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Anatomical specificity of functional amygdala imaging of responses to stimuli with positive and negative emotional valence

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ABSTRACT

Non-invasive neuroimaging is increasingly used for investigating the human amygdala. Accurate functional localization in the amygdala region is, however, challenging and quantitative data on the anatomical specificity of functional amygdala imaging is lacking. We have therefore retrospectively investigated 114 recently published human functional imaging studies concerned with the amygdala. We determined the anatomical assignment probabilities of a total of 339 reported activation sites to the amygdala defined using a cytoarchitectonically verified probabilistic atlas system. We find that approximately 50% of reported responses were located in the region with high probability (≥80%) of belonging to the amygdala. This group included responses related both to stimuli of positive and negative emotional valence. Approximately 10% of reported response sites were assigned to the hippocampus, with up to 100% assignment probability. The remaining peaks were either located in the border regions of the amygdala and/or hippocampus or outside of both of these structures. Within the amygdala, the majority of peaks (96.3%) were found in the laterobasal (LB) and superficial (SF) subregions. Only 3.7% of peaks were found in the centromedial group (CM), possibly because anatomically delineating the CM region of the amygdala is particularly difficult and hence its extent might have been underestimated. Moreover, these results show that a core region of the amygdala is responsive to stimuli both of positive and negative emotional valence. The current findings highlight the usefulness of probabilistic amygdala maps and also point to a need for the development of accurate in vivo delineation and parcellation of the amygdala.

1. Introduction

Over the last years, there is increasing functional neuroimaging research on the human amygdala, a brain structure in the anterior medial temporal lobe (Zald, 2003; LeDoux, 2007). A motivation behind many of these studies is to understand the role of the amygdala in neuro-psychiatric diseases, such as depression and anxiety disorders (Birbaumer et al., 1998; Phillips et al., 2003). The amygdala is involved in the emotional processing of stimuli from multiple sensory modalities including chemosensory information (Winston et al., 2005), visual stimuli such as facial expression (Kim et al., 2003), and auditory stimuli including communication sounds (Sander and Scheich, 2005) and music (Köelsch et al., 2006; Ball et al., 2007). Furthermore, the amygdala might play an important role in evaluating stimulus salience and initiating behavioral responses based on the assessment of a given stimulus (Sander et al., 2003).

For successful functional amygdala imaging, anatomical specificity is crucial. Some of the anatomical borders of the amygdala such as to adjacent white matter can be delineated on current structural brain scans. Other anatomical borders of the amygdala, such as to the hippocampus, to the caudate nucleus, to the nucleus basalis, or to the adjacent neocortex can not as easily be determined (Amunts et al., 2005). This difficulty may compromise the anatomical specificity of functional imaging of the amygdala because responses of neighboring brain structures might be mistaken to originate in the amygdala. Conversely, true amygdala responses might be erroneously assigned to neighboring structures. The situation is further complicated because in many current functional imaging studies the anatomical criteria used for delineating

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the amygdala are neither clearly reported nor discussed in terms of their limitations to reliably delineate the complete anatomical extent of the amygdala.

Recently, a cytoarchitectonic map of the amygdala and of the hippocampus has become available which is based on histological analysis of ten human post-mortem brains (Amunts et al., 2005). The advantage of probabilistic anatomical maps is that they provide information about location and inter-individual variability of brain areas in standard reference space. This approach allows assignment of activation sites to histologically defined brain regions in a probabilistic fashion, even if these brain regions are not discernible in structural brain images. In the great majority of previous functional imaging studies reporting amygdala responses, anatomical assignments were, however, made without taking into account information from probabilistic anatomical maps but were based on information from structural brain scans or on other, conventional atlas systems. It is therefore not clear which anatomical probabilities can be assigned to reported amygdala peaks if they are re-assessed using the now available probabilistic map. Furthermore, it is not clear whether all major anatomical subregions of amygdala, i.e. the laterobasal group (LB), the superficial group (SF), and the centromedial group (CM), are equally represented in the reported amygdala responses. The aim of the present study was therefore to provide data on these issues by conducting a meta-analysis of a large sample of recent functional imaging studies of the human amygdala published between the years 2000 and 2008. Using the probabilistic anatomical maps of the amygdala and the hippocampus as described in the work by Amunts et al. (2005), the probabilities with which reported peaks belong to the amygdala or to the hippocampus as a whole, and to the amygdala subregions LB, SF, and CM, were determined.

Furthermore, we have also addressed anatomical specificity of responses to stimuli of positive and negative emotional valence, respectively. On the background of a large field of animal research on the role of amygdala in fear conditioning, many imaging studies have focused on emotions of negative valence and have used experimental paradigms such as presentation of faces with fearful expression to evoke amygdala responses (Morris et al., 1996; Vuilleumier et al., 2001; Etkin et al., 2004; Whalen et al., 2004; Das et al., 2005; L.M. Williams et al., 2005). Indeed, there is evidence for a strong link of fear and the amygdala: in a recent meta-analysis, 60% of studies that examined fear activated the amygdala (Phan et al., 2002). However, an increasing number of neuroimaging studies also report the involvement of the amygdala in processing of positively valenced stimuli (Sergerie et al., 2008; Zald, 2003; Ball et al., 2007). A further aim of the present study was therefore to determine the anatomical specificity of responses to positive and negative stimuli and to test whether responses to negative stimuli are more likely to originate in the amygdala than those from positive ones.

2. Materials and methods

Using the National Center for Biotechnology Information (NCBI) database 'PubMed' (http://www.ncbi.nlm.nih.gov/sites/entrez/) and 'Google Scholar' (http://scholar.google.com) we searched for studies reporting amygdala activation. The following inclusion criteria were applied in order to select studies for the present meta-analysis: (1) Studies had to investigate healthy adults (healthy controls from clinical studies were also included). (2) Acquisition techniques had to be functional MRI (fMRI) or positron emission tomography (PET). (3) At least one peak of 'amygdala' activation had to be clearly reported. Ambiguously labeled peaks were excluded. Examples of such excluded labels are: 'periamygdaloid complex', 'peri-amygdala', or 'amygdala region'. Also peaks assigned to a border region of the amygdala were not included (e.g. 'parahippocampal gyrus/amygdala'). (4) In order to select studies thematically concerned with the amygdala, the term amygdala had to occur in the title or in the abstract. (5) We only included results from data sets that were pre-processed by any version of SPM later than SPM95 to ensure that the original analysis was in standard MNI space (SPM versions used were SPM96, SPM97, SPM99, SPM2, SPM2b, and SPM5). This point is important because the probabilistic maps used for further analysis of the response peaks are also in (anatomical) MNI space. (6) Some studies do not report the original MNI coordinates from SPM but coordinates transformed to Talairach space. For those studies reporting Talairach coordinates derived from the original MNI coordinates, either the transformation algorithm had to be apparent from the article (in all such studies included in the present meta-analysis this was the 'mni2tal' MATLAB script publicly available from http://eeg.sourceforge.net/doc_m2htmlbioelectromagnetism/mni2tal.html) and the reported co-ordinates were thus re-transformed to MNI space using the 'tal2mni' script based on the same algorithm (from http://eeg.sourceforge.net/doc_m2html/bioelectromagnetism/tal2mni.html). Otherwise, if the transformation could not be reversed in this way, the authors of the paper in question were asked by e-mail to provide us with software that could be used for accurate re-transformation of the reported coordinates to MNI space or to provide us with the original MNI coordinates of the reported amygdala responses. If the MNI coordinates could also not be obtained in this last way, the study was not included. (7) Studies had to be published between the years 2000 and 2008 (inclusively).

For all included peaks, assignment probabilities to the amygdala subregions LB, SF, and CM, and to the hippocampus were determined using the probabilistic maps of Amunts et al. (2005). In these maps, LB comprises the lateral, basolateral, basomedial, and paralaminar nuclei, CM the central and medial nuclei, and SF includes the anterior amygdaloid area, the ventral and posterior cortical nuclei. The probabilistic anatomical maps can be freely accessed through http://www.fz-juelich.de/ime/spm_anatomy_toolbox. In this way, for each coordinate the 'raw' anatomical probabilities were obtained (such as, for instance, 60% probability for amygdala LB, 30% for amygdala SF, and 20% for hippocampus/cornu ammonis (CA), etc.). Based on these raw probabilities an assignment to one of the candidate regions was made.

An anatomical assignment algorithm that has been proposed for this aim is the maximum probability map (MPM) approach of Eickhoff et al. (2006). MPMs are based on the idea of assigning each voxel to the most likely cytoarchtectonic area at this position. If several areas have the same probability, information from the neighboring voxels and from smoothed probability maps is also used. A feature of the maps obtained is that they are continuous without any gaps between the single areas. However, there are also alternative assignment procedures conceivable, as illustrated by the following examples. For instance, the voxel at MNI coordinates −30, −8, −30 has 40% probability for LB, 40% for hippocampus/cornu ammonis, 10% for entorhinal cortex, 10% for hippocampus/FD, and 40% for hippocampus/subiculum (SUB). In this case, the summed probability of the hippocampus is 100%, but for the amygdala only 40% (note that through effects possibly including partial volume effects occurring during image normalization the summed raw anatomical probabilities at some voxels may surpass 100%). Based on the much higher summed probability for the hippocampus, it seems intuitive to assign this voxel to the hippocampus rather than to the amygdala. The MPM algorithm as described by Eickhoff et al. (2006), however, disregards anatomical hierarchies and treats each subregion separately. In the present example, three regions (LB, CA, SUB) have the same probability of 40%. In this case, the MPM algorithm of Eickhoff and colleagues uses probabilities of neighboring

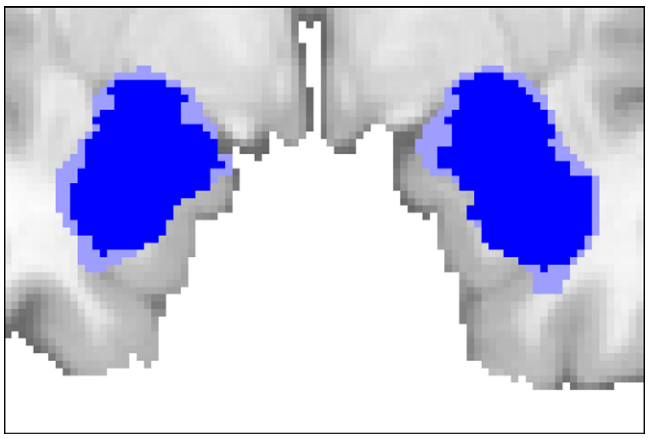

Fig. 1. Anatomical assignment to the amygdala. The probabilistically defined amygdala volume is shown superimposed on a coronal anatomical slice. The dark blue region corresponds to the core region of the amygdala with ≥80% assignment probability determined through a hierarchical assignment algorithm (see Section 2 for further details). The volume of this core region with high assignment probability was close to the mean total volume of the amygdala as has been recently determined micro-anatomically (3042 mm^3) (Amunts et al., 2005). The light blue region corresponds to the anatomical border region of the amygdala (see Section 2 for further details). Voxels in this outer border region had lower amygdala probability than the core region (down to 20%). The main conclusions of our study are based on assignments to the core area. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

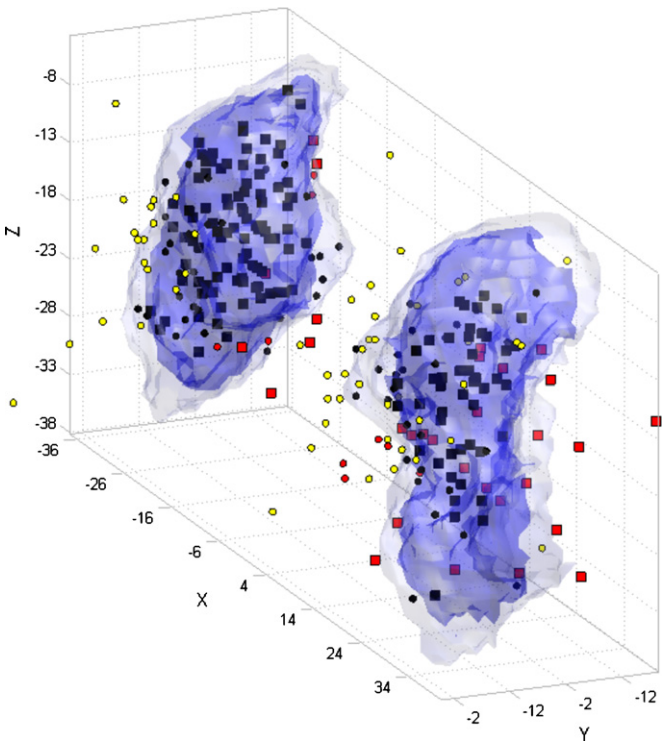

Fig. 2. 3D positions of the 339 amygdala response peaks included in the present study are shown in relation to the probabilistically defined right and left amygdala. Anterior is to the right. The core region of the amygdala with high (≥80%) probability is shown in dark blue. Peaks assigned to this region with high probability (48.4% of all peaks) are indicated by black squares, peaks assigned to the core area of the hippocampus by red squares. The border region of the amygdala is shown in light blue (see Section 2 for further details). Peaks assigned to the border region of the amygdala area are indicated by black dots. For the border region of the hippocampus, peaks are marked by red dots. Unassigned peaks are shown in yellow. These unassigned peaks had down to 0% probability to be located either in the amygdala or in the hippocampus. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

voxels and sometimes also of a smoothed probability map to arrive at an anatomical assignment, which in this case favors LB over any of the hippocampus subareas, although the summed hippocampus probability is in this example higher than the summed amygdala probability. Another property of the MPM algorithm of Eickhoff and colleagues is that voxels with only 10% or 20% probability for a certain area can already be assigned to this area. For instance, the position at MNI coordinates −13, −11, −18 is assigned to SF using the MPM algorithm, although the raw probability for SF at these coordinates is only 20%.

We have therefore analyzed our data using a hierarchical assignment algorithm (Fig. 1), which makes use of anatomical hierarchies and was restricted to the anatomical core regions of the amygdala and hippocampus with high anatomical probability. To this end, the probabilities for the amygdala and hippocampus subregions were first summed up and an assignment to the amygdala as a whole or the hippocampus as a whole was then made based on the probability sum. As we were interested in the region with high anatomical specificity, the probability limit for assignment was set to ≥80%. Using this approach, the voxel at MNI coordinates −30, −8, −30 with summed amygdala probability of 40% and summed hippocampus probability of 100% (see above), was now assigned to the hippocampus. The voxel at MNI coordinates −13, −11, −18 with only 20% probability to belong to SF was neither assigned to the amygdala nor to the hippocampus but remained unassigned. As the second step in our hierarchical assignment procedure, we made an assignment to the subregions of the amygdala and hippocampus based on the maximal probability for any of the subregions. Furthermore, we defined a border region of the amygdala as the region that was assigned to the amygdala by the MPM algorithm by Eickhoff and colleagues, but was outside of the ≥80% anatomical core region.

We required a relatively high (≥80%) probability as a prerequisite for an anatomical assignment. We have previously used a similar assignment based on high (≥80%) anatomical probabilities for investigating fMRI responses in the amygdala subregions LB, SF, and CM during auditory processing, arguing for restricting the assigned volume to the core areas with high probability in order to increase the robustness against localization errors, which are especially important to consider in the amygdala region (Ball et al., 2007).

Few peaks were found in CM (i.e. only six peaks, see Section 3). We therefore tested, using a permutation test assigning all peaks to randomly selected positions within the amygdala (10,000 permutations), whether the observed number of peaks assigned to CM was compatible with the assumption of an equal random distribution of peaks throughout the whole amygdala volume.

Finally, the same analyses that were carried out for all peaks were also separately repeated for peaks from studies using stimuli with either clearly positive or negative valence. Stimuli of questionable of rather neutral valence were excluded from this analysis. For instance erotic stimuli (if no explicit valence ratings are given) might either be conceived as pleasant or possibly also as embarrassing and were hence excluded. Differences in the anatomical probabilities for belonging to either the amygdala or the hippocampus between the group of peaks related to positive and negative stimuli was assessed using a Wilcoxon rank sum test.

3. Results

A total of 106 fMRI and 8 PET studies were included, resulting in 335 amygdala response peaks. A complete reference list of all included studies is given in Table 1 . The 3D distribution of all peaks in relation to the probabilistically defined amygdala is shown in Fig. 2. Using the hierarchical assignment to the core regions of the amygdala and the hippocampus (with ≥80% anatomical assignment

Table 1
Summary of all studies included in the present meta-analysis. For each study, meeting the inclusion criteria, the methods of acquisition (PET or fMRI), the full width at half maximum (FWHM) of the applied spatial smoothing filter (largest filter width for anisotropic filters), the number of subjects investigated, the type of the reported response (activation, deactivation, correlation), the modality of the stimulus material, its valence, and the MNI coordinates of the reported amygdala response peaks are given. The assignment probabilities of a specific response peak listed in this table to individual amygdala and hippocampus subareas can be obtained using the SPM 'Anatomy' toolbox (Eickhoff et al., 2006) based on the maps of (Amunts et al., 2005).

Authors (year)	Method	Smoothing (FWHM)	Subjects	In-/decrease/correlation	Modality	Valence	Coordinates (MNI)		
							x	*y*	*z*
Anderson et al. (2003)	fMRI	6 mm	12	Increase	Visual	Negative	22	2	−33
Ashwin et al. (2007)	fMRI	6 mm	13	Increase	Visual	–	−24	5	−15
			13	Increase	Visual	–	−16	−6	−11
			13	Increase	Visual	–	20	−8	−13
Baumgartner et al. (2006)	fMRI	12 mm	9	Increase	Visual/auditory	–	−20	−4	−24
			9	Increase	Visual/auditory	–	−17	−4	−20
Beauregard et al. (2001)	fMRI	12 mm	10	Increase	Visual	–	25	−2	−17
Beaver et al. (2006)	fMRI	8 mm	12	Increase	Visual	–	−20	−2	−12
Beer et al. (2008)	fMRI	8 mm	16	Increase	Visual	–	30	0	−14
Berns et al. (2005)	fMRI	8 mm	32	Increase	Visual	Neutral	15	−3	−18
Berthoz et al. (2006)	fMRI	8, 6 mm	12	Increase	Visual	Negative	24	−4	−26
			12	Increase	Visual	Negative	−10	−2	−24
			12	Increase	Visual	Negative	22	−2	−26
			12	Increase	Visual	Negative	−16	−6	−22
Bishop et al. (2004)	fMRI	8 mm	27	Increase	Visual	Negative	20	−8	−22
			27	Positive correlation	Visual	Negative	−18	−10	−20
			27	Positive correlation	Visual	Negative	26	−12	−18
			27	Positive correlation	Visual	Negative	−14	−8	−22
Bishop et al. (2007)	fMRI	–	18	Increase	Visual	Negative	18	2	−16
Bornhovd et al. (2002)	fMRI	6 mm	9	Increase	Pain	Negative	−27	0	−27
			9	Increase	Pain	Negative	24	0	−24
Britton et al. (2005)	PET	12 mm	14	Increase	Auditory	Negative	−28	2	−26
Canli et al. (2005)	fMRI	10 mm	29	Increase	Visual	Negative	−22	0	−18
			29	Increase	Visual	Negative	24	−8	−12
			29	Increase	Visual	Positive	−16	−8	−14
			29	Increase	Visual	Positive	24	−2	−14
			29	Increase	Visual	Negative	−22	−8	−12
Carter et al. (2006)	fMRI	8 mm	14	Positive correlation	Visual/pain	Negative	−27	−3	−12
Cheng et al. (2007)	fMRI	6 mm	20	Increase	Visual	–	−16	−4	−16
			20	Increase	Visual	–	−16	−4	−14
Corden et al. (2006)	fMRI	8 mm	24	Increase	Visual	–	−27	0	−18
			24	Increase	Visual	–	30	−6	−21
			24	Increase	Visual	–	−21	−3	−21
			24	Increase	Visual	–	21	−5	−15
			12	Increase	Visual	–	−27	−3	−15
			12	Increase	Visual	–	21	−6	−12
Coricelli et al. (2005)	fMRI	8 mm	15	Increase	Visual	–	−8	−4	−24
Critchley et al. (2000)	PET	12 mm	6	Increase	Low stress	–	−30	5	−21
			6	Positive correlation	Low heart rate	–	−22	−8	−15
Cunningham et al. (2004)	fMRI	12 mm	20	Positive correlation	Visual	–	−20	−4	−16
Das et al. (2005)	fMRI	8 mm	28	Increase	Visual	Negative	−24	4	−18
			28	Increase	Visual	Negative	22	−6	−12
			28	Negative correlation	Visual	Negative	−26	−2	−18
			28	Negative correlation	Visual	Negative	29	−4	−16
de Araujo et al. (2005)	fMRI	10 mm	12	Increase	Olfactory	–	20	4	−25
			12	Positive correlation	Olfactory	–	22	−2	−20
			12	Positive correlation	Olfactory	–	−18	0	−16
De Martino et al. (2006)	fMRI	8 mm	20	Increase	Visual	–	−14	2	−24
			20	Increase	Visual	–	12	2	−20
			20	Increase	Visual	–	18	−4	−24
			20	Increase	Visual	–	−16	0	−26
			20	Increase	Visual	–	12	2	−22
Del Ben et al. (2005)	fMRI	10 mm	12	Increase	Visual	Negative	−24	−12	−15
Desseilles et al. (2006)	PET	16 mm	13	Increase	Sleep	–	−30	−2	−18
Dresel et al. (2005)	fMRI	8 mm	15	Increase	Auditory/motor	–	−22	0	−16
			15	Increase	Auditory/motor	–	26	0	−14

Table 1 (*Continued*)

Authors (year)	Method	Smoothing (FWHM)	Subjects	In-/decrease/correlation	Modality	Valence	Coordinates (MNI)		
							x	*y*	*z*
Eippert et al. (2007)	fMRI	12 mm	24	Increase	Visual	Negative	−24	−3	−12
			24	Increase	Visual	Negative	30	−3	−12
			24	Increase	Visual	–	−27	−3	−21
			24	Increase	Visual	–	21	3	−18
			24	Increase	Visual	–	−18	0	−12
			24	Increase	Visual	–	24	0	−21
			24	Increase	Visual	–	−24	−9	−12
			24	Positive correlation	Visual	–	−18	−3	−21
			24	Positive correlation	Visual	–	18	−3	−15
Elliott et al. (2003)	fMRI	10 mm	12	Increase	Visual	Positive	24	−6	−18
Ernst et al. (2002)	PET	10 mm	20	Increase	Visual	–	−28	2	−26
Etkin et al. (2004)	fMRI	8 mm	17	Positive correlation	Visual	Negative	28	−10	−22
			17	Increase	Visual	Negative	16	−8	−12
Etkin et al. (2006)	fMRI	8 mm	19	Increase	Visual	–	18	2	−16
			19	Negative correlation	Visual	–	16	0	−16
Eugene et al. (2003)	fMRI	12 mm	10	Increase	Visual	Negative	−30	0	−18
Evans et al. (2002)	fMRI	6 mm	6	Increase	Air hunger	Negative	−20	2	−14
			6	Increase	Air hunger	Negative	24	4	−14
Fischer et al. (2004)	fMRI	12 mm	24	Increase	Visual	–	−20	−2	−24
Fitzgerald et al. (2006)	fMRI	8 mm	20	Increase	Visual	–	−24	−2	−24
			20	Increase	Visual	Negative	−22	−8	−24
			20	Increase	Visual	Negative	−20	2	−22
			20	Increase	Visual	Negative	−20	−4	−22
			20	Increase	Visual	Negative	−26	−6	−24
			20	Increase	Visual	Neutral	−20	−8	−18
			20	Increase	Visual	Positive	−20	−4	−22
Garrett and Maddock (2006)	fMRI	4 mm	9	Increase	Visual	Negative	−22	4	−20
			9	Increase	Visual	Negative	20	−2	−12
George et al. (2001)	fMRI	10 mm	7	Positive correlation	Visual	Neutral	−18	6	−24
			7	Positive correlation	Visual	Neutral	18	3	−21
Glascher et al. (2004)	fMRI	11 mm	11	Increase	Visual	–	18	0	−18
			11	Increase	Visual	–	−15	0	−15
Goldstein et al. (2005)	fMRI	8 mm	12	Increase	Visual	Negative	−24	−9	−12
			12	Increase	Visual	Negative	24	0	−21
			12	Increase	Visual	Negative	−21	−3	−21
			12	Positive correlation	Visual	Negative	−21	−9	−12
Gottfried et al. (2002)	fMRI	8 mm	15	Increase	Olfactory/visual	–	−14	−10	−18
			15	Increase	Olfactory/visual	–	24	−8	−18
			15	Increase	Olfactory/visual	Negative	24	−12	−16
			15	Increase	Olfactory/visual	Negative	18	−6	−16
Gottfried and Dolan (2003)	fMRI	8 mm	15	Increase	Olfactory/visual	–	−21	−6	−24
Gottfried et al. (2003)	fMRI	6 mm	13	Increase	Olfactory/visual	–	−24	−12	−12
			13	Increase	Olfactory/visual	–	−15	−6	−18
			13	Increase	Olfactory/visual	–	−15	−6	−18
			13	Increase	Olfactory/visual	–	−24	−12	−12
Gottfried and Dolan (2004)	fMRI	6 mm	16	Increase	Olfactory/visual	–	12	−6	−15
			16	Increase	Olfactory/visual	–	−15	−9	−21
			16	Increase	Olfactory/visual	–	33	−3	−27
			16	Increase	Olfactory/visual	–	−27	−9	−24
			16	Increase	Olfactory/visual	–	18	3	−27
			16	Increase	Olfactory/visual	–	−27	−9	−15
			16	Increase	Olfactory/visual	–	−9	−9	−21
Hamann and Mao (2002)	fMRI	8 mm	14	Increase	Visual	Positive	−24	−7	−24
			14	Increase	Visual	Negative	−24	−7	−19
Hamann et al. (2004)	fMRI	8 mm	28	Increase	Visual	Positive	−16	0	−20
			28	Increase	Visual	Positive	16	0	−16
			14	Increase	Visual	Positive	−16	0	−24
			14	Increase	Visual	Positive	20	0	−20
			28	Increase	Visual	Positive	−20	−4	−20
			28	Increase	Visual	Positive	−16	0	−16
			28	Increase	Visual	Positive	24	−4	−24
			28	Increase	Visual	Positive	16	0	−16

Table 1 (*Continued*)

Authors (year)	Method	Smoothing (FWHM)	Subjects	In-/decrease/correlation	Modality	Valence	Coordinates (MNI)		
							x	*y*	*z*
Hardee et al. (2008)	fMRI	8 mm	13	Increase	Visual	Negative	26	−6	−18
			13	Increase	Visual	Negative	−22	−4	−18
			13	Increase	Visual	–	24	−6	−20
			13	Increase	Visual	–	−22	−6	−18
			13	Increase	Visual	Positive	24	−6	−18
			13	Increase	Visual	Positive	−24	−6	−18
			13	Increase	Visual	–	24	−6	−18
			13	Increase	Visual	–	−22	−6	−18
			13	Increase	Visual	Negative	22	2	−12
			13	Increase	Visual	Negative	−20	4	−14
			13	Increase	Visual	Negative	28	−4	−22
			13	Increase	Visual	Negative	−20	4	−14
			13	Increase	Visual	Negative	22	2	−12
			13	Increase	Visual	Negative	−20	4	−14
Hariri et al. (2000)	fMRI	6 mm	16	Increase	Visual	–	−24	−9	−27
			16	Increase	Visual	–	24	−1	−26
			16	Increase	Visual	–	−22	−7	−29
			16	Increase	Visual	–	34	−18	−20
			16	Positive correlation	Visual	–	36	−7	−29
Hariri et al. (2002)	fMRI	8 mm	12	Increase	Visual	Negative	−22	−5	−19
			12	Increase	Visual	Negative	16	−3	−19
Hariri et al. (2003)	fMRI	8 mm	11	Increase	Visual	Negative	−22	−5	−15
			11	Increase	Visual	Negative	26	−5	−15
			11	Increase	Visual	Negative	−26	−8	−15
			11	Increase	Visual	Negative	26	−8	−15
			11	Positive correlation	Visual	Negative	24	−5	−19
Holstege et al. (2003)	PET	10 mm	11	Decrease	Ejaculation	Positive	−18	2	−24
Hooker et al. (2006)	fMRI	8 mm	12	Increase	Visual	–	22	0	−18
Keightley et al. (2003)	fMRI	10 mm	6	Increase	Visual	–	−28	−4	−15
			6	Increase	Visual	–	16	−3	−24
Killgore et al. (2000)	fMRI	15 mm	7	Increase	Visual	–	−27	−7	−11
			7	Increase	Visual	–	−23	−2	−23
			7	Increase	Visual	–	24	−10	−35
			7	Increase	Visual	–	−19	−6	−23
			7	Increase	Visual	–	32	−10	−29
Killgore et al. (2003)	fMRI	10 mm	13	Increase	Visual	–	22	−4	−21
			13	Increase	Visual	–	−20	0	−24
Killgore and Yurgelun-Todd (2004)	fMRI	10 mm	12	Increase	Visual	Positive	−20	−6	−18
			12	Increase	Visual	Positive	22	0	−20
			12	Increase	Visual	Positive	24	0	−24
			12	Increase	Visual	–	−28	−6	−18
Kilpatrick and Cahill (2003)	PET	8 mm	11	Increase	Visual/auditory	Negative	20	−4	−24
Kim and Hamann (2007)	fMRI	6 mm	10	Increase	Visual	Positive	18	3	−18
			10	Increase	Visual	–	−27	0	−21
Koch et al. (2007)	fMRI	10 mm	40	Positive correlation	Olfactory/visual	Negative	−22	−2	−12
Labar et al. (2001)	fMRI	7 mm	17	Increase	Visual	–	−21	−3	−27
			17	Increase	Visual	–	−33	6	−30
			17	Increase	Visual	–	−15	−12	24
Labar et al. (2003)	fMRI	8 mm	10	Increase	Visual	Negative	−19	−8	−23
			10	Increase	Visual	Negative	26	−4	−23
			10	Increase	Visual	Negative	11	−11	−19
			10	Increase	Visual	Negative	−15	−15	−11
			10	Increase	Visual	Negative	26	−4	−26
			10	Increase	Visual	Neutral	−15	−8	−19
Lenzi et al. (2008)	fMRI	8 mm	16	Increase	Visual	–	26	2	−17
			16	Increase	Visual	–	−28	4	−8
			16	Increase	Visual	–	18	−2	−8
			16	Increase	Visual	–	−20	−4	−9
Levesque et al. (2003)	fMRI	12 mm	20	Increase	Visual	Negative	−24	−3	−18
Lewis et al. (2007)	fMRI	8 mm	19	Positive correlation	Visual	Negative	−24	−2	−12
			19	Positive correlation	Visual	–	−20	−8	−14

Table 1 (*Continued*)

Authors (year)	Method	Smoothing (FWHM)	Subjects	In-/decrease/correlation	Modality	Valence	Coordinates (MNI)		
							x	*y*	*z*
Liddell et al. (2005)	fMRI	8 mm	22	Increase	Visual	Negative	−18	2	−20
			22	Increase	Visual	Negative	28	−4	−12
Lotze et al. (2006)	fMRI	9 mm	20	Increase	Visual	–	−21	−6	−18
			20	Increase	Visual	–	21	−6	−18
McClure et al. (2004)	fMRI	8 mm	17	Increase	Visual	Negative	34	−6	−12
			17	Increase	Visual	Negative	36	−2	−20
			17	Increase	Visual	Negative	36	0	−14
			17	Increase	Visual	Negative	38	2	−18
			17	Increase	Visual	Negative	−28	2	−20
			8	Increase	Visual	Negative	−20	−8	−6
			9	Increase	Visual	Neutral	−22	−10	−8
Ochsner et al. (2002)	fMRI	6 mm	15	Increase	Visual	Negative	16	−12	−20
Ochsner et al. (2004)	fMRI	6 mm	24	Increase	Visual	Negative	−30	−2	−20
			24	Increase	Visual	Negative	−28	−4	−14
			24	Increase	Visual	Negative	20	0	−24
O'Doherty et al. (2002)	fMRI	10 mm	8	Increase	Taste/visual	Positive	28	−8	−14
O'Doherty et al. (2003)	fMRI	8 mm	15	Increase	Visual	Neutral	−27	−3	−27
			15	Increase	Visual	Neutral	−27	−3	−30
Ogino et al. (2007)	fMRI	10 mm	10	Increase	Visual	Negative	−20	4	−16
Onoda et al. (2008)	fMRI	8 mm	18	Increase	Visual	–	−24	0	−22
Phan et al. (2003)	fMRI	8 mm	8	Increase	Visual	Negative	−21	−6	−15
			8	Increase	Visual	Negative	−18	−3	−15
Phan et al. (2004)	fMRI	6 mm	12	Positive correlation	Visual	–	33	−6	−12
			12	Positive correlation	Visual	–	−27	0	−15
			12	Increase	Visual	–	−21	−6	−12
Phan et al. (2005)	fMRI	6 mm	14	Increase	Visual	Negative	−32	−4	−24
			14	Increase	Visual	Negative	26	2	−24
			14	Increase	Visual	Negative	−28	0	−28
			14	Increase	Visual	Negative	16	0	−28
			14	Increase	Visual	Negative	−26	6	−26
			14	Increase	Visual	Negative	−18	−4	−20
Plailly et al. (2005)	fMRI	10 mm	14	Increase	Olfactory	–	−24	−6	−12
			14	Increase	Olfactory	–	20	−16	−10
Protopopescu et al. (2005)	fMRI	–	21	Decrease	Visual	–	−21	0	−24
			21	Increase	Visual	–	−27	−3	−24
			21	Increase	Visual	–	18	−3	−24
			21	Increase	Visual	–	−21	−6	−12
			21	Increase	Visual	–	−27	−3	−27
Royet et al. (2000)	PET	16 mm	12	Increase	Olfactory	–	−22	0	−12
Royet et al. (2003)	fMRI	10 mm	28	Increase	Olfactory	–	−22	−2	−12
			28	Increase	Olfactory	–	−14	−8	−22
Ruby and Decety (2004)	PET	10 mm	10	Increase	Visual	–	−26	14	−32
			10	Increase	Visual	–	26	−2	−24
Sato et al. (2004)	fMRI	6 mm	10	Positive correlation	Visual	–	−20	−6	−10
			10	Increase	Visual	Negative	−22	−11	−16
			10	Increase	Visual	Negative	−22	−9	−16
Schendan et al. (2003)	fMRI	–	15	Increase	Visual	–	21	6	−21
Schienle et al. (2005)	fMRI	9 mm	63	Increase	Visual	Negative	−18	−6	−18
			63	Increase	Visual	Negative	24	0	−24
			63	Positive correlation	Visual	Negative	21	−6	−12
			63	Positive correlation	Visual	Negative	21	−6	−12
			63	Positive correlation	Visual	Negative	18	−3	−15
			63	Positive correlation	Visual	Negative	24	−9	−15
Sergerie et al. (2006)	fMRI	8 mm	18	Increase	Visual	Negative	−24	−8	−20
			18	Increase	Visual	Negative	30	2	−34
			18	Increase	Visual	Negative	−20	−4	−12
			18	Increase	Visual	Negative	−14	−8	−24
			18	Increase	Visual	Negative	30	0	−34
			18	Increase	Visual	Negative	−28	−4	−18

Table 1 (*Continued*)

Authors (year)	Method	Smoothing (FWHM)	Subjects	In-/decrease/correlation	Modality	Valence	Coordinates (MNI)		
							x	*y*	*z*
Sergerie et al. (2007)	fMRI	8 mm	20	Positive correlation	Visual	Negative	22	−8	−28
			20	Positive correlation	Visual	Positive	−26	2	−26
			20	Positive correlation	Visual	Positive	−24	0	−24
			20	Positive correlation	Visual	Positive	22	−2	−24
			20	Positive correlation	Visual	–	22	−6	−26
Seymour et al. (2005)	fMRI	6 mm	19	Increase	Pain/temperature	–	−20	2	−26
Singer et al. (2004)	fMRI	10 mm	11	Increase	Visual	–	−21	0	−18
			11	Increase	Visual	–	−21	0	−21
Small et al. (2003)	fMRI	7 mm	9	Increase	Gustatory	–	15	−10	−15
			9	Increase	Gustatory	Positive	−24	−6	−21
			9	Increase	Gustatory	Positive	−12	−12	−21
			9	Increase	Gustatory	Negative	27	−9	−12
Small et al. (2005)	fMRI	7 mm	11	Increase	Olfactory	Positive	−27	0	−21
Smith et al. (2006)	fMRI	8 mm	16	Increase	Visual	Negative	−24	−3	−18
			16	Increase	Visual	–	−24	−6	−15
Smith et al. (2009)	fMRI	6 mm	25	Increase	Visual	–	22	−4	−18
Somerville et al. (2006)	fMRI	6 mm	16	Increase	Visual	–	−21	−4	−15
			16	Increase	Visual	–	18	−7	−15
			16	Increase	Visual	–	15	−9	−12
Stark et al. (2004)	fMRI	9 mm	24	Increase	Visual	Negative	−18	−3	−27
			24	Increase	Visual	Negative	21	−6	−18
			24	Increase	Visual	Negative	18	−9	−18
			24	Increase	Visual	Negative	18	6	−24
Stark et al. (2005)	fMRI	6 mm	24	Increase	Visual	Negative	−21	−3	−15
			24	Increase	Visual	–	24	6	−18
			24	Increase	Visual	–	−21	−3	−18
			24	Increase	Visual	–	30	−3	−15
			24	Increase	Visual	–	−18	−6	−18
			24	Increase	Visual	–	27	−3	−27
Stark et al. (2007)	fMRI	9 mm	66	Increase	Visual	Negative	33	0	−24
			66	Increase	Visual	Negative	−30	−3	−21
			66	Increase	Visual	Negative	36	0	−27
			66	Increase	Visual	Negative	30	3	−21
			66	Increase	Visual	Negative	−24	−6	−15
			66	Increase	Visual	Negative	33	0	−24
			66	Increase	Visual	Negative	33	0	−24
			66	Increase	Visual	Negative	−24	−3	−24
			66	Increase	Visual	Negative	30	0	−27
			66	Increase	Visual	Negative	−21	−3	−27
			66	Increase	Visual	Negative	24	−3	−18
			66	Increase	Visual	Negative	−24	−6	−18
Sterpenich et al. (2006)	fMRI	8 mm	30	Positive correlation	Visual	Neutral	8	−6	−24
Tabbert et al. (2006)	fMRI	9 mm	33	Increase	Sensory/visual	Negative	27	3	−18
			17	Increase	Sensory/visual	Negative	27	3	−18
			16	Increase	Sensory/visual	Negative	−30	0	−27
			16	Increase	Sensory/visual	Negative	27	3	−21
			17	Increase	Sensory/visual	Negative	−30	0	−27
			17	Increase	Sensory/visual	Negative	33	3	−21
			33	Increase	Sensory/visual	Negative	21	0	−15
Takahashi et al. (2006)	fMRI	8 mm	22	Increase	Visual	Negative	22	2	−14
			22	Increase	Visual	Negative	22	2	−14
Taylor et al. (2006)	fMRI	8 mm	30	Negative correlation	Visual	Negative	−20	−8	−18
			30	Increase	Visual	Negative	−24	0	−24
			30	Increase	Visual	Negative	−26	2	−22
Tessitore et al. (2005)	fMRI	10 mm	12	Increase	Visual	Negative	−17	−8	13
			12	Increase	Visual	Negative	17	−2	−19
			15	Increase	Visual	Negative	−21	−11	−13
			15	Increase	Visual	Negative	21	−8	−15
			27	Increase	Visual	Negative	29	1	−19
van der Veen et al. (2007)	fMRI	8 mm	11	Increase	Visual	–	28	−5	−27
Vuilleumier et al. (2001)	fMRI	8 mm	12	Increase	Visual	Negative	−20	−2	−18
			12	Increase	Visual	Negative	16	−10	−18
			12	Increase	Visual	Negative	−26	−2	−20
			12	Increase	Visual	Negative	−26	0	−20

Table 1 (*Continued*)

Authors (year)	Method	Smoothing (FWHM)	Subjects	In-/decrease/correlation	Modality	Valence	Coordinates (MNI)		
							x	*y*	*z*
Vuilleumier et al. (2003)	fMRI	8 mm	13	Increase	Visual	Negative	−20	−10	−28
			13	Increase	Visual	Negative	20	−10	−30
			13	Positive correlation	Visual	–	−22	4	−18
			13	Positive correlation	Visual	–	−16	−8	−18
			13	Positive correlation	Visual	–	18	2	−20
			13	Positive correlation	Visual	–	22	0	−30
Vuilleumier et al. (2004)	fMRI	8 mm	13	Increase	Visual	Negative	−15	−3	−21
			13	Increase	Visual	Negative	24	−3	−21
Walter et al. (2008)	fMRI	8 mm	21	Increase	Visual	–	18	−3	−15
			21	Increase	Visual	–	−15	3	−18
			21	Increase	Visual	–	18	0	−18
Wang et al. (2006)	fMRI	8 mm	20	Increase	Visual	Negative	−22	−8	−15
			20	Increase	Visual	Negative	26	−8	−18
			20	Increase	Visual	Negative	−19	−8	−15
			20	Increase	Visual	Negative	22	−8	−15
Wild et al. (2003)	fMRI	9 mm	10	Increase	Visual/motor	–	30	−9	−9
L.M. Williams et al. (2005)	fMRI	6 mm	20	Increase	Visual	Negative	−28	−2	−24
			20	Increase	Visual	Negative	26	−2	−24
			19	Increase	Visual	Negative	26	−6	−10
Williams et al. (2006)	fMRI	8 mm	15	Increase	Visual	Negative	−16	2	−16
			15	Increase	Visual	Negative	18	2	−16
M.A. Williams et al. (2005)	fMRI	8 mm	13	Increase	Visual	–	32	−12	−22
			13	Decrease	Visual	–	−20	−8	−16
			13	Decrease	Visual	–	28	−4	−22
Winston et al. (2002)	fMRI	8 mm	14	Increase	Visual	Negative	18	0	−24
			14	Increase	Visual	Negative	−16	−4	−20
Winston et al. (2003)	fMRI	8 mm	11	Increase	Visual	–	34	0	−26
			11	Increase	Visual	–	−24	−6	−18
			11	Increase	Visual	–	30	−4	−22
			11	Increase	Visual	–	−24	−2	−24
Winston et al. (2007)	fMRI	8 mm	26	Increase	Visual	–	−24	0	−24
			26	Positive correlation	Visual	–	27	0	−24
			26	Positive correlation	Visual	–	27	0	−21
			26	Positive correlation	Visual	–	−15	−9	−27
			26	Positive correlation	Visual	–	−21	−3	−33
Wood et al. (2005)	fMRI	12 mm	23	Increase	Visual	–	28	−8	−31
Zink et al. (2008)	fMRI	8 mm	24	Increase	Visual	–	24	−3	−21

probability), 48.4% of all peaks could be assigned to the amygdala. 11.8% of peaks were assigned to the core region of the hippocampus.

The anatomical probabilities of belonging to the amygdala and to the hippocampus are given in Fig. 3 for all peaks included in the study. The assignment probability to the amygdala was in most cases high, often 100%. There were, however, also a considerable number of reported amygdala peaks with low or very low amygdala assignment probabilities. 50 peaks had 0% amygdala probability according to the currently available probabilistic anatomical maps used in the present study. Hippocampus assignment probability was typically low. There were, however, 56 peaks with ≥80% assignment probability to the hippocampus. 34 peaks had 100% probability to be located in the hippocampus.

157 peaks were related to stimuli of clearly negative and 27 peaks were related to stimuli of clearly positive emotional valence. The remaining peaks were either (rather) neutral in emotional valence or could not clearly be judged in respect to their valence. 3D distributions of all peaks related to positive and negative stimuli are shown in Fig. 4. From the 157 peaks related to stimuli of clearly negative emotional valence 76 peaks could be assigned to the core area of the amygdala (48.4% of all peaks related to negative stimuli). From 27 peaks related to clearly positive stimuli 16 were assigned to the amygdala core region (59% of all peaks related to positive stimuli). There was no difference in the anatomical probabilities for belonging to either the amygdala or the hippocampus between the group of peaks related to positive and negative stimuli (Wilcoxon rank sum test, $p > 0.5$).

Of the peaks assigned to the core region of the amygdala, 102 (62.2%) were assigned to LB, 56 (34.2%) to SF, and 6 (3.7%) to CM (Fig. 4). The observed number of 6 peaks was significantly smaller than expected assuming an equal random distribution of peaks throughout the amygdala (permutation test, $p < 0.01$) (Fig. 5).

4. Discussion

The aim of the present study was to assess the anatomical specificity of current functional imaging studies reporting amygdala activation and to test whether responses related to stimuli both of positive and negative emotional valence are located in a region with high probability to belong to the amygdala. Our study is based on 339 amygdala response peaks reported in 114 neuroimaging studies (8 using PET and 106 applying fMRI) published from 2000 to 2008. The findings of the present meta-analysis indicate a high variability of the anatomical specificity of functional amygdala imaging, ranging from studies reporting peaks with very high probability to be located in the amygdala to other studies

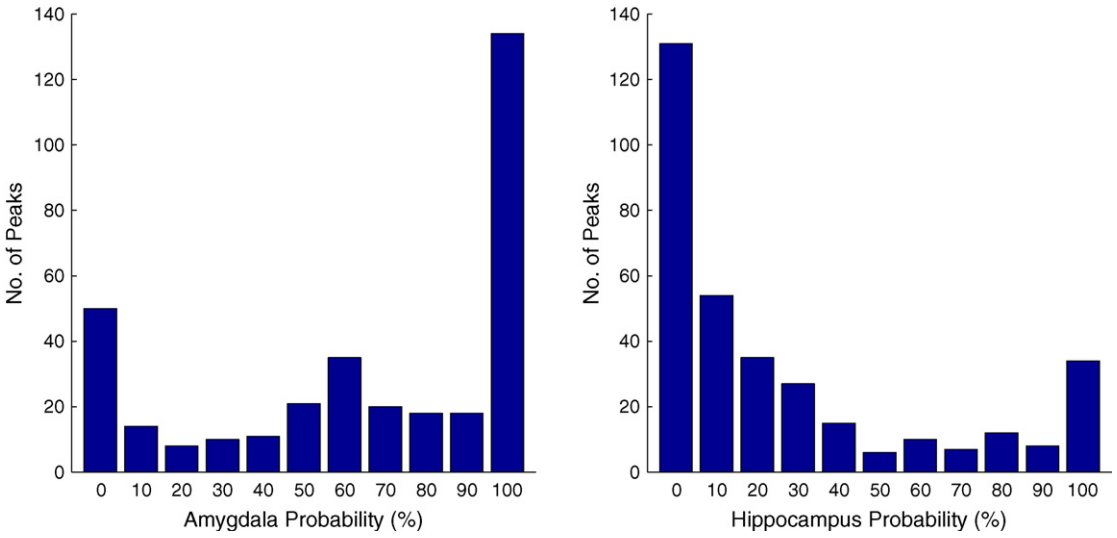

Fig. 3. Anatomical assignment probabilities for all analyzed peaks to the amygdala (left) and to the hippocampus (right). For each probability, the corresponding number of response peaks is given. While in most cases assignment probability to the amygdala was high and assignment probability to the hippocampus was low, there were also a considerable number of exceptions with low amygdala and high hippocampus assignment probabilities (down to 0% and up to 100%, respectively).

reporting peaks that were highly likely to be located outside of the amygdala, based on retrospective anatomical assignment of reported responses using a recently published cytoarchitectonically verified probabilistic anatomical map (Amunts et al., 2005). Such probabilistic maps provide information about the location and inter-individual variability of micro-anatomically defined brain areas in standard reference space, allowing anatomical assignment even if these brain regions are not discernible in structural brain images (Roland and Zilles, 1994; Toga et al., 2006).

In many cases, the anatomical probability of the reported responses to belong to the amygdala was high (e.g. 80% and above). There were, however, also a considerable number of counterexamples where anatomical probability for the amygdala was low (down to 0%) and probability for the hippocampus was high (up to 100%). Therefore, already these 'raw' anatomical probabilities support the main conclusion that, on the one side, the anatomical specificity of results reported in many amygdala studies is very good, but on the other side there are also many examples where the anatomical specificity requires further improvement in order to avoid wrong labeling of response peaks as belonging to the amygdala. Such improvements may be achieved by application of probabilistic anatomical maps of the amygdala (Amunts et al., 2005) as they allow to avoid anatomically unlikely assignments. The findings of the present study also point to an urgent need for accurate in vivo delineation and parcellation of the amygdala using MRI.

The raw anatomical probabilities obtained at a given coordinate can be combined in a summary map that assigns each voxel to one cytoarchitectonic area. To this aim we used a hierarchical assignment algorithm that first determines the assignment to major anatomical regions, such as the amygdala or the hippocampus, and then to the respective subregions. Particularly we were interested in the number of peaks that can be assigned to the core area

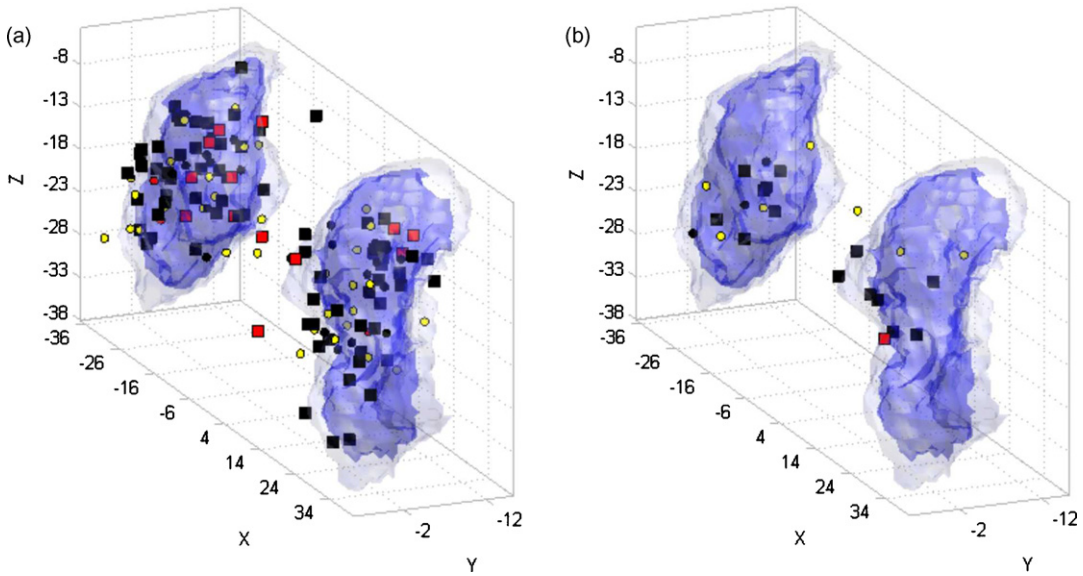

Fig. 4. (a) 3D positions of all reported amygdala responses (157 peaks) related to stimuli of clearly negative emotional valence. 76 of these peaks could be assigned to the core area with at least 80% anatomical probability to belong to the amygdala (black squares). All conventions are as in Fig. 2. (b) 3D distribution of all responses related to stimuli of clearly positive emotional valence (27 peaks). 16 of these peaks were assigned to the core area with at least 80% anatomical probability to belong to the amygdala (black squares).

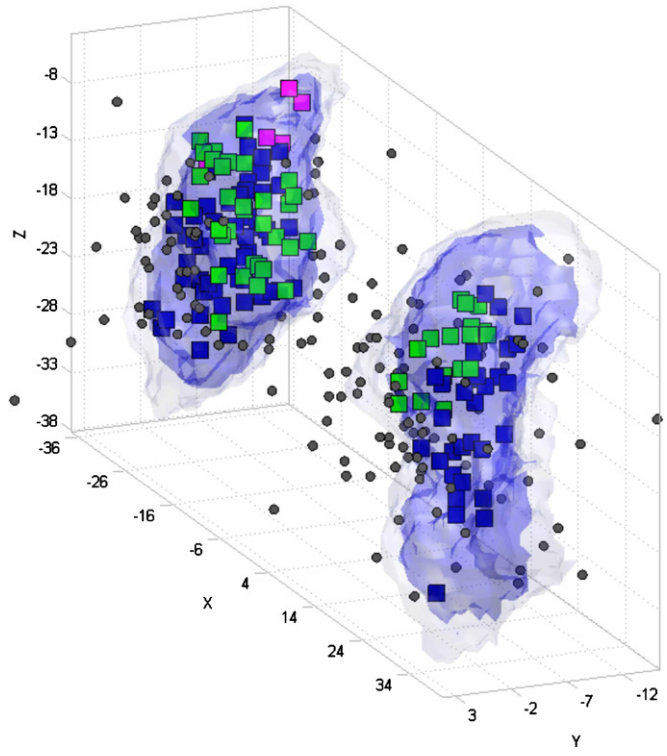

Fig. 5. Subregional assignment within the amygdala. This figure shows the result of the second step of the hierarchical assignment procedure that was used in the present study: after assigning peaks to the 'core' region of the amygdala with high anatomical probability (dark blue volume, cf. Figs. 1 and 2), these peaks were assigned to the amygdala subregions LB (blue squares), SF (green squares), and CM (magenta squares). Peaks outside of the amygdala core area are indicated by grey dots. Only 6 peaks (3.7% of all peaks assigned to the core region of the amygdala) were found in CM. All of them were located in the left CM region. Note that not all of these peaks can be easily seen, some of the CM peaks are (mostly) obscured by other peaks. These results from subregional assignment indicate that in particular the right CM region is, judging from the available evidence in this study, a 'white spot' in the functional map of the human amygdala. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

of the amygdala with high anatomical probability. As probability threshold we used ≥80% as in a previous fMRI study on subregional responses in the amygdala (Ball et al., 2007). In the present study, only 48.4% of all peaks could be assigned to the core area of the amygdala. 11.8% of peaks were assigned to the core region of the hippocampus, indicating that some of the functional responses that were previously reported and thought to originate from the amygdala might rather have originated in the hippocampus. An issue for further investigations would be the question whether, conversely, also some reported hippocampus responses might have had a high probability of being located in the amygdala.

Many response peaks included in our study were related to clearly negative stimuli (46.3%). Overall, there were much fewer peaks related to stimuli of clearly positive emotional valence (8%). Within the core region of the amygdala with high anatomical probability, responses to both clearly positive and clearly negative stimuli were found. There was no significant difference in the anatomical specificity of responses to stimuli of positive and negative emotional valence to belong to the amygdala. This finding provides further support for the assumption that the amygdala is not only involved in the processing of stimuli of negative but also of positive emotional valence.

Within the amygdala, the majority of peaks were located in LB and SF (62.2% and 34.2% of all peaks assigned to the amygdala, respectively). In contrast, only six peaks (3.7%) were assigned to CM. CM is the smallest of the three amygdala subregions comprising only 10.3% of the total volume that is assigned to the ≥80% probability core region of the amygdala. The observed number of only six peaks assigned to CM was, however, highly unlikely to result from an equal random distribution of peaks throughout the whole amygdala ($p < 0.01$) and can therefore not be readily explained by the relatively small size of CM. The few CM peaks that we found in the literature were reported in three studies investigating responses to faces (Das et al., 2005), social independence (Berns et al., 2005), and pain evoked by laser stimulation (Bornhovd et al., 2002). Thus, there was no obvious commonality regarding the stimuli used in the studies reporting CM responses. Nevertheless, the small number of CM peaks might at least to some degree be related to the experimental paradigms currently used in amygdala studies, which might more often result in differential effects in LB and SF than in CM. On the other hand, delineation from the neighboring structures is particularly difficult in the region of the amygdala that constitutes CM. If the true extent of the amygdala was underestimated in the CM region in previous studies, this might have biased response reports towards LB and SF. In this respect, usage of probabilistic maps might facilitate identification of CM responses by providing objective criteria for delineating CM from the surrounding structures. CM receives information from the basolateral amygdala (LeDoux, 2007) and is thought to mediate behavioral responses to emotional stimuli through connections to the hypothalamus, brainstem (Barbas et al., 2003), and anterior insula (Shelley and Trimble, 2004). According to this view, CM is the main output region of the amygdala. A better identification of CM responses might hence contribute to a more comprehensive picture of amygdala function, in particular of the regulation of its output to other brain structures.

It is important to emphasize that assignments underlying the present retrospective study are probability based. For instance, a reported peak with 70% probability to belong to the hippocampus and 30% probability to belong to the amygdala was in the present study assigned to the hippocampus as the most probable choice. The possibility that this peak may still belong to the amygdala could, however, not be ruled out and could only be described as 'less likely'. It was therefore the aim of the present study to investigate and characterize a large sample of reported amygdala responses, rather than labeling results of individual studies as 'correct' or 'incorrect'. Furthermore, amygdala responses must not necessarily result in a response peak within the amygdala. Specifically, in the case of a large area of activation, there might be strong evidence of amygdalar activation, even though the peak falls outside of the amygdala. Therefore, we have also not included the assignments of the individual studies to either the amygdala or hippocampus, etc. in Table 1. The assignment probabilities of a specific response peak can be conveniently obtained using the SPM 'Anatomy' toolbox (Eickhoff et al., 2006) based on the maps of Amunts et al. (2005).

A further important issue is that in the present retrospective analysis, we could not include any quantitative data on the magnitude of the localization error of the reported peaks. Such localization errors are, however, practically inevitable. They constitute a fundamentally different class of errors as compared to the assignment errors that were the subject of the present study. In case of fMRI – as used in the majority of studies included in our meta-analysis – sources of localization errors include image distortions (Merboldt et al., 2001), draining vein effects (Turner, 2002), and inaccuracies arising from spatial data pre-processing (Krishnan et al., 2006). Image distortions are more severe in the amygdala region as compared with other commonly examined brain regions, while it can be argued that the draining vein problem is probably less pronounced in the amygdala (for a discussion of this issue see Ball et al., 2007). It would be an important step for further research to include an estimate of the localization errors in the anatomical assignment algorithms. Assignments to the amygdala core region

with high anatomical probability as in the present study are useful because they provide increased robustness against localization errors.

In summary, there are many examples of studies that have reported peaks as belonging to the amygdala at coordinates where anatomical amygdala probability is, based on the currently available evidence, only very low. On the other side, there are also many studies which report peaks which fall into the core region of the amygdala with high assignment probability, including peaks from responses to stimuli both of positive and negative emotional valence. Application of probabilistic anatomical assignment procedures such as the hierarchical assignment methods we have described in the present study are most likely a useful tool to improve the anatomical specificity of future functional amygdala imaging, at least until in vivo imaging of the complete anatomical amygdala borders and of the amygdala subregions becomes feasible.

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