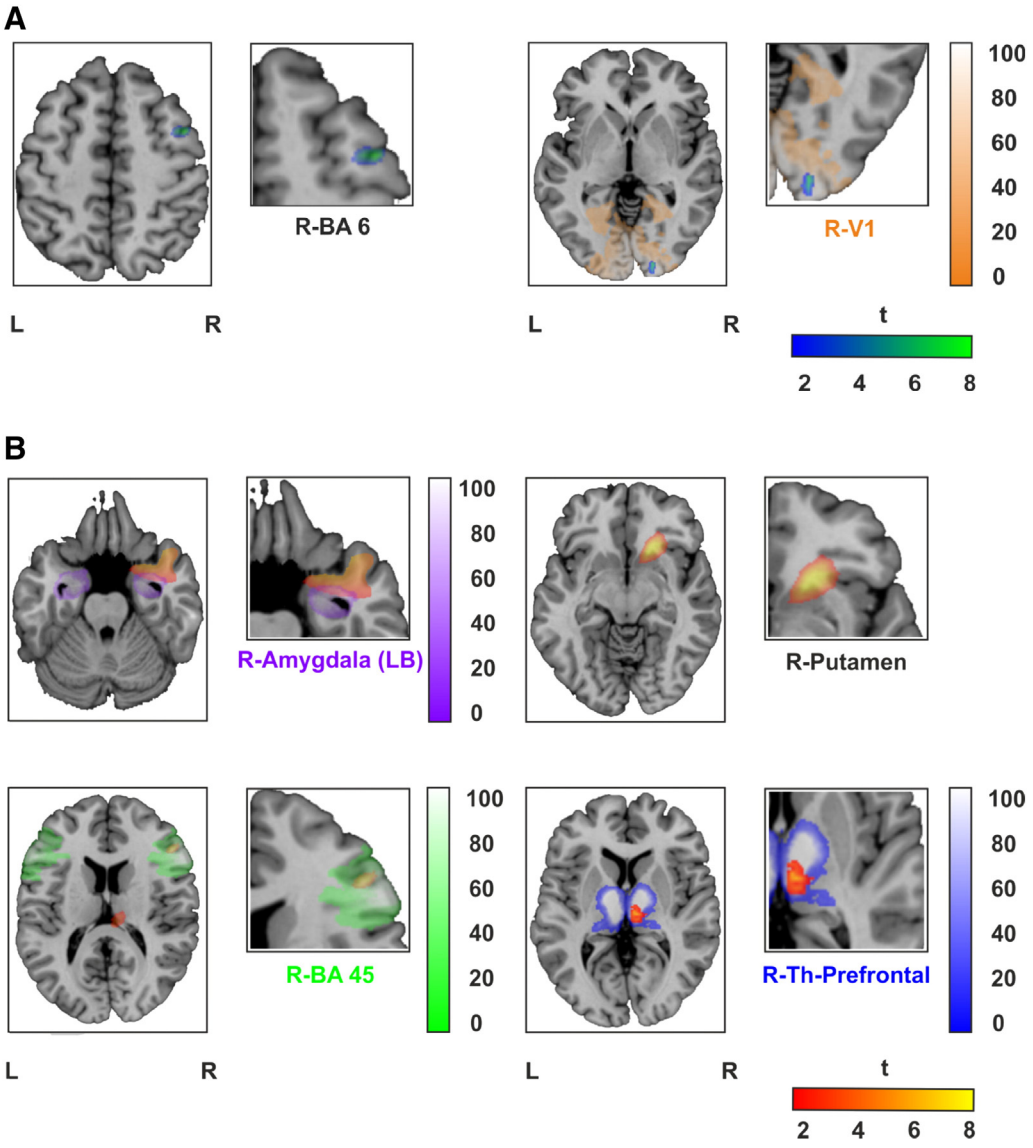

Fig. 4. Group parametric (T) maps for valence. (i) The effect of pleasant pictures (A) was localized on the right middle frontal gyrus (BA 6) and right primary visual cortex (V1). (ii) The effect of unpleasant pictures (B) was localized on the right amygdala (LB), right putamen, right broca area (BA 45) and right thalamus. Points counted as left or right were at least 6 mm from the midline. The brain region is superimposed with orthogonal sections (sagittal, coronal, and axial) of an anatomical scan rendered in standard MNI space and overlaid by the cytoarchitectonic regions. The corresponding t-value is shown in blue to green color scale for pleasant stimuli and in red to yellow scale for unpleasant stimuli. Uncorrected $p < 0.001$ was adopted as the height threshold for valence, minimum is thirty contiguous voxels.

in the right insula (Id1), see Table 2/Fig. 8B. This is the neural area where the arousal effect was larger for unpleasant than for pleasant pictures.

4. Discussion

Investigating amygdala responses to emotion's two dimensions, namely valence and arousal, by using neuroimaging tools has not so far provided univocal results. A key factor in establishing clear distinctions between valence and arousal contributions on amygdala activity is to treat them as orthogonal entities and consider their interaction which is often neglected in emotional studies. Following previous suggestions (Ball et al., 2007), we treated amygdala as a complex structure and performed our results interpretation under the anatomical specificity of its sub-divisions. We speculated that this approach would aid in disentangling the precise nature of amygdala response to the affective stimuli characteristics as well as enrich the functional roles of amygdala's sub-divisions by assigning to them specific emotional attributes. In order to achieve these results we related the amygdala generators identified in the localization analysis of evoked fields to the cytoarchitectonic organization of the amygdala as described by the PCMs. The identified foci of activity were transformed onto the MNI space and then were superimposed with cytoarchitectonic probability maps. It was hypothesized that the evoked responses will involve excitation of well-defined amygdala cytoarchitectonic areas. Indeed, our findings support the view that amygdala's anatomical sub-divisions serve different functions in emotional processing. Right (LB) and left (CM) amygdala activity was found to mediate valence (effect of unpleasant pictures) and its interaction by arousal (arousing pleasant pictures) respectively. Amygdala activation due to arousal modulation was not observed in the present study. High and low arousing pictures were mediated by other brain regions (ACC, TP, SPL). These findings indicate a distinct functional role for two amygdala's anatomical sub-divisions: the laterobasal (LB) and the centromedial (CM) amygdala.

Previous studies have shown that amygdala is activated by emotionally salient stimuli, particularly those in relation to threat, danger

Please cite this article as: Styliadis, C., et al., Amygdala responses to valence and its interaction by arousal revealed by MEG, International Journal of Psychophysiology (2013), http://dx.doi.org/10.1016/j.ijpsycho.2013.05.006

Table 2
Local statistical maxima in activated brain regions for valence, arousal and interaction.

	H	PCM/BA	MNI coordinates (mm)			CS	T
			x	y	z		
Pleasant							
Middle frontal	R	BA 6	44	0	58	35	3.75
Occipital	R	V1/BA 17	18	−104	2	30	3.55
Unpleasant							
Amygdala	R	LB	30	−4	−24	38	3.92
Putamen	R		18	14	−6	296	4.09
Broca	R	BA 45	50	22	23	43	3.77
Thalamus	R	Th-prefrontal	8	−24	8	84	3.78
High arousal							
Anterior Cingulate*	R	BA 24	4	40	8	113	3.12
Low arousal							
Inferior parietal lobule	R	IPC (PFop)	48	−32	33	282	5.03
Temporal pole	R		44	2	−12	236	4.25
Superior parietal lobule	L	SPL (7A)	−14	−78	50	73	4.00
Superior parietal lobule	L	SPL (5L)	−18	−44	62	84	4.02
Arousal by valence							
Amygdala	L	CM	−24	−12	−4	42	3.31
Insula	R	Id1	44	−8	−5	56	3.65

Note: Results are superimposed on standardized MNI coordinates; H, hemisphere; PCM, Propabistic Cytoarchitectonic Maps BA, Brodmann Area; x, left/right; y, anterior/posterior; z, superior/inferior; CS, cluster size in number of activated voxels; T, t-values for each peak; L, left; R, right; Significant at $p < 0.001$ (uncorrected, except for results with * that are at $p < 0.005$, uncorrected).

or aversion (Lane et al., 1997; Liberzon et al., 2000). Our findings on valence, engaging amygdala in unpleasant stimuli mediation are in line with this view. Recent reports have also found responses to high arousing pleasant stimuli, for instance, sexually explicit movies or pictures (Hamann et al., 1999, 2002; Garavan et al., 2001; Aalto et al., 2002). We are in agreement with this view since the amygdala was responsible for the interaction of valence by arousal (high arousing pleasant stimuli) employed in our design.

Our results for valence and its interaction by arousal engaged the right and left amygdala respectively. Previous findings have highlighted a hemispheric processing difference between the left and right amygdala. The following models were proposed, despite the discrepancies for this asymmetry between studies. The left amygdala is regarded to encode emotional information in close relation to language as well as to detailed feature extraction (Markowitsch, 1998; Phelps et al., 2001) whereas the right amygdala is regarded to retrieve emotional information in close relation to pictorial or image-related material (Markowitsch, 1998; Murphy et al., 2003). Also, the right amygdala may be a part of a dynamic emotional stimulus detection system, while the left is better equipped for sustained stimulus evaluations (Wright et al., 2001; Sergerie et al., 2008). While, the left amygdala may decode the arousal signaled by the specific stimulus, the right may automatically engage in an autonomic activation by any arousing stimulus (Glascher and Adolphs, 2003; Sergerie et al., 2008). Regarding sex differences (Cahill et al., 2001; Cahill, 2006), the right amygdala modulates right hemispheric processing of global/central aspects of a situation (an effect more pronounced in males), while the left amygdala modulates left hemispheric processing of more local/fine detail aspects of a situation (an effect more pronounced in females). Until proper statistical analysis of laterality effects in neuroimaging studies are strictly followed, it will not be possible to sort out whether asymmetric activation in the amygdala is associated with different patterns of affective response. In short, we express our reservations on whether the laterality of our findings between the left and right amygdala reflects genuine connectivity and/or processing differences.

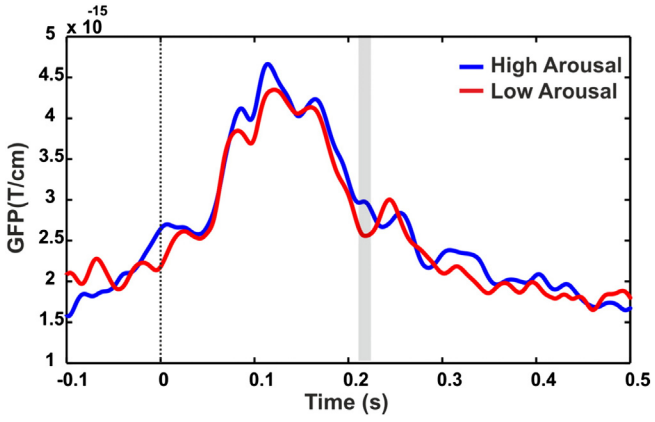

Fig. 5. Whole-head MEG GFP activity for arousal. Stimulus onset is at 0 s. Waveforms for high and low arousing stimuli are in blue and red color respectively. Statistical significance is reported across a confidence level of $p < 0.001$ (gray-colored shadow); minimum is 6 contiguous samples (4.8 ms). The difference between arousal levels is at 224 ms.

The probabilistically defined human amygdala LB sub-division among other regions such as the thalamus, the putamen and the VLPFC was found to mediate unpleasant stimuli. The LB sub-division is thought to play a significant role in assigning emotional value to stimuli (LeDoux, 2000; Davis and Whalen, 2001; Cardinal et al., 2002; Sah et al. 2003; Phelps and LeDoux, 2005). The LB sub-division receives most of the sensory information that arrive to the amygdala. It has strong connections with the cerebrum that allow for projections to the striatum (putamen) and to the dorsomedial thalamus which projects to the prefrontal cortex. These projections enable it to influence complex behavior (Everitt and Robbins, 1992; Everitt et al., 1999, 2000). We note that in our study LB's projections (thalamus, putamen, VLPFC) were co-activated for unpleasant stimuli. We speculate that these areas are co-activated with amygdala LB in support of processing of the emotional information so as to organize the behavior against aversive stimuli. The LB sub-division is regarded as inhibitory and reflective of the external environment. Thus, regardless that this sub-division was activated by unpleasant stimuli, the extent of activation for unpleasant effects highlights amygdala's role as a signaling detector that projects to cerebrum regions so as to initiate appropriate behavioral responses (Sander et al., 2003).

Rodent evidence has indicated that amygdala responds to emotional stimuli via a fast subcortical route (thalamus-amygdala) (LeDoux, 2000).

Please cite this article as: Styliadis, C., et al., Amygdala responses to valence and its interaction by arousal revealed by MEG, International Journal of Psychophysiology (2013), http://dx.doi.org/10.1016/j.ijpsycho.2013.05.006

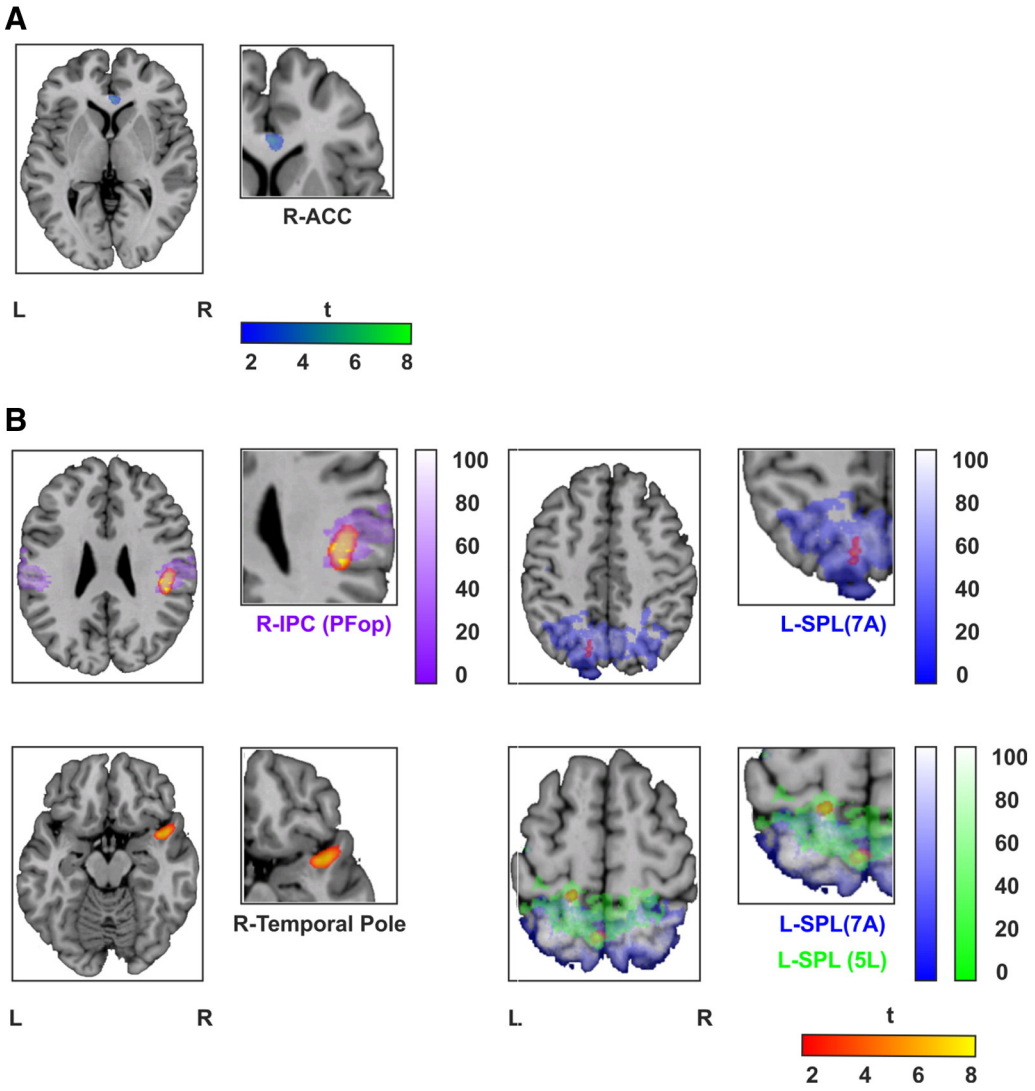

Fig. 6. Group parametric (T) map for arousal. (i) High arousal (A) was localized on the right middle anterior cingulate cortex (BA 24). (ii) Low arousal (B) was localized on the right inferior parietal lobule (IPC(PFop)), right temporal pole, left superior parietal lobule (SPL(7A), SPL(5 L)). Points counted as left or right were at least 6 mm from the midline. The brain region is superimposed with orthogonal sections (sagittal, coronal, and axial) of an anatomical scan rendered in standard MNI space and overlaid by the cytoarchitectonic regions. The corresponding t-value is shown in blue to green color scale for high arousal and in red to yellow scale for low arousal. Uncorrected $p < 0.005$ was adopted as the height threshold for high arousal, uncorrected $p < 0.001$ was adopted as the height threshold for low arousal, minimum is thirty contiguous voxels.

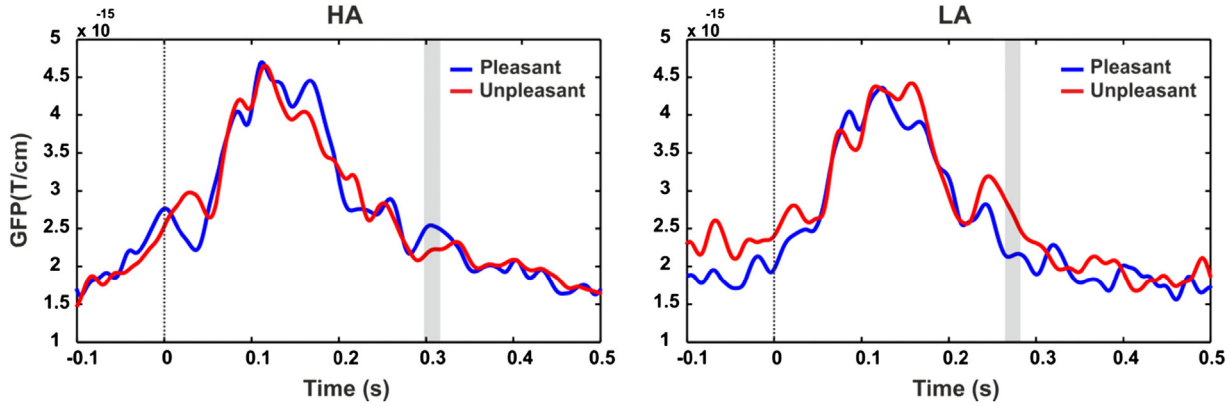

Fig. 7. Whole-head MEG GFP activity for valence by arousal interaction for HA (left) vs LA (right). Stimulus onset is at 0 s. Waveforms for pleasant and unpleasant stimuli are in blue and red color respectively. Statistical significance is reported across a confidence level of $p < 0.001$ (gray-colored shadow); minimum is 6 contiguous samples (4.8 ms). The difference between valence levels is at 265 ms for high arousal and at 298 ms for low arousal.

Please cite this article as: Styliadis, C., et al., Amygdala responses to valence and its interaction by arousal revealed by MEG, International Journal of Psychophysiology (2013), http://dx.doi.org/10.1016/j.ijpsycho.2013.05.006

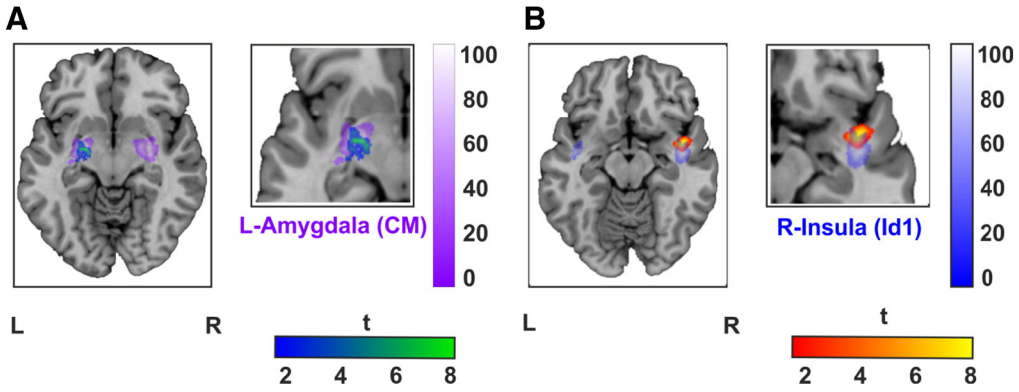

Fig. 8. Group parametric (T) map for valence by arousal interaction. (i) High arousing pictures differentiated from low arousing ones while the valence was pleasant (A) by activating the left amygdala (CM). (ii) High arousing pictures differentiated from low arousing ones while the valence was unpleasant (B) by activating the right insula (Id1). Points counted as left or right were at least 6 mm from the midline. The brain region is superimposed with orthogonal sections (sagittal, coronal, and axial) of an anatomical scan rendered in standard MNI space and overlaid by the cytoarchitectonic regions. The corresponding t-value is shown in blue to green color scale for pleasant stimuli by arousal and in red to yellow scale for unpleasant stimuli by arousal. Uncorrected $p < 0.001$ was adopted as the height threshold for valence by arousal interaction, minimum is thirty contiguous voxels.

This route is also present in humans. In line with this, impaired emotional behavior has been consistently observed after damage to the thalamus and amygdala (Fukatsu et al., 1997; Adolphs, 1999). In a similar vein, it has been suggested that the right amygdala, in terms of its temporal dynamics response to emotional stimuli, is engaged in the rapid detection of an emotional stimulus (Whalen et al., 1998; Wright et al., 2001, 2003). Similarly, Glascher and Adolphs (2003) suggested that the right amygdala participates in the initial detection, probably automatic, of an affective stimulus. Liu and Ioannides (2010) found the right basolateral complex of the amygdala to be involved in emotion separation especially within 100 ms post stimulus. We must emphasize that our study was not designed to link brain activations with behavior directly. Thus, though speculative, we report that the right LB region of the human amygdala may be the region that automatically detects unpleasant stimuli via a fast subcortical route and serves habituation to the stimuli so as to organize behavioral responses. Nevertheless, our rather speculative statement may be clarified in futures studies.

The GFP results for valence may advocate our speculation. Generally, processing of emotional information can be analyzed by analyzing amplitudes (size) and latencies (timing). Significant valence effects occur as early as 25 ms after the stimulus onset and the amplitude for the unpleasant stimuli is quite larger than the one for the pleasant stimuli. It is well acknowledged that the valence dimension expresses initial selective attention capture due to salient image content (appetitive, threatening). Additionally, unpleasant stimuli can produce stronger emotional effects than pleasant stimuli (Cacioppo et al., 1999; Crawford and Cacioppo, 2002; Ohman and Mineka, 2001). This "negativity bias" may express rapid amygdala processing of aversive information (LeDoux, 1995; Morris et al., 1998) allowing attentional resources to be engaged more easily for unpleasant relative to neutral or pleasant stimuli (Cacioppo and Bernston, 1994; Ito et al., 1998). Thus, valence effects may generate from a predisposition towards rapid attentional orientation to threatening stimuli so as to accommodate processing efficiency.

This interpretation is supported by detailed tomographic analysis of MEG data from normal and schizophrenic patients (Ioannides et al., 2004). In the latter study right amygdala showed different patterns of activation between healthy and schizophrenic individuals, when responses to emotional and neutral faces were contrasted using a 100 ms window. Intermittent activity was identified in the amygdala of the patients in both pre-stimulus and post-stimulus periods. This activation was in general highly variable from trial to trial and thus produced low SNR values and no obvious features in the average signal. In the first 100 ms, however, and for each patient, highly significant increases in amygdala activity were identified by the SPM analysis when single trial responses elicited by emotional faces were contrasted with the corresponding responses elicited by neutral faces. The corresponding comparison for the control subjects showed no sustained activation in the amygdala; a more detailed analysis of the data of the normal subjects revealed instead a short lived change in activity of the right amygdala for fearful faces that influenced activity in V1 around 70 ms, i.e. the latency of the first strong response evoked by the stimulus in V1 (Ioannides et al., 2002; Ioannides, 2001, 2007). A confirmation of the early amygdala activation was provided by Luo et al. (2010) who also demonstrated that the degree of automaticity of the amygdala response is a function of time. An early (40–140 ms) amygdala response to emotional information was identified to be independent of attention modulation. Their speculation was formed on the basis that early amygdala activity was generated by the stimulation of the amygdala via the subcortical route.

Once the emotional information is processed in the LB, it is transmitted to the CM region (LeDoux, 2007). This region, projects the information to the hypothalamus and the brainstem (Barbas et al., 2003) and the anterior insula (Shelley and Trimble, 2004), where it influences behavioral responses to emotional stimuli such as modulation of autonomic activity (Pitkanen et al., 1997; LeDoux, 2000). This posits the CM region as the main output region of the amygdala and is regarded to facilitate and reflect the internal environment. This region is probably governing learning and/or subserving behavioral expression (Hatfield et al., 1996; Everitt et al., 2000; Parkinson et al., 2000; Hitchcott and Phillips, 1998).

The interaction of valence and arousal we have identified provides a new direction for reconciling early results and linking under a uniform framework the responses of amygdala to affective stimuli. Our results show that the neural responses to pleasant and unpleasant stimuli were differently modulated by the arousal level. Highly arousing pleasant stimuli were processed by the left amygdala (CM). The left amygdala is considered to participate in a more elaborate stimulus evaluation (Phelps et al., 2001). Also, left amygdala activity is thought to mediate a more detailed and specific analysis of variations in the magnitude of arousal associated with the stimulus (Whalen et al., 1998). This makes evolutionary sense: there is time to adjust behavior for a pleasant stimulus but it might be too late to do so for a life threatening fear-evoking stimulus, which should fire an aversive (fast) response.

Our results for the centromedial region of the amygdala on the valence by arousal interaction may be in line with the existence of a slower, more detail-oriented cortical pathway (Quirk et al., 1995, 1997; LeDoux, 2000). GFP results indicate that the processing of

Please cite this article as: Styliadis, C., et al., Amygdala responses to valence and its interaction by arousal revealed by MEG, International Journal of Psychophysiology (2013), http://dx.doi.org/10.1016/j.ijpsycho.2013.05.006

emotional information requires the extraction both of valence and arousal at such latencies (~25 for valence, and ~250 ms for arousal) so as to be followed by the encoding of their interaction that takes place at latencies of about 300 ms. The time instance where valence and arousal interact may represent an automatic evaluative processing of the incoming stimulus (Robinson et al., 2004). Most ERP studies (Dolcos and Cabeza, 2002; Gianotti et al., 2008) agree that the interaction takes place at latencies later than 300 ms and, with a few exceptions (Feng et al., 2012), only after the modulation of valence and arousal (Keil et al., 2002; Esslen et al., 2004; Codispoti et al., 2007; Olofsson and Polich, 2007). Luo et al. (2010) identified as well a later (290–410 ms) amygdala response which depended on significant attentional modulation and was speculated to express competing task-relevant representations within the cortical route.

5. Conclusions

Amygdala's distinct sub-divisions have unique inputs and outputs and each plays specific functional roles in emotional learning and motivational control of behavior (Cardinal et al., 2002). Though much is known about the functions of the human amygdala as a homogenous structure, the precise contribution of its sub-divisions have been so far obscured. The function of the amygdala is more general than often thought, yet it is also more specific. Our findings contribute by assessing amygdala's sub-divisions to significant processes of emotion. We suggest contrasting though parallel roles for LB and CM in mediating the effects of unpleasant stimuli and for interweaving the effects of pleasure by high arousal respectively. We note that Ball et al. (2007) suggested that the LB is important in valence encoding and that laterality may depend on the duration of the stimuli. LB is essential for linking a stimulus with specific features of emotion (e.g. unpleasantness), thus mediating a specific affective reaction. CM is essential for linking a stimulus with general affective properties of emotion (pleasant and high arousal), thus promoting appropriate autonomic responses, the performance of which may be influenced by increased arousal. It is suggested that differentiating between LB, CM and SF might be crucial for affective studies on lateralization of amygdala function. It was evident that amygdala's structural and functional sub-division (LB) contributed to the processing of emotion (valence) through interactions with other subcortical and cortical structures (thalamus, putamen, VLPFC). However, we could not confirm amygdala's role on arousal. Future studies using similar or different methods (e.g. choice of frequency band) may report such a role.

6. Methodological issues

Neuroimaging results (fMRI, positron emission tomography (PET), MEG) are usually specified by their relation to the surrounding gyral and sulcal landmarks. The anatomical interpretation of the activation sites most commonly relies on the Brodmann map (Brodmann, 1909), which does not take the considerable inter-subject variability into account. Many cortical areas show high variability in the sulcal and gyral pattern across subjects (Amunts et al., 2000), thus making it quite a task to identify the activation sites in respect to cortical areas.

Cytoarchitectonic analysis of postmortem human brains provides the exact borders of a given cortical area on a microscopic level (Schleicher et al., 1999; Amunts and Zilles, 2001; Zilles et al., 2002) and is closely associated with functional specialization (Roland and Zilles, 1998; Luppino et al., 1991; Matelli et al., 1991; Passingham et al., 2002). The neuroanatomical landmarks do not have a fixed relationship to cytoarchitectonic boundaries and their gyri and sulci may vary independently from borders of cortical areas (Zilles et al., 1997; Amunts et al., 1999, 2000; Grefkes et al., 2001; Morosan et al., 2001; Rademacher et al., 2001).

We considered PCMs ideal for amygdala's identification since they provide stereotactic information on the MNI reference space (Amunts and Zilles, 2001; Mohlberg et al., 2003; Zilles et al., 2002). PCMs have been successfully applied in MEG studies (Barnikol et al., 2006; Dammers et al., 2007; Prieto et al., 2007; Liu and Ioannides, 2010; Papadelis et al., 2011) and to our knowledge this is the second time they have been used for amygdala characterization at an MEG study (Liu and Ioannides, 2010). Generally, PCMs improve significantly the analysis of the structural and functional relationships in the human brain.

Acknowledgments

Part of the work was supported by the grant ΕΠΙΧΕΙΡΗΣΕΙΣ/ΠΡΟΙΟΝ/0609/76 from the Cyprus Research Promotion Foundation and the European Regional Development Fund of the E.U.. Another part of this work was benefited from a grant by the Greek General Secretariat for Research and Technology (Grant Code 05NON-EU-221; the Affection Project) and the Cyprus Research Promotion Foundation (grant Upgrade/0308/09). Another part of this work was funded by the Operational Program "Education and Lifelong Learning" of the Greek Ministry of Education and Religious Affairs, Culture and Sports (ref. number 2012ΣΕ24580284). Data acquisition of the modalities described as well as a part of the analysis was conducted at the Laboratory for Human Brain Dynamics (1998–2009), Brain Science Institute (BSI), RIKEN, Japan. The main part of the analysis was conducted at the Laboratory for Human Brain Dynamics, in Nicosia, Cyprus. Authoring of the study was completed at the Laboratory of Medical Informatics, Aristotle University of Thessaloniki, in Thessaloniki, Greece.

References

Aalto, S., Naatanen, P., Wallius, E., Metsahonkala, L., Stenman, H., Niem, P.M., Karlsson, H., 2002. Neuroanatomical substrata of amusement and sadness: a PET activation study using film stimuli. Neuroreport 13, 67–73.

Adolphs, R., 1999. Social cognition and the human brain. Trends in Cognitive Sciences 3, 469–479.

Adolphs, R., Spezio, M.L., 2006. Role of the amygdala in processing visual social stimuli. Progress in Brain Research 156, 363–378.

Adolphs, R., Tranel, D., Damasio, H., Damasio, A., 1994. Impaired recognition of emotion in facial expressions following bilateral damage to the human amygdala. Nature 15, 669–672.

Adolphs, R., Tranel, D., Hamann, S., Young, A.W., Calder, A.J., Phelps, E.A., Anderson, A., Lee, G.P., Damasio, A.R., 1999. Recognition of facial emotion in nine individuals with bilateral amygdala damage. Neuropsychologia 37, 1111–1117.

Amunts, K., Zilles, K., 2001. Advances in cytoarchitectonic mapping of the human cerebral cortex. Neuroimaging Clinics of North America 11, 151–169.

Amunts, K., Schleicher, A., Burgel, U., Mohlberg, H., Uylings, H.B.M., Zilles, K., 1999. Broca's region revisited: cytoarchitecture and intersubject variability. Journal of Comparative Neurology 412, 319–341.

Amunts, K., Malikovic, A., Mohlberg, H., Schormann, T., Zilles, K., 2000. Brodmann's areas 17 and 18 brought into stereotaxic space — where and how variable? NeuroImage 11, 66–84.

Amunts, K., Kedo, O., Kindler, M., Pieperhoff, P., Mohlberg, H., Shah, N.J., Habel, U., Schneider, F., Zilles, K., 2005. Cytoarchitectonic mapping of the human amygdala, hippocampal region and entorhinal cortex: inter-subject variability and probability maps. Anatomy and Embryology 210, 343–352.

Anonkin, A.P., Golosheykin, S., Sirevaag, E., Kristjansson, S., Rohrbaugh, J.W., Heath, A.C., 2006. Rapid discrimination of visual scene content in the human brain. Brain Research 1093, 167–177.

Armony, J.L., 2012. Current emotion research in behavioral neuroscience: the role(s) of the amygdala. Emotion Review 1–12.

Ball, T., Rahm, B., Eickhoff, S.B., Schulze-Bonhage, A., Speck, O., Mutschler, I., 2007. Response properties of human amygdala subregions: evidence based on functional MRI combined with probabilistic anatomical maps. PLoS One 2, e307.

Ball, T., Derix, J., Wentlandt, J., Wieckhorst, B., Speck, O., Schulze-Bonhage, A., Mutschler, I., 2009. Anatomical specificity of functional amygdala imaging of responses to stimuli with positive and negative emotional valence. Journal of Neuroscience Methods 180, 57–70.

Barbas, H., Saha, S., Rempel-Clower, N., Ghashghaei, T., 2003. Serial pathways from primate prefrontal cortex to autonomic areas may influence emotional expression. BMC Neuroscience 4, 25.

Barnikol, U.B., Amunts, K., Dammers, J., Fieseler, T., Malikovic, A., Mohlberg, H., Zilles, K., Niedeggen, M., Tass, P.A., 2006. Pattern reversal visual evoked responses of V1/V2 and V5 as revealed by MEG combined with probabilistic cytoarchitectonic maps. NeuroImage 31, 86–108.

Bayle, D.J., Henaff, M.A., Krolak-Salmon, P., 2009. Unconsciously perceived fear in peripheral vision alerts the limbic system: a MEG study. PLoS One 4 (12), e8207.

Please cite this article as: Styliadis, C., et al., Amygdala responses to valence and its interaction by arousal revealed by MEG, International Journal of Psychophysiology (2013), http://dx.doi.org/10.1016/j.ijpsycho.2013.05.006

Beauregard, M., Levesque, J., Bourgouin, P., 2001. Neural correlates of the conscious self-regulation of emotion. Journal of Neuroscience 21 (RC165), 1–6.

Bernat, E., Patrick, C.J., Benning, S.D., Tellengen, A., 2006. Effects of picture content and intensity on affective physiological response. Psychophysiology 43, 93–103.

Bradley, M.M., Lang, P.J., 1994. Measuring emotion: the self-assessment manikin and the semantic differential. Journal of Behavior Therapy and Experimental Psychiatry 25, 49–59.

Bradley, M.M., Lang, P.J., 2000. Measuring emotion: behavior, feeling & physiology. In: Lane, R.D., Nadel, L. (Eds.), Cognitive Neuroscience of Emotion. Oxford University Press, New York, pp. 24–61.

Bradley, M.M., Codispoti, M., Sabatinelli, D., Lang, P.J., 2001. Emotion and motivation II: sex differences in picture processing. Emotion 1, 300–319.

Brodmann, K., 1909. Vergleichende Lokalisationslehre der Grohirnrinde in ihren Prinzipien dargestellt auf Grund des Zellenbaues. Barth JA, Leipzig.

Cacioppo, J.T., Bernston, G.G., 1994. Relationships between attitudes and evaluative space: a critical review with emphasis on the separability of positive and negative substrates. Psychological Bulletin 115, 401–423.

Cacioppo, J., Gardner, W., Berntson, G., 1999. The affect system has parallel and integrative processing components: form follows function. Journal of Personality And Social Psychology 76, 839–855.

Cahill, L., 2006. Why sex matters for neuroscience. Nature Reviews. Neuroscience 7, 477–484.

Cahill, L., Haier, R.J., White, N.S., Fallon, J., Kirkpatrick, L., Lawrence, C., Potkin, S.G., Alkire, M.T., 2001. Sex-related difference in amygdala activity during emotionally influenced memory storage. Neurobiology of Learning and Memory 75, 1–9.

Cardinal, R.N., Parkinson, J.A., Hall, J., Everitt, B.J., 2002. Emotion and motivation: the role of the amygdala, ventral striatum, and prefrontal cortex. Neuroscience and Biobehavioral Reviews 26, 321–352.

Caspers, S., Geyer, S., Schleicher, A., Mohlberg, H., Amunts, K., Zilles, K., 2006. The human inferior parietal lobule: cytoarchitectonic parcellation and inter individual variability. NeuroImage 33, 430–448.

Cheyne, D., Bakhtazad, L., Gaetz, W., 2006. Spatiotemporal mapping of cortical activity accompanying voluntary movements using an event-related beamforming approach. Human Brain Mapping 27, 213–229.

Codispoti, M., Bradley, M.M., Lang, P.J., 2001. Affective reactions to briefly presented pictures. Psychophysiology 38, 474–478.

Codispoti, M., Ferrari, V., Bradley, M.M., 2007. Repetition and event-related potentials: distinguishing early and late processes in affective picture perception. Journal of Cognitive Neuroscience 19, 577–586.

Cohen, D., 1972. Magnetoencephalography: detection of the brain's electrical activity with a superconducting magnetometer. Science 175, 664–666.

Cornwell, B.R., Carver, F.W., Coppola, R., Johnson, L., Alvarez, R., Grillon, C., 2008. Evoked amygdala responses to negative faces revealed by adaptive MEG beamformers. Brain Research 1244, 103–112.

Crawford, L.E., Cacioppo, J.T., 2002. Learning where to look for danger: integrating affective and spatial information. Psychological Science 13, 449–453.

Cuthbert, B.N., Bradley, M.M., Lang, P.J., 1996. Probing picture perception: activation and emotion. Psychophysiology 33, 103–111.

Cuthbert, B.N., Schupp, H.T., Bradley, M.M., Birbaumer, N., Lang, P.J., 2000. Brain potentials in affective picture processing: covariation with autonomic arousal and affective report. Biological Psychology 52, 95–111.

Dammers, J., Mohlberg, H., Boers, F., Tass, P., Amunts, K., Mathiak, K., 2007. A new toolbox for combining magnetoencephalographic source analysis and cytoarchitectonic probabilistic data for anatomical classification of dynamic brain activity. NeuroImage 34, 1577–1587.

Davidson, R.J., Irwin, W., 1999. The functional neuroanatomy of emotion and affective style. Trends in Cognitive Science 3, 11–21.

Davis, M., 1992. The role of the amygdala in fear and anxiety. Annual Review of Neuroscience 15, 353–375.

Davis, M., Whalen, P.J., 2001. The amygdala: vigilance and emotion. Molecular Psychiatry 6, 13–34.

Delplanque, S., N'Diaye, K., Scherer, K., Grandjean, D., 2007. Spatial frequencies or emotional effects? A systematic measure of spatial frequencies for IAPS pictures by a discrete wavelet analysis. Journal of Neuroscience Methods 165, 144–150.

Dolcos, F., Cabeza, R., 2002. Event-related potentials of emotional memory: encoding pleasant, unpleasant, and neutral pictures. Cognitive, Affective, & Behavioral Neuroscience 2, 252–263.

Eickhoff, S., Stephan, K.E., Mohlberg, H., Grefkes, C., Fink, G.R., Amunts, K., Zilles, K., 2005. A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. NeuroImage 25, 1325–1335.

Eickhoff, S., Heim, S., Zilles, K., Amunts, K., 2006. Testing anatomically specified hypotheses in functional imaging using cytoarchitectonic maps. NeuroImage 32, 570–582.

Emery, N.J., Amaral, D.G., 2000. The role of the amygdala in primate social cognition. In: Lane, R.D., Nadel, L. (Eds.), Cognitive Neuroscience of Emotion. Oxford University Press, New York, pp. 156–191.

Esslen, M., Pascual-Marqui, R.D., Hell, D., Kochi, K., Lehmann, D., 2004. Brain areas and time course of emotional processing. NeuroImage 21, 1189–1203.

Everitt, B.J., Robbins, T.W., 1992. Amygdala-ventral striatal interactions and reward-related processes. In: Aggleton, J.P. (Ed.), The Amygdala. John Wiley & Sons Inc., New York, pp. 401–430.

Everitt, B.J., Parkinson, J.A., Olmstead, M.C., Arroyo, M., Robledo, P., Robbins, T.W., 1999. Associative processes in addiction and reward: the role of amygdala–ventral striatal subsystems. Annals of the New York Academy of Sciences 412–438.

Everitt, B.J., Cardinal, R.N., Hall, J., Parkinson, J.A., Robbins, T.W., 2000. Differential involvement of amygdala subsystems in appetitive conditioning and drug addiction. In: Aggleton, J.P. (Ed.), The Amygdala: a Functional Analysis. Wiley-Liss, New York, pp. 353–390.

Feng, C., Wang, L., Liu, C., Zhu, X., Dai, R., Mai, X., Luo, Y.J., 2012. The time course of the influence of valence and arousal on the implicit processing of affective pictures. PLoS One 7, e29668.

Ferretti, A., Caulo, M., Del Gratta, C., Di Matteo, R., Merla, A., Montorsi, F., Pizzella, V., Pompa, P., Rigatti, P., Rossini, P.M., Salonia, A., Tartaro, A., Romani, G.L., 2005. Dynamics of male sexual arousal: distinct components of brain activation revealed by fMRI. NeuroImage 26, 1086–1096.

Fitzgerald, D.A., Angstadt, M., Jelsone, L.M., Nathan, P.J., Phan, K.L., 2006. Beyond threat: amygdala reactivity across multiple expressions of facial affect. NeuroImage 30, 1441–1448.

Fukatsu, R., Fujii, T., Yamadori, A., Nagasawa, H., Sakurai, Y., 1997. Persisting childish behavior after bilateral thalamic infarcts. European Neurology 37, 230–235.

Garavan, H., Pendergrass, J.C., Ross, T.J., Stein, E.A., Risinger, R.C., 2001. Amygdala response to both positively and negatively valenced stimuli. Neuroreport 12, 2779–2783.

Gianotti, L.R.R., Faber, P.L., Schuler, M., Pasqual-Marqui, R.D., Kochi, K., Lehmann, D., 2008. First valence, then arousal: the temporal dynamics of brain electric activity evoked by emotional stimuli. Brain Topography 20, 143–156.

Glascher, J., Adolphs, R., 2003. Processing of the arousal of subliminal and supraliminal emotional stimuli by the human amygdala. Journal of Neuroscience 23, 10274–10282.

Grefkes, C., Geyer, S., Schormann, T., Roland, P., Zilles, K., 2001. Human somatosensory area 2: observer-independent cytoarchitectonic mapping, interindividual variability, and population map. NeuroImage 14, 617–631.

Hamalainen, M., Hari, R., Ilmoniemi, R.J., Knuutila, J., Lounasmaa, O.V., 1993. Magnetoencephalography — theory, instrumentation, and applications to noninvasive studies of the working human brain. Reviews of Modern Physics 65, 413–497.

Hamann, S., Mao, H., 2002. Positive and negative emotional verbal stimuli elicit activity in the left amygdala. Neuroreport 13, 15–19.

Hamann, S.B., Ely, T.D., Grafton, S.T., Kilts, C.D., 1999. Amygdala activity related to enhanced memory for pleasant and aversive stimuli. Nature Neuroscience 2, 289–293.

Hamann, S.B., Ely, T.D., Hoffmann, J.M., Kilts, C.D., 2002. Ecstasy and agony: activation of the human amygdala in positive and negative emotions. Psychological Science 13, 135–141.

Hamann, S., Herman, R.A., Nolan, C.L., Wallen, K., 2004. Men and women differ in amygdala response to visual sexual stimuli. Nature Neuroscience 7, 411–416.

Hatfield, T., Han, J.S., Conley, M., Gallagher, M., Holland, P., 1996. Neurotoxic lesions of basolateral, but not central amygdala interfere with Pavlovian second-order conditioning and reinforcer-devaluation effects. Journal of Neuroscience 16, 5256–5265.

Hillebrand, A., Singh, K.D., Holliday, I.E., Furlong, P.L., Barnes, G.R., 2005. A new approach to neuroimaging with magnetoencephalography. Human Brain Mapping 25, 199–211.

Hironaga, N., Schellens, M., Ioannides, A.A., 2002. Accurate co-registration for MEG reconstructions. In: Nowak, H., Hueisen, J., GieBler, F., Huonker, R. (Eds.), Proceedings of the 13th International Conference on Biomagnetism. VDE Verlag, Berlin, pp. 931–933.

Hitchcott, P.K., Phillips, G.D., 1998. Double dissociation of the behavioural effects of R(+) 7-OH-DPAT infusions in the central and basolateral amygdala nuclei upon Pavlovian and instrumental conditioned appetitive behaviours. Psychopharmacology 140, 458–469.

Hoffman, K.L., Gothard, K.M., Schmid, M.C., Logothetis, N.K., 2007. Facial-expression and gaze-selective responses in the monkey amygdala. Current Biology 17, 766–772.

Ioannides, A.A., 2001. Real time human brain function: observations and inferences from single trial analysis of magnetoencephalographic signals. Clinical EEG 32, 98–111.

Ioannides, A.A., 2007. MEG single-event analysis: networks for normal brain function and their changes in schizophrenia. Complex Medical Engineering.Springer 361–374.

Ioannides, A.A., Liu, M.J., Liu, L.C., Bamidis, P.D., Hellstrand, E., Stephan, K.M., 1995. Magnetic field tomography of cortical and deep processes: examples of 'real-time mapping' of averaged and single trial MEG signals. International Journal of Psychophysiology 20, 161–175.

Ioannides, A.A., Liu, L.C., Kwapien, J., Drozdz, S., Streit, M., 2000. Coupling of regional activations in a human brain during an object and face affect recognition task. Human Brain Mapping 11, 77–92.

Ioannides, A.A., Poghosyan, V., Liu, L.C., Streit, M., 2002. Early amygdala activations in normal and schizophrenic subjects. Society for Neuroscience — Abstracts 521–525.

Ioannides, A.A., Poghosyan, V., Dammers, J., Streit, M., 2004. Real-time neural activity and connectivity in healthy individuals and schizophrenia patients. NeuroImage 23, 473–482.

Ito, T.A., Larsen, J.T., Smith, N.K., Cacioppo, J.T., 1998. Negative information weighs more heavily on the brain: the negativity bias in evaluative categorizations. Journal of Personality and Social Psychology 75, 887–900.

Keil, A., Bradley, M.M., Hauk, O., Rockstroh, B., Elbert, T., Lang, P.J., 2002. Large-scale neural correlates of affective picture processing. Psychophysiology 39, 641–649.

Kensinger, E.A., Schacter, D.L., 2006. Amygdala activity is associated with the successful encoding of item, but not source, information for positive and negative stimuli. Journal of Neuroscience 26, 2564–2570.

Kim, H., Somerville, L.H., Johnstone, T., Alexander, A., Whalen, P.J., 2003. Inverse amygdala and medial prefrontal cortex responses to surprised faces. Neuroreport 14, 2317–2322.

Kim, H.J., Kim, N., Kim, S., Hong, S., Park, K., Lim, S., Park, J., Na, B., Chae, Y., Lee, J., Yeo, S., Choe, I., Cho, S., Cho, G., 2012. Sex differences in amygdala subregions: evidence from subregional shape analysis. NeuroImage 60, 2054–2061.

Please cite this article as: Styliadis, C., et al., Amygdala responses to valence and its interaction by arousal revealed by MEG, International Journal of Psychophysiology (2013), http://dx.doi.org/10.1016/j.ijpsycho.2013.05.006

Kim, J.E., Dager, S.R., Lyoo, I.K., 2012. The role of the amygdala in the pathophysiology of panic disorder: evidence from neuroimaging studies. Biology of Mood & Anxiety Disorders 2 (1), 20.

Kurth, F., Eickhoff, S.B., Schleicher, A., Hoemke, L., Zilles, K., Amunts, K., 2010. Cytoarchitecture and probabilistic maps of the human posterior insular cortex. Cerebral Cortex 20, 1448–1461.

Lane, R.D., Reiman, E.M., Ahern, G.L., Schwartz, G.E., Davidson, R.J., 1997. Neuroanatomical correlates of happiness, sadness, and disgust. The American Journal of Psychiatry 154, 926–933.

Lang, P.J., Bradley, M.M., Cuthbert, B.N., 1997. Motivated Attention: Affect, Activation, and Action. In: Lang, P.J., Simons, R.F., Balaban, M. (Eds.), Attention and orienting: sensory and motivational processes. Erlbaum Associates, Hillsdale, NJ, pp. 97–135.

Lang, P.J., Bradley, M.M., Fitzsimmons, J.R., Cuthbert, B.N., Scott, J.D., Moulder, B., Nangia, V., 1998. Emotional arousal and activation of the visual cortex: an fMRI analysis. Psychophysiology 35, 199–210.

Lang, P.J., Bradley, M.M., Cuthbert, B.N., 2008. International affective picture system (IAPS): affective ratings of pictures and instruction manual. Technical Report A-8. University of Florida, Gainesville, FL.

LeDoux, J.E., 1995. Emotion: clues from the brain. Annual Review of Psychology 46, 209–235.

LeDoux, J.E., 1996. The Emotional Brain: the Mysterious Underpinnings of Emotional Life. Simon and Schuster, New York.

LeDoux, J.E., 2000. Emotion circuits in the brain. Annual Review of Neuroscience 23, 155–184.

LeDoux, J.E., 2007. The amygdala. Current Biology 17, 868–874.

Lehmann, D., Skrandies, W., 1980. Reference-free identification of components of checkerboard-evoked multichannel potential fields. Electroencephalography and Clinical Neurophysiology 48, 609–621.

Lehmann, D., Skrandies, W., 1984. Spatial analysis of evoked potentials in man—a review. Progress in Neurobiology 23, 227–250.

Lewis, P.A., Critchley, H.D., Rotshtein, P., Dolan, R.J., 2007. Neural correlates of processing valence and arousal in affective words. Cerebral Cortex 17, 742–748.

Liberzon, I., Taylor, S.F., Fig, L.M., Decker, L.R., Koeppe, R.A., Minoshima, S., 2000. Limbic activation and psychophysiologic responses to aversive visual stimuli: interaction with cognitive task. Neuropsychopharmacology 23, 508–516.

Lithari, C., Frantzidis, C.A., Papadelis, C., Vivas, A.B., Klados, M.A., Kourtidou-Papadeli, C., Pappas, C., Ioannides, A.A., Bamidis, P.D., 2010. Are females more responsive to emotional stimuli? A neurophysiological study across arousal and valence dimensions. Brain Topography 23, 27–40.

Liu, L., Ioannides, A.A., 2010. Emotion separation is completed early and it depends on visual field presentation. PLoS One 5, e9790.

Luo, Q., Holroyd, T., Jones, M., Hendler, T., Blair, J., 2007. Neural dynamics for facial threat processing as revealed by gamma band synchronization using MEG. NeuroImage 34, 839–847.

Luo, Q., Holroyd, T., Majestic, C., Cheng, X., Schechter, J., Blair, R.J., 2010. Emotional automaticity is a matter of timing. Journal of Neuroscience 30, 5825–5829.

Luppino, G., Matelli, M., Camarda, R., Gallese, V., Rizzolatti, G., 1991. Multiple representations of body movements in mesial area 6 and the adjacent cingulate cortex: an intracortical microstimulation study. The Journal of Comparative Neurology 311, 463–482.

Markowitsch, H.J., 1998. Differential contribution of right and left amygdala to affective information processing. Behavioural Neurology 11, 233–244.

Matelli, M., Luppino, G., Rizzolatti, G., 1991. Architecture of superior and mesial area 6 and of the adjacent cingulate cortex. The Journal of Comparative Neurology 311, 445–462.

McDonald, A.J., 1998. Cortical pathways to the mammalian amygdala. Progress in Neurobiology 55, 257–332.

McDonald, A.J., 2003. Is there an amygdala and how far does it extend? An anatomical perspective. Annals of the New York Academy of Sciences 985, 1–21.

Mohlberg, H., Lerch, J., Amunts, K., Evans, A.C., Zilles, K., 2003. Probabilistic cytoarchitectonic maps transformed into MNI space. Presented at the 9th International Conference on Functional Mapping of the Human Brain, June 19–22, New York (Available on CD-Rom in Neuroimage 19).

Morosan, P., Rademacher, J., Schleicher, A., Amunts, K., Schormann, T., Zilles, K., 2001. Human primary auditory cortex: cytoarchitectonic subdivisions and mapping into a spatial reference system. NeuroImage 13, 684–701.

Morris, J.S., Frith, C.D., Perrett, D.I., Rowland, D., Young, A.W., Calder, A.J., Dola, R.J., 1996. A differential response in the human amygdala to fearful and happy facial expressions. Nature 383, 812–815.

Morris, J.S., Ohman, A., Dolan, R.J., 1998. Conscious and unconscious emotional learning in the human amygdala. Nature 393, 467–470.

Morris, J.S., Buchel, C., Dolan, R.J., 2001. Parallel neural responses in amygdala subregions and sensory cortex during implicit fear conditioning. NeuroImage 13, 1044–1052.

Murphy, F.C., Nimmo-Smith, I., Lawrence, A., 2003. Functional neuroanatomy of emotions: a meta-analysis. Cognitive, Affective, & Behavioral Neuroscience 3, 207–233.

Ohman, A., Mineka, S., 2001. Fears, phobias, and preparedness: toward an evolved module of fear and fear learning. Psychological Review 108, 483–522.

Olofsson, J.K., Polich, J., 2007. Affective visual event-related potentials: arousal, repetition, and time-on-task. Biological Psychology 75, 101–108.

Papadelis, C., Ioannides, A.A., 2007. Localisation accuracy and temporal resolution of MEG: a phantom experiment. International Congress Series 1300, 257–260.

Papadelis, C., Poghosyan, V., Ioannides, A.A., 2007. Phantom study supports claim of accurate localization from MEG data. International Journal of Bioelectromagnetism 9, 163–167.

Papadelis, C., Poghosyan, V., Fenwick, P.B.C., Ioannides, A.A., 2009. MEG's ability to localise accurately weak transient neural sources. Clinical Neurophysiology 120, 1958–1970.

Papadelis, C., Eickhoff, S.B., Zilles, K., Ioannides, A.A., 2011. BA3b and BA1 activate in a serial fashion after median nerve stimulation: direct evidence from combining source analysis of evoked fields and cytoarchitectonic probabilistic maps. NeuroImage 54, 60–73.

Papadelis, C., Leonardeli, E., Staudt, M., Braun, C., 2012. Can magnetoencephalography track the afferent information flow along white matter thalamocortical fibers? NeuroImage 60, 1092–1105.

Parkinson, J.A., Robbins, T.W., Everitt, B.J., 2000. Dissociable roles of the central and basolateral amygdala in appetitive emotional learning. European Journal of Neuroscience 12, 405–413.

Passingham, R.E., Stephan, K.E., Kotter, R., 2002. The anatomical basis of functional localization in the cortex. Nature Reviews. Neuroscience 3, 606–616.

Phan, K.L., Wager, T., Taylor, S.F., Liberzon, I., 2002. Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. NeuroImage 16, 331–348.

Phelps, E.A., LeDoux, J.E., 2005. Contributions of the amygdala to emotion processing: from animal models to human behavior. Neuron 48, 175–187.

Phelps, E.A., O'Connor, K.J., Gatenby, J.C., Gore, J.C., Grillon, C., Davis, M., 2001. Activation of the left amygdala to a cognitive representation of fear. Nature Neuroscience 4, 437–441.

Pitkanen, A., Savander, V., LeDoux, J.E., 1997. Organization of intra-amygdaloid circuitries in the rat: an emerging framework for understanding functions of the amygdala. Trends in Neurosciences 20, 517–523.

Prieto, E.A., Barnikol, U.B., Soler, E.P., Dolan, K., Hesselmann, G., Mohlberg, H., Amunts, K., Zilles, K., Niedeggen, M., Tass, P.A., 2007. Timing of V1/V2 and V5+ activations during coherent motion of dots: an MEG study. NeuroImage 37, 1384–1395.

Quirk, G.J., Repa, C., LeDoux, J.E., 1995. Fear conditioning enhances short-latency auditory responses of lateral amygdala neurons: parallel recordings in the freely behaving rat. Neuron 15, 1029–1039.

Quirk, G.J., Armony, J.L., LeDoux, J.E., 1997. Fear conditioning enhances different temporal components of toned-evoked spike trains in auditory cortex and lateral amygdala. Neuron 19, 613–624.

Rademacher, J., Bürgel, U., Geyer, S., Schormann, T., Schleicher, A., Freund, H.J., Zilles, K., 2001. Variability and asymmetry in the human precentral motor system. A cytoarchitectonic and myeloarchitectonic brain mapping study. Brain 124, 2232–2258.

Robinson, S.E., Vrba, J., 1999. Functional neuroimaging by synthetic aperture magnetometry (SAM). In: Yoshimoto, T., Kotani, M., Kuriki, S., Karibe, H., Nakasato, N. (Eds.), Recent Advances in Biomagnetism. Tohoku University Press, Sendai, pp. 302–305.

Robinson, M.D., Storbeck, J., Meier, B.P., Kirkeby, B.S., 2004. Watch out! That could be dangerous: valence-arousal interactions in evaluative processing. Personality and Social Psychology Bulletin 30, 1472–1484.

Roland, P.E., Zilles, K., 1998. Structural divisions and functional fields in the human cerebral cortex. Brain Research. Brain Research Reviews 26, 87–105.

Rozenkrants, B., Polich, J., 2008. Affective ERP processing in a visual oddball task: arousal, valence, and gender. Clinical Neurophysiology 119, 2260–2265.

Rudrauf, D., David, O., Lachaux, J.P., Kovach, C.K., Martinerie, J., Renault, B., Damasio, A., 2008. Rapid interactions between the ventral visual stream and emotion-related structures rely on a two-pathway architecture. Journal of Neuroscience 28, 2793–2803.

Sah, P., Faber, E.S., Lopez, D.A., Power, J., 2003. The amygdaloid complex: anatomy and physiology. Physiological Reviews 83, 803–834.

Sander, D., Grafman, J., Zalla, T., 2003. The human amygdala: an evolved system for relevance detection. Reviews in the Neurosciences 14, 303–316.

Scheperjans, F., Hermann, K., Eickhoff, S.B., Amunts, K., Schleicher, A., Zilles, K., 2008. Observer-independent cytoarchitectonic mapping of the human superior parietal cortex. Cerebral Cortex 18, 846–867.

Schleicher, A., Amunts, K., Geyer, S., Morosan, P., Zilles, K., 1999. Observer-independent method for microstructural parcellation of cerebral cortex: a quantitative approach to cytoarchitectonics. NeuroImage 9, 165–177.

Sergerie, K., Chochol, C., Armony, J.L., 2008. The role of the amygdala in emotional processing: a quantitative meta-analysis of functional neuroimaging studies. Neuroscience and Biobehavioral Reviews 32, 811–830.

Sheline, Y.I., Gado, M., Price, J.L., 1998. Amygdala core nuclei volumes are decreased in recurrent major depression. Neuroreport 9, 2023–2028.

Shelley, B.P., Trimble, M.R., 2004. The insular lobe of Reil—its anatomicofunctional, behavioural and neuropsychiatric attributes in humans—a review. The World Journal of Biological Psychiatry 5, 176–200.

Singh, K.D., Barnes, G.R., Hillebrand, A., Forde, E.M., Williams, A.L., 2002. Task-related changes in cortical synchronization are spatially coincident with the hemodynamic response. NeuroImage 16, 103–114.

Singh, K.D., Barnes, G.R., Hillebrand, A., 2003. Group imaging of task-related changes in cortical synchronisation using non-parametric permutation testing. NeuroImage 19, 1589–1601.

Streit, M., Dammers, J., Simsek-Kraues, S., Brinkmeyer, J., Wolwer, W., Ioannides, A.A., 2003. Time course of regional brain activations during facial emotion recognition in humans. Neuroscience Letters 342, 101–104.

Taniguchi, M., Kato, A., Fujita, N., Hirata, M., Tanaka, H., Kihara, T., Ninomiya, H., Hirabuki, N., Nakamura, H., Robinson, S.E., Cheyne, D., Yoshimine, T., 2000. Movement-related desynchronization of the cerebral cortex studied with spatially filtered magnetoencephalography. NeuroImage 12, 298–306.

Vrba, J., Robinson, S.E., 2001. Differences between synthetic aperture magnetometry (SAM) and linear beamformers. In: Neonen, J., Ilmoniemi, T., Katila, T. (Eds.), Biomag 2000. Proceedings of the 12th International Conference on Biomagnetism. Helsinki University of Technology, Espoo, Finland, pp. 681–684.

Wager, T.D., Phan, K.L., Liberzon, I., Taylor, S.F., 2003. Valence, gender, and lateralization of functional brain anatomy in emotion: a meta-analysis of findings from neuroimaging. NeuroImage 19, 513–531.

Please cite this article as: Styliadis, C., et al., Amygdala responses to valence and its interaction by arousal revealed by MEG, International Journal of Psychophysiology (2013), http://dx.doi.org/10.1016/j.ijpsycho.2013.05.006

Whalen, P.J., Phelps, E.A., 2009. The Human Amygdala. Guilford Press, New York.
Whalen, P.J., Bush, G., McNally, R., Wilhelm, S., McInerney, S.C., Jenike, M.A., Rauch, S.L., 1998. The emotional counting Stroop paradigm: a functional Magnetic Resonance Imaging probe of the anterior cingulate affective division. Biological Psychiatry 44, 1219–1228.
Whalen, P.J., Kagan, J., Cook, R.G., Davis, F.C., Kim, H., Polis, S., McLaren, D.G., Somerville, L.H., McLean, A.A., Maxwell, J.S., Johnstone, T., 2004. Human amygdala responsivity to masked fearful eye whites. Science 306, 2061.
Winston, J.S., Gottfried, J.A., Kilner, J.M., Dolan, R.J., 2005. Integrated neural representations of odor intensity and affective valence in human amygdala. Journal of Neuroscience 25, 8903–8907.
Wright, C.I., Fischer, H., Whalen, P.J., McInerney, S.C., Shin, L.M., Rauch, S.L., 2001. Differential prefrontal cortex and amygdala habituation to repeatedly presented emotional stimuli. Neuroreport 12, 379–383.
Wright, C.I., Martis, B., Schwartz, C.E., Shin, L.M., Fischer, H.H., McMullin, K., Rauch, S.L., 2003. Novelty responses and differential effects of order in the amygdala, substantia innominata, and inferior temporal cortex. NeuroImage 18, 660–669.
Zikopoulos, B., Barbas, H., 2012. Pathways for emotions and attention converge on the thalamic reticular nucleus in primates. Journal of Neuroscience 32, 5338–5350.
Zilles, K., Schleicher, A., Langemann, C., Amunts, K., Morosan, P., Palomero-Gallagher, N., Schormann, T., Mohlberg, H., Buergel, U., Steinmetz, H., 1997. Quantitative analysis of sulci in the human cerebral cortex: development, regional heterogeneity, gender difference, asymmetry, intersubject variability and cortical architecture. Human Brain Mapping 5, 218–221.
Zilles, K., Schleicher, A., Palomero-Gallagher, N., Amunts, K., 2002. Quantitative analysis of cyto- and receptor architecture of the human brain. In: Mazziotta, J., Toga, A. (Eds.), Brain Mapping, the Methods. Elsevier, pp. 573–602.

Please cite this article as: Styliadis, C., et al., Amygdala responses to valence and its interaction by arousal revealed by MEG, International Journal of Psychophysiology (2013), http://dx.doi.org/10.1016/j.ijpsycho.2013.05.006