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A meta-analysis of instructed fear studies: Implications for conscious appraisal of threat

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ABSTRACT

In classical Pavlovian fear conditioning, a neutral stimulus (conditioned stimulus, CS) comes to be evaluated as threatening due to its association with an aversive stimulus (unconditioned stimulus, UCS), and elicits fear. In a subtype of fear conditioning paradigms, called instructed fear or anticipatory anxiety, subjects are made aware of the CS–UCS association prior to actually experiencing it. Initial fear elicitation during this type of conditioning results from the negative evaluation of the CS as a consequence of CS–UCS contingency awareness. Prior reports have suggested that this conscious appraisal process is mediated by a variety of brain regions, including rostral dorsomedial prefrontal/dorsal anterior cingulate cortex (dmPFC/dACC), lateral prefrontal cortex (lPFC), posterior cingulate, hippocampus/parahippocampus, and nucleus accumbens, but there is little overlap between results. We reasoned that a formal meta-analysis of existing instructed fear studies should help narrow down the search for conscious appraisal areas in fear conditioning to those consistently activated across studies. We found consistent activation in rostral dmPFC but not in the other candidate areas. These results allow for maintaining the theory that the rostral dmPFC is involved in conscious threat appraisal. We also report a meta-analysis of uninstructed (classical) fear conditioning studies in which we found notable activation in more posterior parts of the dmPFC/dACC that overlapped with some of the instructed fear activations. These data suggest that mid regions of the dmPFC/dACC are part of a "core" fear network that is activated irrespective of how fear was learnt.

Introduction

The appraisal of stimuli in terms of their emotional–motivational significance to the organism is thought to be causal in the generation of emotional responses (Roseman and Smith, 2001). Theorists have made a distinction between non-conscious, often quick and less elaborate, appraisal processes and conscious forms of appraisal which include propositional analysis (Leventhal and Scherer, 1987; Robinson, 1998). The working of non-conscious appraisals can be observed in those classical Pavlovian conditioning experiments in which the CS is presented below the perceptual threshold, yet evokes conditioned responses (CRs) (e.g., Critchley et al., 2002; Esteves et al., 1994; Morris et al., 1998; Ohman, 2005; Olsson and Phelps, 2004). As subjects cannot consciously predict the UCS from the CS in this type of paradigm, CRs must necessarily be a result of non-conscious processing. The opposite is true for instructed fear paradigms where subjects are told before the experiment that a given CS will be followed by a UCS. Because subjects have never experienced actual CS–UCS pairing, initial CRs must be caused by a conscious appraisal of the CS as threatening on the basis of the explicit knowledge about its relation to the UCS (i.e., CS–UCS contingency awareness). This conclusion is further supported by results from a recent instructed fear conditioning study in which subjects never actually received a UCS (preventing them from learning through experience) and produced skin conductance CRs to a CS when it was presented supra-threshold but, critically, not when it was presented sub-threshold and thus remained unperceived (Olsson and Phelps, 2004). Hence, contingency awareness is likely to be causal for CR generation in instructed fear.

Conscious appraisal of threat thus comprises explicit knowledge of the CS–UCS contingency as well as consequential cognitive elaborations about the CS and its implications. It may additionally include awareness of, and reflections about, the bodily and subjective responses induced by the CS (which have emotional stimulus quality in their own right and can thus also generate negative reactions). Various experimental approaches have been taken to dissociate the neural substrates of non-conscious and conscious appraisal in fear conditioning. Bechara et al. (1995) and Clark and Squire (1998) explicitly asked subjects about CS–UCS contingencies following uninstructed conditioning, showing that hippocampal patients cannot acquire contingency knowledge. Carter et al. (2006) tracked the emergence of contingency awareness online by having subjects rate shock expectancy while undergoing conditioning, finding activity correlated with explicit shock

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expectancy in the lPFC (bilateral middle frontal gyrus at MNI coordinates x, y, $z = -36$, 51, 30 and 36, 51, 36) and, just below the statistical threshold, in the parahippocampal gyrus. Kalisch et al. (2006) limited conscious processing by combining instructed fear conditioning with an attention- and working memory-demanding task, finding reduced conditioning-related rostral dmPFC/dACC activation (at -8,38,28) in the high- compared to the low-load condition. Tabbert et al. (2006) compared an instructed to an uninstructed (classical) fear conditioning group, of which only the former developed contingency awareness. The authors found rostral dmPFC, temporal, and parietal activation in the aware group, which was, however, not significantly stronger than in the unaware group. Klucken et al. (2009a) compared subjects that accidentally developed contingency awareness during uninstructed conditioning to those that did not, finding stronger nucleus accumbens activation in the aware group. Finally, Knight et al. (2009) presented the same CS both sub- and supra-threshold during uninstructed conditioning. This manipulation was associated with explicit shock expectancy and hippocampal and parahippocampal as well as posterior cingulate activation in the supra-threshold trials. One lesion study (Funayama et al., 2001) showed that the left, but not right, amygdala is necessary to produce skin conductance CRs in instructed fear conditioning.

This rather divergent pattern of areas associated with conscious threat appraisal led us to wonder if any of these areas are consistently activated by instructed fear conditioning across studies. As subjects are aware of the CS–UCS contingency throughout an instructed fear experiment, and thus likely to reflect upon the threatening situation, we reasoned that those areas most consistently activated by instructed fear are the strongest candidates for mediating conscious appraisal of threat. This does not imply that non-conscious processing does not contribute to the fear reaction in instructed fear paradigms, in particular when these involve CS–UCS pairings and thus also permit direct learning from experience. Likewise, the mere consistent activation of an area X in instructed fear studies does not prove the area subserves conscious appraisal (as it may also, for example, subserve non-conscious processing). However, it is reasonable to argue that areas that are *not* consistently active across instructed fear studies are unlikely candidates for this function.

The most appropriate method for determining such overlap is formal quantitative meta-analysis since, unlike the traditional method of providing scatter plots of activation maxima, formal meta-analysis generates quantitative scores of activation consistency that can be tested for significance using established statistical methods (Wager et al., 2007). Further, random between-study variance can be taken into account (Wager et al., 2007).

One prior meta-analysis had analyzed a mixed sample of instructed and uninstructed conditioning studies (Etkin and Wager, 2007). In addition to reporting a meta-analysis of instructed fear, we therefore also calculated a meta-analysis of "pure" uninstructed fear and attempted to determine regional overlap between both. Our rationale was that areas that are activated by both instructed and uninstructed fear conditioning, irrespective of the contribution of conscious appraisal processes, can be regarded as belonging to a "core" fear network.

Materials and methods

Terminology and study selection

In a typical uninstructed fear conditioning experiment, a subject learns over repeated trials that a CS (often a visual or auditory stimulus) is often or always followed by a UCS such as electric shock, heat pain, painful pressure, aversive sounds or pictures, unpleasant odor, or loss of money. Human fear conditioning paradigms usually involve discrimination between one or several such CSs (termed CS+) and one or several CS−'s which is/are never paired with the UCS, thereby controlling for non-associative effects. Instructed fear conditioning experiments (also referred to as "anticipatory anxiety") follow the same pattern, with the exception of subjects being told beforehand which CS will be associated with the UCS. In both paradigms, the acquired predictive value of the CS produces an expectation of an aversive event (the UCS) that lasts until delivery of the UCS. This anticipatory state is functionally different from the emotional state induced by the UCS itself, driving preparatory or avoidance behavior. We here employ the term "fear" for this type of state, in order to emphasize the distinction from aversive states in general. We acknowledge that only a minority of conditioning studies use explicit fear ratings to demonstrate successful induction of fear (but instead rely on autonomic or behavioral indices). It thus cannot be excluded that some studies induced only weak subjective fear states despite other indices of successful conditioning. Nonetheless, we argue that such a distinction between studies is of an incremental, and not categorical, nature.

In addition to conforming to this general design, studies had to fulfil the following criteria: they had to be published in a peer-reviewed scientific journal in English language prior to December 2008; they had to be performed in $n > 1$ healthy normal subjects; they had to employ functional magnetic resonance imaging (fMRI); they had to report a CS+>CS− comparison; they had to report significant peaks across the entire imaged volume, rather than only within a predefined region of interest, thus decreasing the risk that our meta-analysis would be biased towards or against a specific part of the brain [Note that some studies did not image dorsocaudal parts of the brain, notably in the parietal cortex, which is why the reported meta-analyses are uninformative about this area. In the following, we nevertheless use the term "whole brain-level analysis" for simplicity when referring to non region-of-interest analyses.]; the data had to be analyzed within a general linear model framework and using a predefined basis function (rather than hypothesis-free models) for prediction of BOLD signal time courses, in order to assure comparability of activation measures; the studies had to report activation coordinates rather than using gross anatomical description of activation loci; they had to report z scores as a quantitative expression of activation magnitude; they had to validate successful CR generation using subjective ratings, reaction times or physiological measures such as skin conductance or stress hormone responses. Studies using a CS with ambiguous meaning, in the sense that it might be followed by either an appetitive or an aversive event, were not included because it is unclear how the presence of an ambiguous CS affects the processing of non-ambiguous CSs. By contrast, we allowed studies with additional appetitive CSs.

We first searched PubMed using keywords instructed fear, fear conditioning, anticipation, expectation, anxiety, aversive, punishment, monetary conditioning, and loss aversion. We then mined articles found in PubMed and fulfilling above criteria for references to other related studies. We finally also searched publications by known researchers in the field for additional reports. Where an identified study also examined patients, only the data from the healthy normal controls were used. Where a study examined the influence of a drug on conditioning, only the placebo group data were used. Where a study fulfilled all criteria except reporting coordinates, a statistical test score (z or t) or whole-brain data for the contrast of interest, we contacted the authors and included the study if the authors provided the missing data (studies IF3, UF6, 9, 10, 12, and 13 in Tables 1 and 2, respectively, which summarize the included studies). T scores were transformed into z scores if necessary. From study IF5 which involved cognitive modulation of fear, only the baseline comparison condition (natural appraisal) was used.

Table 1
Studies included in the instructed fear conditioning meta-analysis.

Study code	Reference	No. subjects	M/F	No. activation peaks	Reinforcement ratio (%)	Average CS–UCS onset delay (ms)	Type of CS	Type of UCS	Concurrent cognitive task
IF1	Abler et al. (2007)	12	0/12	2	100	7920	Visual	Aversive picture	None
IF2	Butler et al. (2007)	42	26/16	17	0[a]	12,000	Visual	Electric shock	None
IF3	Herwig et al. (2007)	12	0/12	26	100	7920	Visual	Aversive picture	None
IF4	Jensen et al. (2003)	11	6/5	5	33	5000	Visual	Electric shock	None
IF5	Kalisch et al. (2005)	16	7/9	35	25	7800	Tone	Electric shock	Natural appraisal
IF6	Kalisch et al. (2006)	15	7/8	56	25	7800	Tone	Electric shock	None
IF7	Kumari et al. (2007)	14	14/0	4	0[a]	30000	Word	Electric shock	None
IF8	Nitschke et al. (2006)	21	10/11	37	100	4000	Visual	Aversive picture	None
IF9	O'Doherty et al. (2002)	8	5/3	3	100	7500	Visual	Salty taste	None
IF10	Phelps et al. (2004)	11	5/6	7	33	4000	Visual	Electric shock	None
		Total: 162	Totals: 80/82	Total: 192	Average: 53	Average: 9400	Totals: 8 visual, 2 auditory	Totals: 6 pain, 3 visual, 1 taste	Totals: 1 with, 9 without

[a] UCS announced but never administered (5 trials only).

Meta-analysis

From the whole brain-level analyses reported in the above studies, we included all activation peaks with a z score$>$3.0 (following a strategy used earlier by us (Kalisch, 2009) that protects against overly liberal results) from all CS+>CS− contrasts, irrespective of whether the peaks represented cluster maxima or local maxima within an activation cluster. Deactivations (CS+<CS−) were not included. Fear studies often report activation decays over time in areas like the amygdala that are known from the animal literature to make critical contributions to fear learning or expression (Buchel et al., 1998; LaBar et al., 1998). In order to also capture those areas, we were liberal in terms of the exact formulation of the CS+>CS− contrasts. For example, in uninstructed fear conditioning studies, authors often reported time by condition interactions (such as an exponential response decay over trials) in addition to the categorical CS+>CS− analysis. In those studies (studies UF2, 5, 6, and 7 in Table 2), activation peaks from both contrasts were included. In a different way of accounting for habituation, one study (UF12) analyzed the first and the second half of conditioning trials separately, finding no whole brain-level activation in the second half. From this study, the data from the first half were included. In one further fear conditioning study (UF10), a first block of conditioning was separated from a second block of conditioning by a block of extinction. As the second block of conditioning represented reacquisition of fear rather than *de novo* conditioning, only data from the first block were included. In two instructed fear studies (IF5 and 6), the authors modelled tonic, phasic, and linearly changing activation time courses over the course of the anticipation period within the same analysis, thus addressing potential within-trial habituation. All peaks resulting from those regressors were included. Talairach coordinates were converted to MNI coordinates as described (http://imaging.mrc-cbu.cam.ac.uk/downloads/MNI2tal/tal2mni.m; Brett et al., 2001). A full list of included peaks is available online (Supplementary Table 1).

Meta-analyses were performed using an established method (multilevel kernel density analysis, MKDA; Wager et al., 2007). Briefly, we constructed indicator maps (I, with values of 1 or 0) of whether each CS+>CS− comparison (study) resulted in activation coordinates within a sphere of 10-mm radius surrounding each voxel in a 2×2×2-mm standard brain (MNI avg152t1.img, SPM2 version; http://www.fil.ion.ucl.ac.uk/spm/spm2.html). The meta-analysis score ("activation density") $\hat{P}v$ at each voxel v was the proportion of studies that activated within 10 mm of that voxel, weighted by the square root of the sample size for each study.

Table 2
Studies included in the uninstructed (classical) fear conditioning meta-analysis.

Study code	Reference	No. subjects	M/F	No. activation peaks	Reinforcement ratio (%)	Average CS–UCS onset delay (ms)	Type of CS	Type of UCS	Concurrent cognitive task
UF1	Armony and Dolan (2002)	6	3/3	8	50	0	Angry face	White noise	Dot probe
UF2	Birbaumer et al. (2005)	10	10/0	8	100	7000	Face	Painful pressure	None
UF3	Buchel et al. (1998)	9	7/2	10	50	5000	Visual	Aversive tone	None
UF4	Buchel et al. (1999)	11	6/5	11	50	4000[a]	Tone	Aversive tone	None
UF5	Critchley et al. (2002)	6	Unclear (x/y)	3	33	38	Angry face[b]	White noise	Like/dislike dec.
UF6	Eippert et al. (2008)	15	15/0	7	50	8500	Visual	Heat pain	Localization dec.
UF7	Gottfried et al. (2002)	17	7/10	5	50	500	Face	Aversive odor	Gender dec.
UF8	Gottfried and Dolan (2004)	18	8/10	5	50	500	Face	Aversive odor	Gender dec.
UF9	Jensen et al. (2008)	13	9/4	3	50	5000	Visual	Aversive tone	None
UF10	Kalisch (2009)	25	0/25	9	80	5700	Visual	Electric shock	Gender dec.
UF11	Knight et al. (2005)	9	4/5	11	80	9500	Tone	Aversive tone	None
UF12	Schiller et al. (2008)	17	9/8	16	33	4000	Visual	Electric shock	None
UF13	Stark et al. (2006)	17	8/9	5	100	8000	Visual	Electric shock	None
UF14	Tabbert et al. (2005)	18	6/12	2	100	8000	Visual	Electric shock	None
UF15	Veit et al. (2002)	7	7/0	13	100	7000	Face	Painful pressure	None
		Total: 198	Totals: 99+x/93+y	Total: 116	Average: 65	Average: 4850	Totals: 13 visual, 2 auditory	Totals: 7 pain, 6 auditory, 2 odor	Totals: 6 with, 7 without

dec., decision.
[a] Trace conditioning.
[b] Masked and unmasked CS.

Table 3
Meta-analysis of instructed fear conditioning studies.

Region	Cluster maximum			No. voxels	Volume (mm^3)	Activation density (P_v)	*P* uncorr.
	x	*y*	*z*				
Bilateral dACC, med. sup. front. G (dmPFC), preSMA	0	16	36	814	6512	0.59	0.0098
R ant. insula, extending into putamen	36	20	0	792	6336	0.58	0.0082
L ant. insula	−32	20	6	460	3680	0.56	0.0082
Bilateral caudate-putamen, ext. into R pallidum, bilateral ant. thalamus	2	0	8	1408	11,264	0.56	0.0082
Bilateral rostr. med. sup. front. G (dmPFC)	6	38	38	127	1016	0.45	0.0053
R inf. front. S	44	24	26	7	56	0.38	0.0005
R lat. fissure (post. segment)	52	−40	32	5	40	0.37	0.0010
L supramarginal G	−64	−28	30	38	304	0.35	0.0015
L sup. temp. S (ascend. post. segment)	−52	−56	34	12	96	0.32	0.0024
L middle temp. G	−54	−56	6	81	648	0.31	0.0031
R lat. fissure (post. segment)	56	−48	28	69	552	0.30	0.0041
L lat. fissure (post. segment)	−46	−42	32	12	96	0.30	0.0041
L sup. temp. S (ascend. post. segment)	−54	−50	34	1	8	0.30	0.0041
L mid insula	−38	0	−2	7	56	0.27	0.0082
L lat. fissure (post. segment)	−56	−36	30	90	720	0.27	0.0082

Statistical threshold: FDR $q<0.01$ ($p\text{ID}<0.0098$). R, right; L, left; G, gyrus; S, sulcus. Coordinates: MNI. Ordering of results according to activation density scores.

These weights allowed the larger, and thus more reliable, studies to carry more weight in the meta-analysis. Weights were normalized by the sum across studies so that for each voxel v in the brain

$$\hat{P}v = \sum_{n=1}^{N} w_n I_n$$

where w_n is the weight for the nth of N study maps.

Tests of statistical significance treated each study as independent and were restricted to a gray matter mask (plus 8-mm border) in the standard brain (SPM2 segmented avg152t1.img with 8-mm Gaussian smoothing). Activation densities $\hat{P}v$ were tested against the null hypothesis of a uniform random distribution of peaks within each study inside the gray matter mask. The null hypothesis density $\hat{P}o$ was established through Monte Carlo simulation. Correction for multiple comparisons was performed using false discovery rate

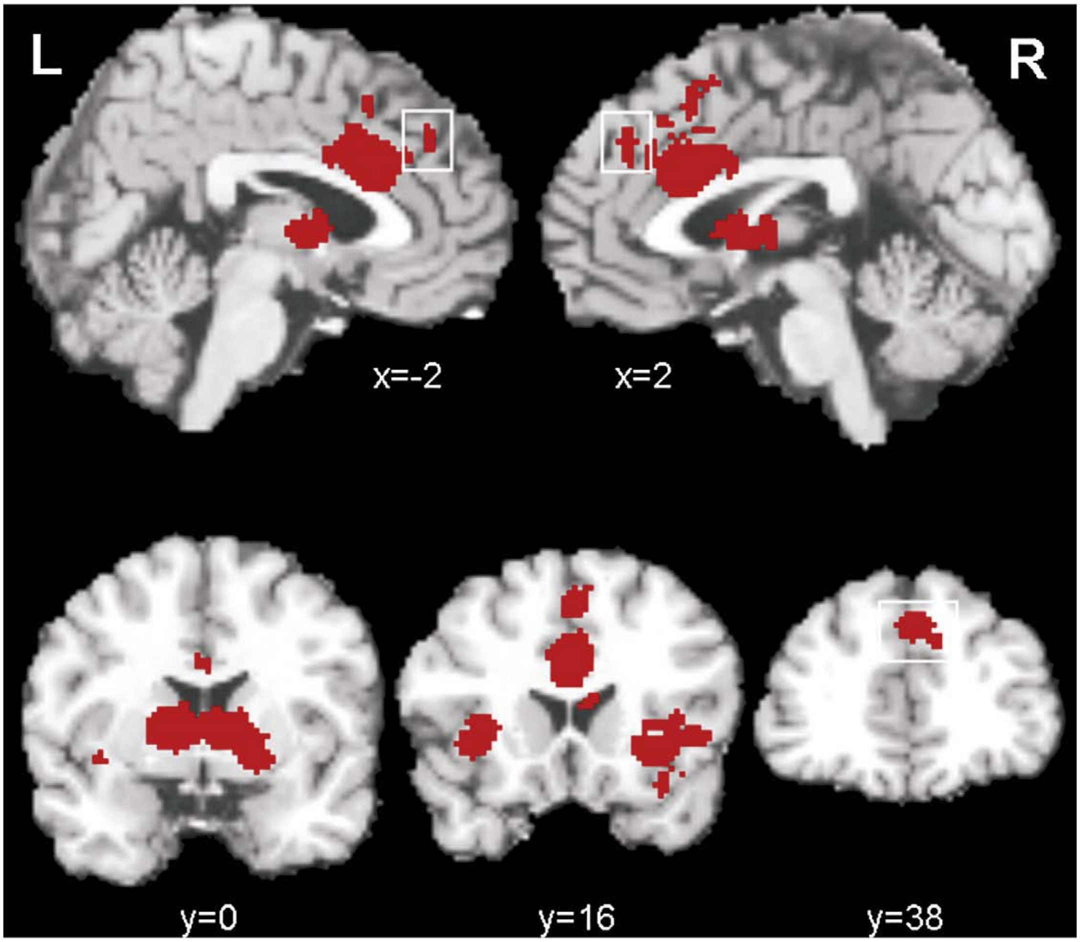

Fig. 1. Meta-analysis of instructed fear conditioning studies. Instructed fear paradigms consistently activated, among other areas, mid and rostral parts of the bilateral dmPFC/dACC (all panels), bilateral caudate–putamen and right pallidum (bottom row, left panel), and bilateral anterior insula (bottom row, middle panel). The rectangle demarcates the rostral dmPFC area earlier identified as a candidate region for conscious appraisal. Voxels significant at FDR $q<0.01$ are superimposed on a canonical structural brain image. Coordinates: MNI.

(FDR) control (Genovese et al., 2002) at $q<0.01$. FDR control is the standard correction methods in meta-analysis and endorsed both by the MKDA (Wager et al., 2007) and the ALE (Laird et al., 2005) software packages and has been used by one of us (Etkin and Wager, 2007) in an earlier meta-analysis. As in that earlier study, an additional threshold of at least two studies activating any given voxel was imposed. Anatomical localization was carried out with reference to the atlas of Duvernoy (1999).

Results

Instructed fear conditioning

At an FDR threshold of $q<0.01$, 15 clusters showed consistent activation across instructed fear studies (Table 3 and Fig. 1). The most consistently activated areas, with an activation density score of $\hat{P}v > 0.5$, were a large cluster in the bilateral mid dmPFC/dACC which extended into the presupplemental motor area (preSMA); a cluster in the bilateral anterior insulae, with an extension into the right putamen; and a cluster in the bilateral caudate–putamen which extended into the anterior thalamus and the right pallidum. Of the candidate areas for conscious appraisal identified in the introduction, only a cluster in the bilateral rostral dmPFC (maximum at 6, 38, 38; $\hat{P}v = 0.45$) showed consistent activation. The same held when lowering the threshold to $q<0.05$ (data not shown). Visual inspection of summed indicator maps showed that the number of studies activating the other candidate areas (hippocampus/parahippocampus, middle frontal gyri, posterior cingulate) was ≤2 (out of 10) in every case.

In meta-analyses with comparatively few included studies, single studies that report multiple nearby peaks may theoretically dominate the analysis and bias the results toward regions heavily represented in those studies. We therefore excluded the study with the largest number of activation peaks (IF6) from the sample and calculated a second analysis. There was still significant activation in the rostral dmPFC at $q<0.01$ (data not shown). These results indicate that the rostral dmPFC is so far the most likely candidate region for mediating conscious threat appraisal, of those identified a priori in the introduction. Note that this latter analysis is entirely non-circular as none of the studies used to define the candidate regions was included.

Uninstructed fear conditioning

There was considerably less consistent activation in the uninstructed fear conditioning sample: only a small cluster in the mid dmPFC/dACC survived a threshold of $q<0.01$ (−2, 14, 40; $\hat{P}v = 0.32$; see Table 4). When lowering the threshold to $q<0.05$, activation in multiple additional areas including the bilateral amygdalae and anterior insulae became evident. However, all significant voxels showed activation densities of $\hat{P}v<0.3$, that is, individual voxels within these regions were active in less than 30% of studies (weighted for sample size; Table 4). These results indicate large between-study variance, a situation that can result from generally weak activations. Given the pronounced differences in activation densities between the instructed and the uninstructed fear conditioning samples, we refrained from any comparison of samples and limit ourselves to the conclusion that activation of the

Table 4
Meta-analysis of uninstructed (classical) fear conditioning studies.

Region	Cluster maximum			No. voxels	Volume (mm^3)	Activation density (P_v)	*P* uncorr.
	x	*y*	*z*				
FDR threshold q<0.01 (pID<0.0001)							
Bilateral mid dACC, med. sup. front. G (dmPFC)	−2	14	40	14	112	0.32	0
FDR threshold q<0.05 (pID<0.0458)							
Bilateral mid and rostr. dACC, med. sup. front. G (dmPFC, preSMA)	−2	14	42	2150	17,200	0.32	0.0270
R amygdala extending into ant. hippocampus, ventr. ant. insula, putamen	24	2	−6	1287	10,296	0.24	0.0458
L amygdala ext. into ant. hippocampus, hypothalamus, ventr. pallidum, sgACC, caudal OFC	−18	4	−18	2082	16,656	0.22	0.0316
R ventr. thalamus, hypothalamus ext. into red nucleus	10	−14	−2	521	4168	0.22	0.0217
R ant. insula, post. lat. OFC, temp. operculum	48	16	−6	722	5776	0.20	0.0254
L lat. fissure	−58	−24	22	522	4176	0.20	0.0270
R lat. fissure, postcentr. G	62	−20	20	208	1664	0.20	0.0206
R ant. middle temp. G	54	2	−32	4	32	0.17	0.0034
L ant. OFC	−24	52	−14	60	480	0.16	0.0045
L ant. insula	−34	20	8	345	2760	0.16	0.0044
L entrorhin. area	−14	−14	−24	36	288	0.15	0.0065
R septum	4	−4	−16	2	16	0.15	0.0065
R septum	4	−2	−12	2	16	0.15	0.0065
R inf. temp. S	46	−10	−26	18	144	0.15	0.0074
Septum	0	6	6	10	80	0.14	0.0084
R inf. occip. S	44	−78	−10	14	112	0.14	0.0100
L caudate–putamen	−12	6	0	2	16	0.14	0.0100
R septum	2	−8	−12	1	8	0.14	0.0125
Substantia nigra	0	−24	−14	1	8	0.13	0.0143
L precentr. G	−50	−6	42	12	96	0.13	0.0143
R subpariet. S	10	−62	42	12	96	0.13	0.0143
L middle front. G	−44	2	50	137	1096	0.13	0.0143
R sup. front. G	12	10	66	60	480	0.13	0.0270
L ant. lat. OFC	−34	54	−6	95	760	0.13	0.0179
R lat. fissure (post. segment)	52	−34	24	19	152	0.13	0.0179
Cerebellum	−34	−46	−28	271	2168	0.12	0.0194
L temp. operculum	−56	12	−4	235	1880	0.12	0.0206
Pons	6	−28	−40	184	1472	0.11	0.0238
R med. sup. front. G (preSMA)	4	4	66	1	8	0.11	0.0254

R, right; L, left; G, gyrus; S, sulcus; OFC, orbitofrontal cortex; sgACC, subgenual ACC. Coordinates: MNI. Ordering of results according to activation density scores.

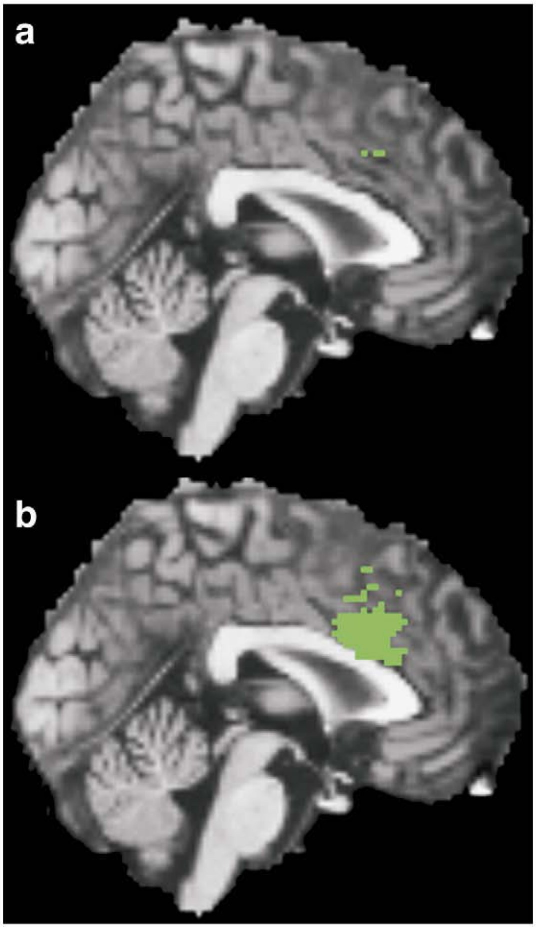

Fig. 2. A mid dmPFC/dACC area commonly activated by instructed and uninstructed fear conditioning. Overlap in activation between instructed and uninstructed fear was observed in voxels in the mid dACC/dmPFC, shown here at FDR thresholds $q<0.01$ (a) and $q<0.05$ (b). $x=0$.

mid dmPFC/dACC is a common feature of instructed and uninstructed conditioning (see Fig. 2).

Discussion

The main result of this study is that instructed fear consistently activates a rostral part of the dorsomedial prefrontal cortex and that activation in the other conscious threat appraisal candidate areas is considerably less consistent. Consistent activation in this paradigm as such does not prove an involvement in conscious appraisal, since many cognitive processes other than conscious appraisal can be assumed to operate during instructed fear conditioning. In particular, during most instructed fear experiments, subjects will directly experience CS–UCS pairings which may result in non-conscious learning and evaluation. Likewise, a CS may become secondarily associated with the aversive physiological and subjective reactions produced during conditioning, and this may be another way in which experience-mediated fear conditioning may take place during instructed fear experiments. Nevertheless, because conscious appraisal is necessarily part of the cognitive response to instructed fear stimuli, the present finding allows us to maintain the theory that the rostral dmPFC is involved in consciously appraising threat. Suggestions that the hippocampus/parahippocampus, the posterior cingulate, or the middle frontal gyri mediate this function did not receive support from this study and thus might need further qualification.

Conscious appraisals may involve the conscious expectation of a UCS (contingency awareness), awareness of the affective quality of a CS and of the accompanying subjective and bodily reactions to it, or reasoning about the effects the CS or the UCS may have on oneself. Non-conscious appraisals, by contrast, may involve automatic computations of UCS probabilities and CS values according to algorithms such as proposed by reinforcement learning theory (Sutton and Barto, 1998). In most situations, both non-conscious and conscious processes can be presumed to contribute to the appraisal of emotionally relevant stimuli and hence to shaping the ensuing emotional reaction. Cases in which one processing level participates exclusively are rare and difficult to construe experimentally. There are, however, experimental contexts in which primarily non-conscious or conscious appraisals may dominate. Thus, conditioning experiments in which the CS is presented below the perceptual detection threshold and thus inaccessible to phenomenal awareness, yet induces CRs (Critchley et al., 2002; Esteves et al., 1994; Morris et al., 1998; Ohman, 2005; Olsson and Phelps, 2004), constitute one (although not uncontroversial (Lovibond and Shanks, 2002)) type of situation wherein non-conscious appraisals can induce measurable emotional reactions. In a similar vein, sub-threshold presentation of secondary reinforcers such as money has been shown to influence motivated behavior (Pessiglione et al., 2007).

Another way of limiting conscious processing is to try to exhaust attentional or working memory resources by a concurrent cognitive task that distracts from the emotional stimulus. Interestingly, while distraction can attenuate emotional reactions relative to a focussing condition, there is also evidence for residual or even unattenuated emotional reactions under distraction (e.g., Kalisch et al., 2006; Seminowicz and Davis, 2007). This again argues for an important role of non-conscious appraisal. In general, however, responses to attended emotional stimuli are stronger than to non-attended emotional stimuli, or those presented outside of awareness, suggesting that conscious appraisals play an important role in driving emotional responding, including during classical fear conditioning (e.g., Carter et al., 2003; Delgado et al., 2008; Hamm and Vaitl, 1996; Tabbert et al., 2006).

The latter point highlights a difficulty one is faced with when trying to disentangle the neural bases of non-conscious and conscious appraisal processes. If the disruption of conscious appraisal is accompanied by a decrease in the strength of the emotional reaction, then it becomes impossible to differentiate between neural activations related to appraisal and those directly mediating response generation. In a previous instructed fear study (Kalisch et al., 2006), we created a situation where distraction was not paralleled by an attenuation of subjective feeling and autonomic system reactions to the CS, allowing us to ascribe rostral dmPFC/dACC activity (which was reduced relative to a non-distraction condition that permitted more extensive conscious processing but produced similar CRs) to conscious appraisal alone. In line with a conscious appraisal function for this area, earlier studies had implicated the dmPFC/dACC in the explicit judgment of, or attention to, emotional stimuli (Blackwood et al., 2004; Cunningham et al., 2003, 2004a, 2004b; Erk et al., 2006; Fichtenholtz et al., 2004; Fossati et al., 2003; Johnson et al., 2002; Kelley et al., 2002; Lane et al., 1997, 1998; Phan et al., 2004; Simpson et al., 2001; Taylor et al., 2003; Vuilleumier et al., 2002), but these studies have not been able to rule out a confound from response generation processes. Likewise, the studies cited in the introduction for comparing a non-conscious and a conscious appraisal condition during fear conditioning have not addressed this potential confound. Therefore, out of the candidate regions for conscious threat appraisal identified in those studies, the rostral dmPFC is currently the only one for which CR generation is not a possible alternative explanation. Together with the results of the present study, this further strengthens our argument for a crucial role of this area in conscious appraisal.

The precise contribution of the rostral dmPFC/dACC to the conscious appraisal process remains to be determined. Based on observations that dmPFC/dACC responses rapidly habituate (Kalisch et al., 2005; Phan et al., 2003) and occur contralateral to the side of electric shock application (where shock is used as UCS) (Kalisch et al. 2005), we have suggested that the region may subserve a primary schematic and stimulus-driven form of conscious awareness of the emotional meaning of a stimulus ("this is bad", "I don't like this") (Kalisch et al., 2006). If needed, more elaborate appraisal may be performed by the lPFC (e.g., Bach et al., 2008; Carter et al., 2006; Critchley et al., 2000; Hariri et al., 2000; Kalisch et al., 2006). Specifically, lPFC areas are active when one asks analytical questions about an emotional situation (Schaefer et al., 2003), deliberately reappraises a situation (Kalisch, 2009) or appraises stimuli with ambiguous meaning (Cunningham et al., 2003). Such more restricted conscious appraisal functions may not be required in any threatening situation, and this may explain why lPFC activation (apart from a small cluster in the right inferior frontal sulcus, see Table 3) was not consistently found in instructed fear in our meta-analysis. Another explanation for a lack of consistent activation in the lPFC may be pronounced anatomical and functional inter-individual variability in this region. We speculate that the role of the dmPFC/dACC may be to pass information judged relevant to higher lateral prefrontal centers for in-depth analysis. Once the dmPFC/dACC has fulfilled its role as a "gate to consciousness," it may be economical to switch it off, thus saving resources. Such a rather transient contribution to the appraisal process would be in agreement with observations of dmPFC/dACC habituation and of a negative functional relationship or connectivity between dmPFC/dACC and lPFC (Erk et al., 2006; Kalisch et al., 2005).

In contrast to the rostral dmPFC, more posterior areas of the dmPFC and the dACC were active during both instructed and uninstructed conditioning. Activation of this area thus seems to be a common feature of both paradigms. Our meta-analysis does not allow us to draw conclusions about the specific functional role of the region. We thus limit ourselves to pointing out that neural activation in that area is positively correlated with sympathetic output (Critchley et al., 2003; Gianaros et al., 2004; Nagai et al., 2004; Patterson et al., 2002), in particular during fear conditioning (Milad et al., 2007). Its proximity and close connectivity with motor areas also suggest a contribution to motoric CR generation. Another possible function is a contribution to reinforcement-based contingency learning processes as may not only occur during uninstructed but also during instructed fear conditioning, as soon as one actually experiences the UCS (Seymour et al., 2004). Likewise, our meta-analysis gives no hints as to the functions of the other areas consistently active in instructed fear (anterior insula, caudate-putamen, and others). One may speculate that the anterior insula is involved in generating the subjective feeling of fear based on interoceptive input (Critchley et al., 2004) or participates in reinforcement learning (Seymour et al., 2004, 2005). It has also been suggested that the anterior insula helps integrate visceral and other affective signals with more cognitive processing outcomes, based on its close functional association with both limbic and medial prefrontal regions in a recent large meta-analysis of emotional processing studies (Kober et al., 2008). The caudate–putamen has been shown to encode reinforcement learning signals (Menon et al., 2007; Seymour et al., 2004, 2005; Seymour et al., 2007). However, these ideas need further testing.

Of the areas *not* found in our instructed fear meta-analysis, two stand out for theoretical reasons: Based on one lesion (Funayama et al., 2001) and one fMRI study (Phelps et al., 2001), it has been argued that the amygdala, in particular the left amygdala, is required for instructed fear, although more in terms of CR expression than contingency learning (Olsson and Phelps, 2007). Most other similar fMRI studies, however, have not reproduced that finding (but see Mackiewicz et al., 2006; Nitschke et al., 2006, 2009). Likewise, we found no evidence for amygdala activation in our instructed fear sample. A potential reason for this discrepancy is that the Funayama and Phelps studies used only six and five CS+ trials, respectively, which may have prevented between-trial response habituation of amygdala activity (Buchel et al., 1998; LaBar et al., 1998), and which is in contrast to most other instructed fear studies which used more trials. We also note that response habituation was not specifically modelled in most of the included studies (except for IF5 and 6) and that, unlike in uninstructed fear conditioning studies, fMRI acquisition protocols were not specifically optimized to detect amygdala activation in most instructed fear conditioning studies. The current data thus do not allow us to definitely rule out a role for the amygdala in instructed fear. By contrast, there is little evidence in the existing data that the hippocampus may be consistently active in instructed fear. This is surprising given clear evidence for absence of contingency knowledge in hippocampal patients (Bechara et al., 1995; Clark and Squire, 1998). One reason may be that the hippocampus serves to acquire, but not necessarily to retrieve and maintain, contingency knowledge. A similar role may be played by ventral striatal areas (Klucken et al., 2009a,b). Perhaps, knowledge acquired with the help of these areas is stored and/or retrieved in the rostral dmPFC, thus permitting a memory-based conscious stimulus analysis. The latter idea would be in agreement with rostral dmPFC activation during a fear retrieval task (Kalisch et al., 2009).

In conclusion, the present study further strengthens the idea that the rostral dmPFC supports a conscious evaluation of threatening stimuli. Future research will have to more precisely determine which specific role it fulfils in this process and also how it interacts with other appraisal areas such as the amygdala (presumably relevant for initial coarse and potentially non-conscious appraisals; Sander et al., 2003) and the lateral PFC (who may subserve more complex forms of analysis). As nearly all of the studies addressing the question of conscious appraisal have used aversive stimulus material, it will also be important to examine whether a similar picture can be drawn for the processing of appetitive emotional stimuli.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2009.09.040.

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