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Review article

Common and distinct neural correlates of fear extinction and cognitive reappraisal: A meta-analysis of fMRI studies

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ABSTRACT

Cognitive reappraisal and fear extinction learning represent two different approaches to emotion regulation. While their respective neural correlates have been widely studied with functional magnetic resonance imaging (fMRI), few direct comparisons between these processes have been conducted. We conducted a meta-analysis of fMRI studies of reappraisal and fear extinction, with the aim of examining both commonalities and differences in their neural correlates. We also conducted independent analyses that focused on specific reappraisal strategies (reinterpretation, distancing). Overall, we observed that the dorsal anterior cingulate cortex (dACC) and the bilateral anterior insular cortex (AIC) were similarly consistently engaged by reappraisal and extinction. Extinction was more consistently linked to activation of sensory and emotion processing regions, whereas reappraisal was more consistently associated with activation of a dorsal fronto-parietal network. Interestingly, the amygdala was preferentially deactivated by distancing. These results suggest that the dACC and the AIC are involved in domain-general regulatory networks. Differences between extinction and reappraisal could be explained by their relative processing demands on visual perceptual versus higher cognitive neural systems.

1. Introduction

Emotions are a fundamental part of our life. They sharpen our perception, enhance our memory, and facilitate action, allowing us to adapt to changing environments (Phelps and LeDoux, 2005). It comes as no surprise that the capacity to regulate our emotions ("emotion regulation") plays a key role in our physical and psychological well-being (Cutuli, 2014; Gross, 1998, 2014; Gross and John, 2003; Webb et al., 2012). Indeed, deficits in emotion regulation seem to have a key role in the development, maintenance and treatment of most mental

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disorders (Aldao et al., 2010; Hu et al., 2014; MacDonald et al., 2017; Picó-Pérez et al., 2017; Reinecke et al., 2014; Zilverstand et al., 2016).

Emotion regulation strategies may be divided into automatic (or *implicit*), such as fear extinction learning, and intentionally deployed (or *explicit*), such as cognitive reappraisal (Gross, 2014; Gyurak and Etkin, 2014). Fear extinction learning[2] (henceforth, "fear extinction") is the process through which learned responses are no longer expressed after repeated presentations of a conditioned fear stimulus (Pavlov, 1927). Fear extinction has been investigated across species and it is hypothesized that abnormal fear extinction characterizes some mental disorders, especially anxiety disorders (Duits et al., 2015). Indeed, effective psychological treatment techniques for these disorders, such as exposure therapy, are largely based on the principles of fear extinction (Myers and Davis, 2002). Cognitive reappraisal, by contrast, refers to the modification of the initial appraisal of a situation to change its emotional significance and has been examined almost exclusively in humans. Reappraisal appears early in the emotion-generative process, regulating emotional responses *before* they have been completely generated (Gross, 1998, 2014). The predominant strategies of cognitive reappraisal that have received the most attention are "reinterpretation" and "distancing". Reinterpretation refers to changing the meaning of an emotional stimulus in a way that it involves more optimistic future scenarios. Distancing refers to thinking of the emotional stimulus as non-realistic or imaging oneself as a third-person observing (but not involved in) the emotional scenario.

The neural systems involved in fear extinction and cognitive reappraisal have been thoroughly investigated. Rodent studies, in particular, have emphasized a primary role of the ventromedial prefrontal cortex (vmPFC) in downregulating fear/threat-related neural activity in the amygdala and its extended circuitry during fear extinction (Milad et al., 2006; Quirk et al., 2006, 2003). These results have been partly corroborated in human neuroimaging studies (Dejean et al., 2015; Hartley and Phelps, 2010; Linnman et al., 2012; Milad and Quirk, 2012; Sehlmeyer et al., 2011). However, a recent meta-analysis of functional magnetic resonance imaging (fMRI) studies of human fear extinction did not find evidence of consistent vmPFC or amygdala involvement across studies. Instead, these studies appear to mainly capture a neural signature that overlaps with studies of fear/threat conditioning, including activations in the dorsal anterior cingulate, and the dorsomedial and dorsolateral prefrontal cortices (dACC, dmPFC and dlPFC, respectively), as well as the anterior insular cortex (AIC), suggesting an enduring activation of the neural systems implicated in fear/threat response generation (Fullana et al., 2018).

Regarding cognitive reappraisal, several meta-analyses of fMRI studies have shown that, overall, it is characterized by consistent activations of a distributed frontoparietal network, involving extended vmPFC, dmPFC, dACC and dlPFC areas, as well as the ventrolateral prefrontal cortex (vlPFC) and the inferior parietal lobule (Buhle et al., 2013; Diekhof et al., 2011; Kohn et al., 2014). There is also meta-analytical evidence of consistent differences in the neural systems supporting reinterpretation vs. distancing reappraisal strategies. Thus, the left vlPFC seems to be preferentially activated during reinterpretation, while activations in the vmPFC and the inferior parietal lobule have been preferentially reported during distancing (Dörfel et al., 2014; Picó-Pérez et al., 2017).

An important question generated from these parallel lines of inquiry, which has received little attention, is the extent to which fear extinction and cognitive reappraisal share common neural substrates in the human brain. The studies mentioned above suggest that there may be overlap in the areas underpinning the deployment of implicit vs. explicit emotion regulation strategies, but this has never been overtly tested. Extant results are markedly heterogeneous and this overlap could be observed in functionally distinct regions such as the dACC, the dmPFC, the dlPFC or the vmPFC. A clearer definition of the areas contributing to both fear extinction and cognitive reappraisal should result in a better characterization of the emotion regulation networks and a deeper understanding of the different emotion regulation strategies.

Here, we take advantage of the large body of previous fMRI research into fear extinction and cognitive reappraisal to investigate through meta-analysis the common and distinct neural correlates supporting these two processes in humans. We compared the neural correlates of fear extinction with cognitive reappraisal overall, as well as with each of the two cognitive reappraisal strategies most commonly assessed in experimental research (i.e., reinterpretation and distancing). With respect to previous fMRI meta-analyses of cognitive reappraisal and fear extinction (Buhle et al., 2013; Fullana et al., 2018; Kohn et al., 2014), we hypothesized that the neural correlates of fear extinction and cognitive reappraisal would mainly converge in the dACC, the dmPFC and the dlPFC, whereas differences would mainly be observed in the vlPFC (especially for the comparison with reinterpretation) and inferior parietal areas (especially for the comparison with distancing), since these regions have almost exclusively been reported in cognitive reappraisal studies. To avoid confounding effects of development and psychopathology, we focused on fMRI studies with healthy adults. Fortunately, neuroimaging research that includes healthy adults constituted a remarkably large number of studies. Moreover, original whole-brain statistical maps were available for more than 60% of the studies included in the meta-analysis, increasing our sensitivity to identify the most robust brain effects across studies (Radua et al., 2012).

2. Methods

2.1. Literature search and study selection

A comprehensive literature search using PubMed, Web of Knowledge and Scopus was conducted for English-language peer-reviewed fMRI studies on conditioned fear extinction learning ('extinction') and cognitive reappraisal ('reappraisal') in human healthy adults (age ≥18 years) (see Supplementary Material for details). After duplicate removal, 261 articles for extinction and 341 for reappraisal were identified (Fig. 1).

For extinction, we included studies that assessed fear extinction using delay differential cue-conditioning paradigms (i.e., where two conditioned stimuli are presented and one (CS+) precedes an aversive stimulus and another (CS-) does not) and that reported direct comparisons between a CS + and CS- during extinction. In certain studies, all CSs trials during extinction were included in the analysis, whereas in others, 'early' and 'late' extinction phases were modelled separately. When more than one contrast was available from a given study, we sought to include the contrast involving all trials. If this contrast was not available, we focused on late extinction (Milad et al., 2007) (Table 1).

For reappraisal, we included studies in which participants were presented with negative visual stimuli (either from the International Affective Picture System – IAPS (Lang et al., 2005), or from other databases) and instructed to reappraise the images by means of reinterpretation, distancing, or both. Typically, this task intercalates blocks in which participants are instructed to maintain the negative emotion elicited by the image, and blocks in which participants are instructed to reappraise. Our contrast of interest was the comparison of these two conditions (Reappraise vs. Maintain) (Table 2).

We excluded studies from which, after contact with the authors, peak information or statistical maps could not be retrieved, or that did not report whole-brain statistical results, and/or in which statistical

[2] Although fear extinction learning experiments in humans do not typically involve explicit instructions, this does not necessarily mean that the extinction process "is" implicit. Our use of the terms "implicit" and "automatic" is based on a recent framework for emotion regulation strategies proposed by Braunstein et al. (2017).

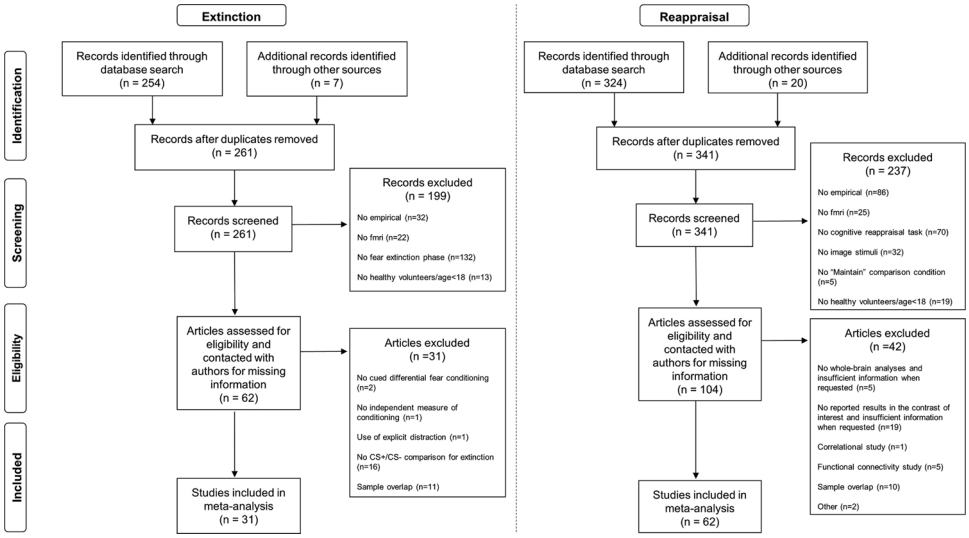


Fig. 1. PRISMA flow diagram of fear extinction (left) and cognitive reappraisal (right) studies. Note: PRISMA = Preferred reporting items for systematic reviews and meta-analyses (http://www.prismastatement.org/).

thresholds varied across the assessment of different brain regions (Fig. 1). We were able to retrieve the original brain activation maps of the contrast of interest for 57 (i.e., 61.29%) datasets, 20 (64.51%) from extinction and 37 (59.67%) from reappraisal studies. For the remaining studies, peak coordinates and effect sizes were extracted and coded from the original publication or from supplementary data provided by corresponding authors.

The literature search, decisions on inclusion and data extraction were all performed independently by two investigators. For each dataset, several sociodemographic variables were extracted (Table 1 and Table 2).

2.2. Meta-analytic approach

fMRI results were meta-analyzed using Anisotropic Effect-Size Signed Differential Mapping (AES-SDM) software, version 5.141 (www.sdmproject.com; Radua et al., 2014, 2012). AES-SDM is a well-validated neuroimaging meta-analytic method, which conducts voxel-wise random-effects meta-analyses (weighing the studies for sample size, intra-study variance and between-study heterogeneity), and is capable of combining tabulated brain activation results (i.e., regional peak statistic and coordinate information) with actual empirical voxel-wise activation maps (Radua et al., 2010, 2012, 2014; Radua and Mataix-Cols, 2009) (see Supplementary Material for details regarding preprocessing steps).

To assess the regions of common activation during extinction and reappraisal, we performed a conjunction analysis by means of the multimodal meta-analysis in AES-SDM. This analysis is conceptually the same than conducting the simple overlap of the meta-analytical maps from individual meta-analyses (i.e., to find the regions that activate during both extinction and reappraisal), but it takes error in the p-values into account (Radua et al., 2013). The same analysis was used to evaluate the regions of common activation during extinction and reinterpretation, and during extinction and distancing.

To assess the regions of differential activation during extinction and reappraisal, we compared the meta-analytical maps obtained from the CS+ > CS- and Reappraisal > Maintain contrasts, which yielded results for Extinction > Reappraisal and Reappraisal > Extinction. The same approach was used to compare reinterpretation and distancing vs. extinction.

We assessed the robustness of our findings by examining the I^2 index and Egger's test to assess for heterogeneity of effect sizes and publication bias, respectively. Statistical significance was determined at the whole-brain level with a $p < 0.05$ False Discovery Rate (FDR) corrected. In addition, a minimum cluster extent of 100 voxels was used. Results are reported in Montreal Neurological Institute (MNI) space.

3. Results

3.1. Included studies and sample characteristics

We included 31 independent datasets for extinction, with a total of 1074 participants (43.66% females, mean age of 25.17 years, s.d. = 4.49) (see Table 1 and Fullana et al., 2018 for details), and 62 independent datasets for reappraisal, including a total of 1869 participants (61.26% females, mean age of 29.74 years, s.d. = 6.87) (see Table 2). For the sub-analyses of the different reappraisal strategies vs. extinction, we classified reappraisal studies into those using reinterpretation (n = 20) and those using distancing (n = 20) (see Table S1 for details regarding the specific instructions given on each study). We excluded 22 reappraisal studies that let the subject choose which strategy to use or did not give specific instructions.

As mentioned in the introduction, the neural correlates of fear extinction have been the focus of a previous meta-analysis (see Fullana et al., 2018). The results for the meta-analysis of cognitive reappraisal studies are presented in the Supplementary Material (Tables S2, S3 and S4).

3.2. Regions of common activation across extinction and reappraisal

Regions that were commonly activated during extinction and during reappraisal included the dACC (MNI coordinates = 8, 36, 18, cluster extent = 110 voxels) and the bilateral AIC (right: MNI coordinates = 32, 22, -14, cluster extent = 67 voxels; left: MNI coordinates = -54, 12 -4, cluster extent = 60 voxels; Fig. 2).

Similar results were obtained in our sub-analyses focusing on specific reappraisal strategies, i.e., regions of consistent common activation during extinction and during reinterpretation included the dACC (MNI coordinates = -2, 40, 22, cluster extent = 78 voxels) and the bilateral AIC (right: MNI coordinates = 40, 22, -12, cluster extent = 12 voxels; left: MNI coordinates = -54, 12, 0, cluster extent = 47 voxels). Analogous regions were observed to be commonly activated during extinction and during distancing, although in this analysis no significant findings were observed in the left AIC (dACC: MNI coordinates = -4, 32, 32, cluster extent = 15 voxels; right AIC: MNI coordinates = 40, 22, -10, cluster extent = 22 voxels).

Table 1
Characteristics of the 31 extinction fMRI studies included in the meta-analysis.

Authors	N (female)	Age, y, Mean (SD)	CS	Reinforcement rate during conditioning (%)	Immediate extinction?	Number of CS+/CS- during conditioning	Number of CS+/CS- during extinction	fMRI analysis
Åhs et al., 2015*	43 (22)	28.7 (10.4)	Dynamic images (VR)	31	YES	16/16	16/16	Early, late
Benson et al., 2014*	29 (14)	23.8 (2.6)	Geometrical figures	75	YES	16/16	12/12	Early, late
Diener et al., 2016*	13 (6)	42.46 (13.69)	Geometrical figures	50	YES	18/18	18/18	Whole
Ewald et al., 2014	13 (5)	23.1 (3)	Lights (VR)	100	YES	16/16	8/8	Early, late
Harrison et al., unpublished*	58 (39)	21.8 (NA)	Geometrical figures	50	YES	32/ 32	16/16	Whole, early, late
Hermann et al., 2012*	74 (37)	24.3 (4.14)	Geometrical figures	100	YES	20/20	15/15	Whole
Holt et al., 2012	17 (0)	34.2 (9.9)	Photographs	60	YES	16/16	16/16	Early
Icenhour et al., 2015*	23 (12)	33.7 (NA)	Geometrical figures	75	YES	16/16	6/6	Early, late
Klumpers et al., unpublished*	106 (0)	21.9 (NA)	Geometrical figures	33	YES	18/18	18/18	Whole, early, late
Krause-Utz et al., 2016	26 (26)	28.16 (8.26)	Geometrical figures	50	YES	36/36	18/18	Whole
Kuhn et al., unpublished*	37 (19)	25.13 (NA)	Geometrical figures	100	YES	18/18	12/12	Whole
Lindner et al., 2015*	15 (15)	22.53 (2.7)	Geometrical figures	100	YES	8/8	4/4	Whole
Linnman et al., 2012	18 (10)	25.7 (5)	Photographs	62	YES	16/16	16/16	Early, late
Lonsdorf et al., 2014*	59 (32)	24 (0.4)	Angry faces	100	NO	15/15	24/24	Whole
Lueken et al., 2014*	60 (41)	35.75 (10.27)	Geometrical figures	50	YES	32/32	16/16	Whole, early, late
Merz et al., 2012*	49 (29)	24.33 (NA)	Geometrical figures	100	YES	20/20	11/11	Whole
Merz et al., 2014*	16 (0)	24.88 (4.3)	Geometrical figures	62	YES	16/16	16/16	Early, late
Milad et al., 2007	14 (NA)	NA (NA)	Photographs	60	YES	16/16	16/16	Late
Milad et al., 2013	16 (NA)	25.8 (NA)	Photographs	62	YES	16/16	16/16	Early vs late
Molapour et al., 2015*	20 (10)	22.39 (3.82)	Neutral faces	100	YES	9/9	12/12	Whole
Morriss et al., 2015*	21 (11)	24.03 (2.75)	Geometrical figures	100	YES	12/12	16/16	Whole
Pejic et al., 2013*	49 (22)	23.49 (3.07)	Neutral faces	100	YES	17/17	2x(13/13)	Whole
Phelps et al., 2004*	11 (6)	NA (NA)	Geometrical figures	33	YES	23/15	15/15	Whole
Rabinak et al., 2014a, 2014b	14 (5)	25.43 (NA)	Geometrical figures	35	YES	23-23/15	30/30	Early, late
Reinhardt et al., 2010	20 (0)	28.8 (6.1)	Geometrical figures	50	YES	32/16	16/16	Whole
Ridder et al., 2012, sample 1	60 (22)	21.25 (3.02)	Geometrical figures	50	YES	18/18	18/18	Whole
Scharfenort et al., unpublished*	77 (41)	24.8 (NA)	Geometrical figures	100	NO	14/14	14/14	Whole
Sehlmeyer et al., 2011	32 (20)	23.6 (4.41)	Neutral faces	25	YES	40/30	25/25	Whole
Soriano-Mas et al., unpublished	18 (8)	35.6 (NA)	Photographs	62	YES	16/16	16/16	Whole
Spoormaker et al., unpublished*	48 (6)	24.9 (NA)	Geometrical figures	50	COMBINED	30/15	15/15	Whole
Wicking et al., 2016*	18 (7)	38.6 (12.21)	Geometrical figures	100	NO	30/30	30/30	Early, late

Abbreviations: SD standard deviation; CS conditioned stimulus; CS + CS followed by unconditioned stimulus; CS − S not followed by unconditioned stimulus; fMRI functional magnetic resonance imaging; NA Not available; VR Virtual Reality.
*Datasets for which statistical parametric maps were available.

Table 2
Characteristics of the 62 reappraisal fMRI studies included in the meta-analysis.

Authors	N (female)	Age, y, Mean (SD)	Cognitive reappraisal strategy	Stimuli
Albein-Urios et al., 2013*	21 (1)	31 (4.6)	Reinterpretation and distancing	Negative images (IAPS)
Chen et al., 2017*	47 (47)	21 (1.4)	Distancing	Negative images (CAPS)
Denny et al., 2015a	21 (11)	29 (6.71)	Distancing	Negative images (IAPS)
Denny et al., 2015b	17 (12)	24.1 (5.16)	Distancing	Negative images (IAPS)
Dillon and Pizzagalli, 2013*	24 (12)	34.42 (14.93)	Distancing	Negative images (IAPS)
Domes et al., 2010	33 (17)	24.89 (1.75)	Distancing	Negative images (IAPS)
Dörfel et al., 2014*	17 (17)	24 (3.22)	Distancing	Negative images (IAPS)
Dörfel et al., 2014*	19 (19)	22.53 (2.86)	Reinterpretation	Negative images (IAPS)
Eippert et al., 2007	24 (24)	23.3 (NA)	Distancing	Negative images (IAPS)
Erk et al., 2010	17 (8)	43.9 (10.1)	Distancing	Negative images (IAPS)
Gaebler et al., 2014*	23 (18)	30 (7.99)	Distancing	Negative images (IAPS)
Gianaros et al., 2014*	157 (80)	42.7 (7.3)	Reinterpretation	Negative images (IAPS)
Goldin et al., 2009	17 (9)	32.1 (9.3)	Reinterpretation and distancing	Harsh facial expressions
Golkar et al., 2012	58 (32)	24.02 (2.26)	Reinterpretation	Negative images (IAPS)
Gorka et al., 2016*	37 (19)	25.68 (5.29)	Reinterpretation and distancing	Negative images (IAPS)
Harenski and Hamann, 2006	10 (10)	23.5 (1)	Distancing	Moral negative images (IAPS)
Hayes et al., 2010	25 (11)	21.6 (2.5)	Distancing	Negative images (IAPS)
Hermann et al., 2016*	27 (27)	21.59 (2.58)	Reinterpretation	Negative images (IAPS)
Kanske et al., 2011*	30 (17)	21.8 (2.1)	Reinterpretation and distancing	Negative images (IAPS)
Kanske et al., 2012*	25 (18)	43.88 (11.21)	Reinterpretation and distancing	Negative images (IAPS)
Kanske et al., 2015, sample 1*	22 (12)	40.5 (11.8)	Reinterpretation and distancing	Negative images (IAPS)
Kanske et al., 2015, sample 2*	17 (8)	35.94 (15.63)	Reinterpretation and distancing	Negative images (IAPS)
Koenigsberg et al., 2010	16 (9)	31.8 (7.79)	Distancing	Social negative images (IAPS)
Krendl et al., 2012	16 (10)	21.87 (3.11)	Reinterpretation	Negative images (IAPS)
Leiberg et al., 2012	24 (24)	24.1 (NA)	Distancing	Negative images (IAPS)
McRae et al., 2008	23 (11)	20.48 (NA)	Reinterpretation and distancing	Negative images (IAPS)
Modinos et al., 2010*	18 (7)	21.1 (2.8)	Reinterpretation and distancing	Negative images (IAPS)
Morawetz et al., 2016a*	59 (20)	32.47 (11.25)	Reinterpretation and distancing	Negative images (IAPS)
Morawetz et al., 2016b*	60 (30)	30.48 (11.1)	Reinterpretation and distancing	Angry faces (FACES database)
Morris et al., 2012*	15 (9)	35 (2)	Distancing	Negative images (IAPS)
New et al., 2009	14 (14)	31.7 (10.3)	Reinterpretation	Negative images (IAPS)
Ochsner et al., 2002	15 (15)	21.9 (NA)	Reinterpretation	Negative images (IAPS)
Ochsner et al., 2004	24 (24)	20.6 (NA)	Reinterpretation and distancing	Negative images (IAPS)
Opitz et al., 2012, young sample*	16 (8)	19.25 (1.43)	Reinterpretation	Negative images (IAPS)
Opitz et al., 2012, old sample*	15 (9)	59.87 (3.14)	Reinterpretation	Negative images (IAPS)
Paschke et al., 2016*	108 (55)	26.12 (3.7)	Distancing	Emotional Picture Set (pictures with social content)
Payer et al., 2012*	10 (6)	27.6 (8.09)	Reinterpretation and distancing	Negative images (IAPS)
Qu and Telzer, 2017	29 (14)	19.2 (NA)	Reinterpretation	Scenes depicting individuals in an emotionally negative situation
Rabinak et al., 2014a, 2014b	21 (21)	34.81 (9.54)	Reinterpretation and distancing	Negative images (IAPS)
Radke et al., 2017*	22 (9)	32.6 (10.9)	Reinterpretation	Angry faces (FACES database)
Reinecke et al., 2015*	18 (14)	32.3 (12.1)	Reinterpretation	Negative images (IAPS)
Schardt et al., 2010*	37 (37)	22.6 (2.2)	Distancing	Negative images (IAPS)
Schulze et al., 2011*	16 (16)	24.53 (3.84)	Distancing	Negative images (IAPS)
Shermohammed et al., 2017*	25 (12)	20.89 (1.71)	Reinterpretation and distancing	Negative images (IAPS)
Silvers et al., 2015	30 (13)	21.97 (NA)	Reinterpretation	Negative images (IAPS)
Simsek et al., 2017	15 (15)	22.53 (1.8)	Reinterpretation	Negative images (IAPS)
Sripada et al., 2014*	49 (23)	23.63 (1.3)	Reinterpretation and distancing	Negative images (IAPS)
Stephanou et al., 2016*	78 (44)	19.91 (2.78)	Reinterpretation and distancing	Negative images (IAPS)
Steward et al., 2016*	14 (8)	21.21 (1.42)	Reinterpretation and distancing	Negative images (IAPS)
Uchida et al., 2015	62 (32)	22.3 (1.6)	Reinterpretation	Negative images (IAPS)
Urry et al., 2006*	17 (9)	62.9 (0.4)	Reinterpretation and distancing	Negative images (IAPS)
Urry et al., 2009*	26 (15)	64.8 (0.5)	Reinterpretation	Negative images (IAPS)
Vanderhasselt et al., 2013	42 (42)	21.26 (2.29)	Reinterpretation	Negative images (IAPS)
Van der Velde et al., 2015a*	51 (23)	37.1 (10.3)	Reinterpretation and distancing	Negative images (IAPS)
Van der Velde et al., 2015b*	16 (8)	22.1 (3.6)	Reinterpretation and distancing	Negative images (IAPS)
Van Reekum et al., 2007*	29 (18)	63.66 (2.45)	Reinterpretation and distancing	Negative images (IAPS)
Vrtička et al., 2011	19 (19)	24.82 (4)	Distancing	Negative images (IAPS)
Wager et al., 2009*	30 (18)	22.3 (NA)	Reinterpretation	Negative images (IAPS)
Walter et al., 2009	20 (20)	24 (3)	Distancing	Negative images (IAPS)
Winecoff et al., 2011*	42 (NA)	44.96 (23.53)	Distancing	Negative images (IAPS)
Zhang et al., 2013*	13 (12)	20.7 (1.21)	Reinterpretation	Negative images (IAPS)
Ziv et al., 2013	27 (13)	32.6 (9.5)	Reinterpretation	Anger and contempt faces

Abbreviations: SD standard deviation; IAPS International Affective Picture System; CAPS Chinese Affective Picture System.
*Datasets for which statistical parametric maps were available.
In the study by Schardt et al. (2010), contrasts from both fear and disgust stimuli were combined.

There were no other regions of whole-brain significant results in any of these analyses.

3.3. Regions of differential activation during extinction versus reappraisal

When comparing extinction to reappraisal, the former was consistently associated with greater activation of the bilateral post-central gyrus, the bilateral rolandic operculum, the bilateral posterior insular cortex, the bilateral supramarginal gyrus, the associative visual cortices, as well as the right hippocampus, the right pallidum, the bilateral putamen, the posterolateral thalamus, the pons, the bilateral cerebellar hemispheres and the cerebellar vermic lobules VI and X (see

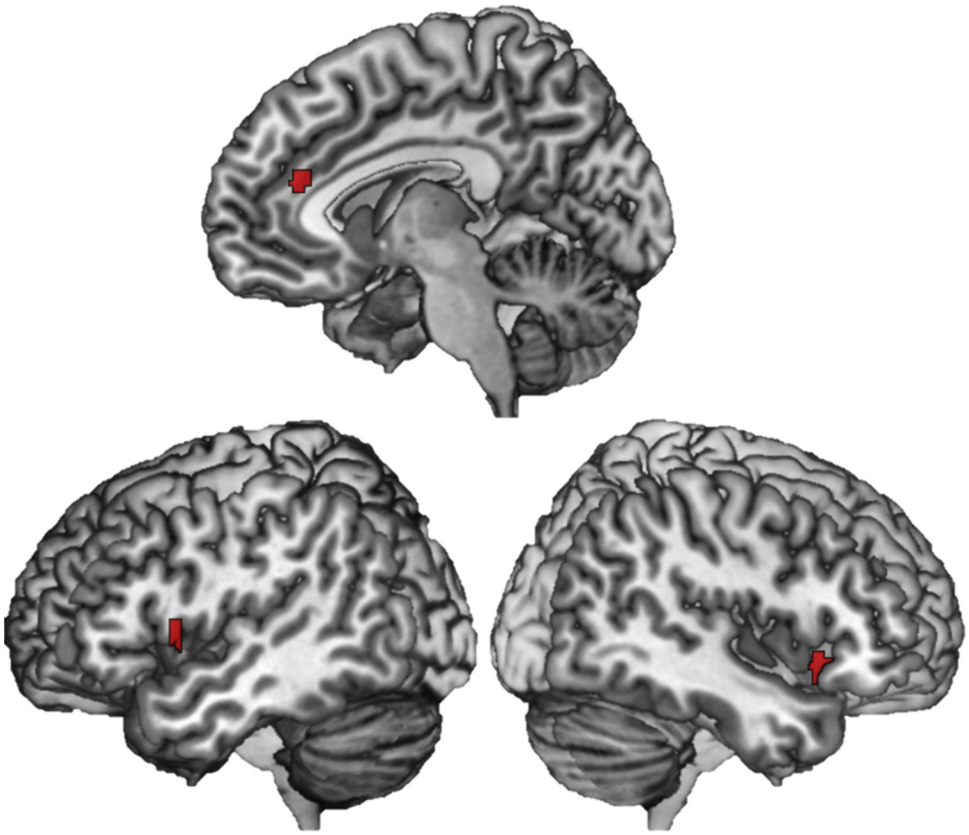


Fig. 2. Brain regions showing significant common activation during fear extinction and cognitive reappraisal.

Table 3, Fig. 3).

When comparing reappraisal to extinction, the former was consistently associated with greater activation of the bilateral vlPFC, dlPFC, dmPFC, and SMA, as well as in the bilateral angular and supramarginal gyri, the left precentral gyrus, the posterior cingulate cortex and the precuneus, the bilateral temporal gyri and the right cerebellum (crus I) (Table 3, Fig. 4).

Findings from these analyses did not show substantial heterogeneity nor evidence of potential publication bias (with the exception of the right parieto-occipital cluster), and remained significant when including only studies with original statistical maps (see Table 3). Importantly, Table 3 also informs about whether the above findings resulted from significant activations or deactivations (or both) during extinction or reappraisal.

3.4. Regions of differential activation during Extinction and Reinterpretation

No consistent differences were observed when comparing *Extinction* > *Reinterpretation*. Conversely, *Reinterpretation* > *Extinction* was associated with consistent activation of the bilateral vlPFC, the left dlPFC, the left dmPFC, the left precentral gyrus, the left angular and supramarginal gyri, and the left middle temporal gyrus (Figure S1, Table 4).

3.5. Regions of differential activation during Extinction and Distancing

When comparing *Extinction* > *Distancing*, consistent activation was observed for the left postcentral gyrus and the insula, the associative visual cortices extending to the inferior temporal lobe, the bilateral cerebellum, the bilateral pons, the left posterolateral thalamus, the right pallidum, the left hippocampus and the bilateral amygdala (Figure S2, Table 4). When contrasting *Distancing* > *Extinction*, a similar pattern of differences was observed to that of *Reinterpretation* > *Extinction*, although results obtained for *Distancing* were more broadly observed bilaterally (vlPFC, dlPFC, dmPFC, SMA, angular, supramarginal and middle and superior temporal gyri) (Figure S3, Table 4). As in Table 3, Table 4 also informs about whether results from these last comparisons stemmed from significant activations or deactivations (or both) during extinction or each reappraisal strategy.

4. Discussion

Humans have a number of strategies to regulate emotional responses that draw on both implicit (as in fear extinction) and explicit (as in cognitive reappraisal) processes. We have compared, via meta-analysis, the neural correlates of fear extinction and cognitive reappraisal, using data from more than 90 fMRI studies of almost 3000 participants. Our results indicate that there are significant commonalities as well as significant differences in the neural correlates of these two emotion regulation strategies.

We found that the dACC and the AIC were the only brain areas involved in *both* explicit and implicit emotion regulation strategies to survive statistical threshold in a formal conjunction analysis. These regions have been shown to participate in a variety of cognitive and behavioral regulation processes. For example, Diekhof et al. (2011) reported a hyperactivation of the dACC and the AIC during cognitive reappraisal and placebo, and Morawetz et al. (2017) found that, together with the left vlPFC, the dACC and the AIC were active across attentional, cognitive (e.g., reappraisal) and response-focused regulation strategies. Likewise, Langner et al. (2018) found these regions, in combination with the temporo-parietal junction, to engage in both emotion and action regulation, which was interpreted in terms of a general control feedback loop implicated in self-regulation across different domains. Far less attention has been devoted to the possible role of the dACC or the AIC in *implicit* emotion regulation, although this was

Table 3
Results from extinction vs. reappraisal meta-analysis.

Comparison	Cluster	Ke	Egger test p	Local peak	MNI coordinates (x,y,z)	SDM-Z	Voxel P	I^2	Original maps only
Extinction > Reappraisal[a]	Left central	5788	0.848	Postcentral gyrus (↓Reapp)	−56, -16, 22	4.987	0.000000119	18.69%	No
				Rolandic operculum (↑Ext, ↓Reapp)	−42, -22, 22	4.927	0.000000119	6.20%	No
				Supramarginal gyrus (↑Ext, ↓Reapp)	−50, -34, 26	4.512	0.000000417	1.53%	No
				Posterior insula (↑Ext, ↓Reapp)	−36, -2, -10	4.116	0.000001431	0%	Yes
				Putamen (↑Ext, ↓Reapp)	−26, -6, -8	4.070	0.000001729	0%	No
				Precentral gyrus (↓Reapp)	−28, -20, 56	3.474	0.000032008	0%	Yes
				Midcingulate gyrus (↓Reapp)	−16, -34, 44	3.256	0.000079274	0%	Yes
				Superior temporal gyrus (↓Reapp)	−64, -14, 10	3.157	0.000120342	0%	Yes
	Right temporo-occipital	1762	0.967	Middle occipital gyrus (↑Ext, ↓Reapp)	26, -92, 10	3.718	0.000009835	29.11%	Yes
				Cuneus (↑Ext, ↓Reapp)	18, -94, 0	3.562	0.000023127	0%	Yes
				Inferior occipital gyrus (↓Reapp)	42, -76, -2	3.353	0.000052512	27.76%	Yes
				Superior occipital gyrus (↓Reapp)	22, -84, 16	3.050	0.000178754	0%	Yes
				Inferior temporal gyrus (↓Reapp)	44, -70, -6	3.015	0.000203669	12.81%	Yes
				Middle temporal gyrus (↑Ext, ↓Reapp)	52, -58, 0	2.802	0.000462174	5.92%	Yes
	Right central	1591	0.159	Rolandic operculum (↑Ext, ↓Reapp)	52, -16, 22	4.998	0.000000119	0%	No
				Supramarginal gyrus (↑Ext, ↓Reapp)	66, -20, 26	4.618	0.000000179	0%	Yes
				Posterior insula (↑Ext, ↓Reapp)	38, 2, 14	3.559	0.000023127	0%	Yes
				Postcentral gyrus (↓Reapp)	66, -18, 34	3.092	0.000152349	0%	No
	Left temporo-occipital	945	0.737	Middle occipital gyrus (↓Reapp)	−26, -88, 2	3.317	0.000061214	37.78%	No
				Inferior occipital gyrus (↓Reapp)	−40, -86, -12	2.867	0.000362396	0%	Yes
				Middle temporal gyrus (↓Reapp)	−42, -58, 0	2.676	0.000729144	0%	Yes
				Cuneus (↓Reapp)	−14, -100, -2	2.610	0.000915408	25.30%	Yes
	Right parieto-occipital	599	0.035	Precuneus (↓Reapp)	22, -62, 28	3.326	0.000059426	0%	Yes
				Postcentral gyrus (↓Reapp)	22, -44, 68	2.908	0.000307977	0%	Yes
				Supramarginal gyrus (↓Reapp)	34, -38, 44	2.808	0.000452518	0%	Yes
				Cuneus (↓Reapp)	18, -68, 34	2.556	0.001111507	0%	No
	Right striato-limbic	546	0.556	Hippocampus (↑Ext, ↓Reapp)	24, -8, -10	4.872	0.000000119	0%	No
				Putamen (↑Ext, ↓Reapp)	30, 4, -2	2.785	0.000490248	0%	Yes
				Pallidum (↑Ext, ↓Reapp)	16, 0, -6	2.583	0.001014411	0%	Yes
	Bilateral cerebellum	588	0.453	Left hemispheric lobule VI (↑Ext, ↓Reapp)	−6, -70, -24	3.721	0.000009477	0%	Yes
				Right hemispheric lobule IV/V (↑Ext, ↓Reapp)	14, -52, -20	3.302	0.000065029	0%	Yes
				Vermic lobule X (↑Ext, ↓Reapp)	0, -48, -26	2.848	0.000387967	0%	Yes
				Right hemispheric lobule VI (↓Reapp)	8, -64, -18	2.758	0.000541031	0%	Yes
				Vermic lobule VI (↓Reapp)	6, -62, -24	2.736	0.000588238	0%	Yes
	Bilateral paracingulate/SMA	479	0.843	Left (↑Ext, ↓Reapp)	−8, -4, 44	4.614	0.000000179	0%	Yes
				Right (↓Reapp)	8, -4, 46	3.496	0.000029325	0%	Yes
	Right subcortical	189	0.258	Pons (↑Ext, ↓Reapp)	12, -22, -2	3.474	0.000032008	0%	No
				Thalamus (↑Ext, ↓Reapp)	14, -20, 10	2.790	0.000483274	0%	No
	Left subcortical	144	0.644	Thalamus (↑Ext, ↓Reapp)	−12, -22, 6	3.590	0.000020564	0%	No
				Pons (↑Ext, ↓Reapp)	−12, -22, -4	3.328	0.000059247	0%	No
	Left lateral occipital	117	0.555	Left superior occipital gyrus (↓Reapp)	−22, -64, 24	3.233	0.000085354	0%	Yes
Reappraisal > Extinction[b]	Bilateral fronto-temporo-parietal	18518	0.451	Right superior frontal gyrus (dmPFC) (↑Reapp)	16, 50, 34	5.004	˜0	19.96%	No
				Left middle frontal gyrus (dlPFC) (↑Reapp, ↓Ext)	−36, 16, 32	5.004	˜0	0%	Yes
				Left middle frontal gyrus (vlPFC) (↑Reapp, ↓Ext)	−42, 44, -8	5.004	˜0	32.70%	Yes
				Left supplementary motor area (↑Reapp)	−6, 18, 52	5.004	˜0	58.37%	Yes
				Left middle temporal gyrus (↑Reapp)	−60, -44, 0	5.003	˜0	38.54%	Yes
				Left angular gyrus (↑Reapp, ↓Ext)	−38, -70, 38	5.000	˜0	35.91%	Yes
				Left superior frontal gyrus (dmPFC) (↑Reapp)	−14, 28, 56	5.000	˜0	9.86%	Yes
				Left supramarginal gyrus (↑Reapp, ↓Ext)	−62, -54, 22	4.990	˜0	20.37%	Yes
				Right middle frontal gyrus (dlPFC) (↑Reapp, ↓Ext)	34, 18, 54	4.981	˜0	2.73%	Yes
				Left precentral gyrus (↑Reapp)	−46, 10, 46	4.911	0.000000119	39.11%	No
				Right supplementary motor area (↑Reapp)	4, 14, 66	4.331	0.000005782	18.70%	Yes
				Left superior temporal gyrus/temporal pole (↑Reapp)	−46, 14, -24	4.265	0.000007033	0%	Yes
				Left inferior temporal gyrus (↑Reapp, ↓Ext)	−54, -8, -28	3.439	0.000246406	0%	Yes

(*continued on next page*)

Table 3 (*continued*)

Comparison	Cluster	Ke	Egger test p	Local peak	MNI coordinates (x,y,z)	SDM-Z	Voxel P	I^2	Original maps only
	Right angular	1767	0.090	Angular gyrus (↑Reapp)	60, -58, 24	4.997	˜0	28.74%	No
				Middle temporal gyrus (↑Reapp)	56, -62, 22	4.987	˜0	36.88%	Yes
				Superior temporal gyrus (↑Reapp)	56, -56, 22	4.986	˜0	39.80%	Yes
	Right vlPFC	1029	0.184	Inferior frontal gyrus (↑Reapp)	48, 48, -6	5.003	˜0	6.37%	Yes
				Middle frontal gyrus (↑Reapp, ↓Ext)	38, 42, -10	5.003	˜0	11.55%	Yes
	Right temporal	1017	0.847	Middle temporal gyrus (↑Reapp)	64, -24, -16	4.786	0.000000536	8.19%	Yes
				Inferior temporal gyrus (↑Reapp, ↓Ext)	58, -18, -24	3.872	0.000039816	6.00%	Yes
	Bilateral precuneus	872	0.333	Left precuneus (↑Reapp)	− 4, -62, 42	4.024	0.000019312	0%	Yes
				Left median cingulate/paracingulate (↑Reapp)	− 10, -44, 36	3.735	0.000075161	0%	Yes
				Left posterior cingulate (↑Reapp)	− 2, -48, 22	3.378	0.000312924	12.14%	Yes
				Right precuneus (↑Reapp)	6, -58, 38	3.088	0.000906229	20.05%	Yes
	Right cerebellum	135	0.113	Cerebellum, crus I (↑Reapp)	40, -70, -36	3.444	0.000241756	0%	Yes

Abbreviations: Ke cluster extent; MNI Montreal Neurological Institute; SDM Signed Differential Mapping; P p-value; I2 percentage of variance attributable to study heterogeneity.
a. Regions of difference stemming from a larger activation in Extinction are indicated by ↑Ext, while regions stemming from a larger deactivation in Reappraisal are indicated by ↓Reapp.
b. Regions of difference stemming from a larger activation in Reappraisal are indicated by ↑Reapp, while regions stemming from a larger deactivation in Extinction are indicated by ↓Ext.

observed in our previous meta-analysis (Fullana et al., 2018), where these two regions consistently showed activity across human fear extinction learning fMRI experiments.

Another explanation for the robust dACC and AIC activity during extinction and reappraisal may be enduring emotional responses to emotional stimuli despite regulation attempts. This idea has been previously put forward in the context of increased activation of these regions during cognitive reappraisal, where aversive stimuli are still present during regulation attempts (Diekhof et al., 2011). More recently, we have suggested that increased activation of the dACC and the AIC during fear extinction could be accounted for by the fact that fear responses to conditioned stimuli are rarely completely abolished during extinction (Fullana et al., 2018). Indeed, co-activation of these two regions is typically observed when processing emotional stimuli, and both are considered core components of the "salience network", whose activity is thought to guide behavior in front of emotionally relevant stimuli by regulating attention and cognitive resources allocation (Menon, 2015; Menon and Uddin, 2010). Activation of these regions has been consistently related with emotional appraisal and autonomic responses, with the AIC encoding the bodily arousal states (Craig, 2009; Paulus and Stein, 2006) that contribute to the conscious appraisal of threat underpinned by dACC responses (Kalisch and Gerlicher, 2014).

Although it is difficult to reconcile these two hypotheses from the current analyses alone, previous research indicates that the role of these regions in emotional processing is likely to be multifaceted and related to both emotional appraisal and regulation across stimuli and strategies. Activity in the dACC, for instance, has been correlated with subjective anxiety during fear conditioning (Harrison et al., 2015), but also with regulation success during cognitive reappraisal (Phan et al., 2005). Likewise, conscious appraisal of emotions via activation of the AIC has been suggested to be the necessary first step to successfully engage in some emotion regulation strategies, such as expressive suppression (Giuliani et al., 2011). In this context, our data may be interpreted as evidence of the importance of conscious appraisal of bodily states to trigger emotion regulation processes, cutting-across different strategies. In this regard, it is worth highlighting that these regions display a high base-rate of activation across all fMRI studies (regardless of the psychological process being studied; Poldrack, 2006), making it difficult to ascribe any particular function to them, especially from studies where causal inference cannot be inferred.

Regarding the patterns of differential activation between implicit and explicit strategies, we observed several regions that were consistently activated during extinction. Contrasting with what was observed for the AIC, activation of the posterior insula and adjacent cortices, involved in somatosensory and interoceptive processing (Craig, 2003), was specific of extinction. The primary somatosensory cortex was also active during extinction. These results are likely to be related to the previous pairing of the to-be extinguished CS + with nociceptive stimuli, reflecting an enduring anticipatory response (see Fullana et al., 2018). Likewise, posterior occipital regions were also active during extinction, probably as a result of the dampened attention to visual emotional stimuli motivated by reappraisal strategies (Wiggins et al., 2016). Of note, our results regarding the right postcentral gyrus and the cuneus and precuneus showed some potential publication bias, and therefore should be interpreted with caution. A range of subcortical regions also emerged during extinction. In close relationship with visual processing cortices, the posterolateral portion of the thalamus contributes to visual processing and is sensitive to the emotional value of complex scene stimuli, modulating visual attention toward relevant cues (Frank and Sabatinelli, 2014). We also observed activation during extinction in the putamen, reported to underlie emotion recognition (Fusar-Poli et al., 2009), the hippocampus, part of a network involved in the recall of fear extinction (Kalisch et al., 2006; Milad et al., 2007), and different lobes of the cerebellum and the cerebellar vermis, described to be associated with both fear conditioning and extinction (Fullana et al., 2015, 2018), as well as with the regulation of autonomic

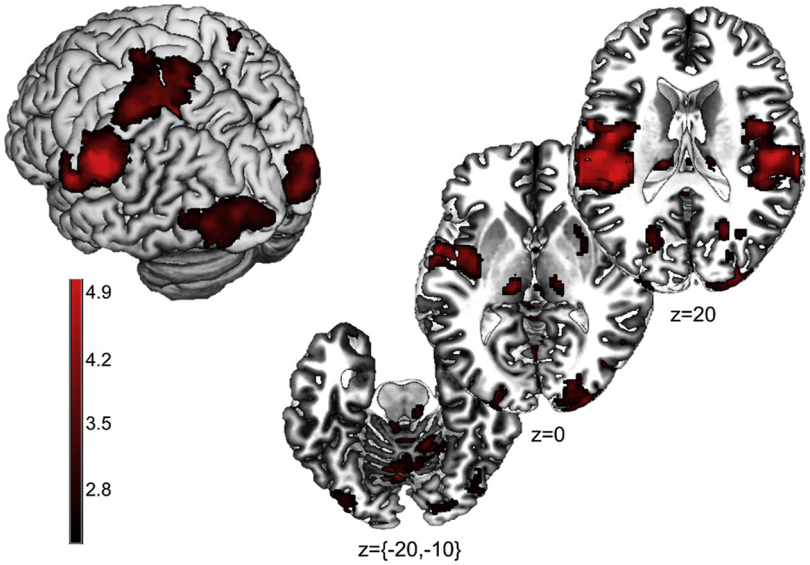


Fig. 3. Brain regions showing consistent activation during extinction in comparison with reappraisal. Results are displayed at $p < 0.05$ FDR corrected at the whole-brain level (cluster size ≥ 100 voxels).

and motor responses during emotional processing (Strata et al., 2011; Strata, 2015). Overall, although different factors may be contributing to the extinction pattern, increased perceptual processing of aversive stimuli seems crucial to differentiate between extinction and reappraisal. It is possible that a more active processing of emotional stimuli is needed for learning to extinguish a previously conditioned response, but not for cognitive reappraisal.

Regarding the pattern of regions preferentially associated with reappraisal, a network of prefronto-parietal regions emerged, concurring with what has been typically found in meta-analyses of cognitive reappraisal (Buhle et al., 2013; Kohn et al., 2014). The dlPFC is critical for executive functioning (Wager and Smith, 2003), and, in the context of reappraisal, it seems to support the active manipulation of information that is needed to reappraise emotional stimuli (Ochsner et al., 2012). Relatedly, the vlPFC has a preponderant role in response selection and inhibition (Aron et al., 2014), particularly in the inhibition of emotional appraisals (Wager et al., 2009). Also, the dmPFC is essential to manage conflict and up-hold motivation for specific goals (Gill et al., 2010; Mitchell et al., 2009; Warden et al., 2012). Finally, the angular and supramarginal gyri are relevant regions for the allocation of attentional resources and monitoring emotional experiences (Pessoa et al., 2003). The activation of this network of regions seems therefore to reflect the use of higher cognitive process characteristic of explicit strategies.

When contrasting extinction with reinterpretation and distancing, we obtained a similar fronto-parietal pattern of regions consistently active during both reappraisal strategies. This indicates that reinterpretation and distancing share neurobiological underpinnings and are probably similarly demanding in cognitive terms as compared to extinction. By contrast, regions consistently active during extinction were exclusively observed in relation to distancing. Distancing strategies might therefore be more effective at decreasing activation in regions important for perception and processing of emotional stimuli, such as the associative visual cortices or the posterolateral thalamus. Notably, in the contrast *Extinction > Distancing* we also observed a significant cluster in the amygdala, although, as can be observed in Table 4, this was not due to a significant activation during extinction, but to a significant deactivation during distancing. It is broadly recognized that the amygdala contributes to the generation of emotional

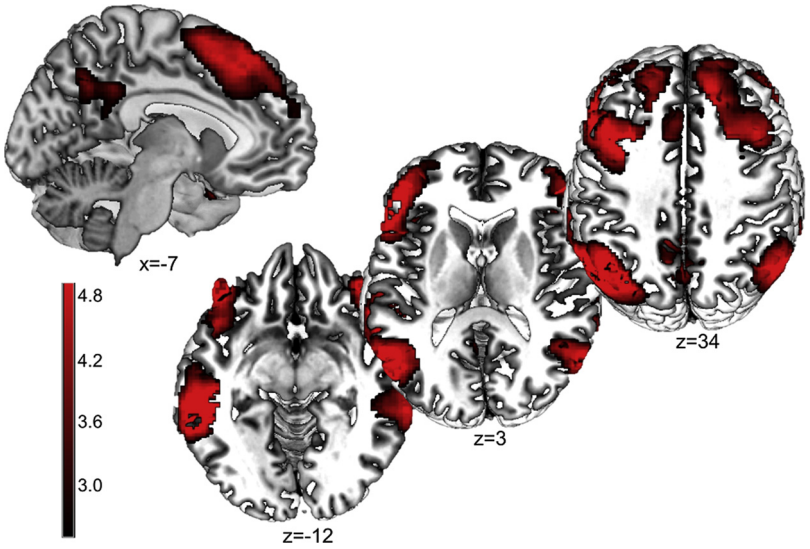


Fig. 4. Brain regions showing consistent activation during reappraisal in comparison with extinction. Results are displayed at $p < 0.05$ FDR corrected at the whole-brain level (cluster size ≥ 100 voxels).

Table 4
Results from extinction vs. reappraisal strategies meta-analysis.

Comparison	Cluster	Ke	Egger test p	Local peak	MNI coordinates (x,y,z)	SDM-Z	Voxel P	I^2
Extinction > Reinterpretation	–							
Reinterpretation > Extinction[a]	Left PFC	1477	0.226	SFG (dmPFC) (↑Reint)	−16, 26, 50	5.003	˜0	0%
				IFG (vlPFC) (↑Reint, ↓Ext)	−42, 40, -16	4.897	0.000010192	2.66%
				MFG (dlPFC) (↑Reint, ↓Ext)	−48, 24, 38	4.859	0.000011981	0.41%
				Precentral gyrus (↑Reint)	−48, 8, 40	3.855	0.000493884	4%
	Left parieto-temporal	928	0.300	Angular gyrus (↑Reint, ↓Ext)	−52, -68, 36	5.000	0.000005960	18.37%
				MTG (↑Reint)	−54, -68, 22	4.988	0.000006199	0%
				Supramarginal gyrus (↑Reint, ↓Ext)	−64, -54, 22	4.756	0.000018477	0%
	Right vlPFC	219	0.124	IFG (↑Reint, ↓Ext)	44, 44, -14	4.995	0.000006080	6.70%
	Left MTG	215	0.191	MTG (↑Reint)	−46, -30, -6	5.001	˜0	4.98%
Extinction > Distancing[b]	Right temporo-occipito-cerebellar	3104	0.790	ITG (↓Dist)	48, -64, -8	5.001	˜0	1.88%
				IOG (↓Dist)	42, -70, -12	5.001	˜0	0%
				MOG (↑Ext, ↓Dist)	28, -94, 14	4.978	0.000004411	0%
				Fusiform gyrus (↓Dist)	36, -76, -12	4.966	0.000004649	0%
				Cerebellum, hemispheric lobule VI (↓Dist)	18, -56, -20	4.957	0.000004828	10.41%
				Cerebellum, hemispheric lobule IV/V (↓Dist)	14, -54, -20	4.860	0.000008345	0%
				Cerebellum, vermic lobule VII (↓Dist)	−2, -72, -24	4.776	0.000010729	0%
				Cuneus (↓Dist)	20, -92, 14	4.466	0.000037670	1.62%
				Lingual gyrus (↓Dist)	14, -88, -10	4.455	0.000039041	23.96%
				Cerebellum, vermic lobule VI (↓Dist)	4, -78, -14	4.239	0.000094414	0%
				Cerebellum, vermic lobule IX (↑Ext)	4, -56, -32	3.920	0.000290632	0%
				SOG (↓Dist)	24, -100, 8	3.670	0.000661194	0%
	Left occipito-cerebellar	1204	0.790	IOG (↓Dist)	−36, -76, -4	4.991	0.000004053	10.32%
				MOG (↓Dist)	−38, -90, 2	4.879	0.000007927	0%
				Cuneus (↓Dist)	−18, -90, 4	4.622	0.000021756	5.08%
				Cerebellum, hemispheric lobule VI (↓Dist)	−28, -58, -22	4.007	0.000215530	0%
	Bilateral pons + left subcortical	1148	0.544	Right pons (↑Ext, ↓Dist)	12, -24, -6	4.928	0.000006318	0%
				Left pons (↑Ext, ↓Dist)	−16, -24, -10	4.801	0.000009835	0%
				Left hippocampus (↓Dist)	−24, -14, -12	4.601	0.000023305	0%
				Left thalamus (↑Ext, ↓Dist)	−12, -18, 6	3.968	0.000245452	0%
				Left amygdala (↓Dist)	−30, 0, -18	3.934	0.000274777	0%
				Left insula (↑Ext)	−36, -2, -10	3.919	0.000291407	0%
	Right subcortical	162	0.544	Amygdala (↓Dist)	24, -4, -12	4.843	0.000008464	0%
				Globus pallidus (↑Ext)	16, 0, -10	4.002	0.000218689	0%
	Left postcentral gyrus	124	0.670	Postcentral gyrus (↓Dist)	−46, -22, 24	4.268	0.000085652	0%
Distancing > Extinction[c]	Bilateral PFC	3390	0.723	Right MFG (dlPFC) (↑Dist, ↓Ext)	30, 20, 44	4.996	0.000005364	0%
				Right SFG (dmPFC) (↑Dist)	20, 8, 56	4.936	0.000006735	0.29%
				Left SMA (↑Dist)	−4, 14, 56	4.472	0.000047386	64.67%
				Left MFG (dlPFC) (↑Dist, ↓Ext)	−30, 26, 40	4.378	0.000068963	0%
				Right SMA (↑Dist)	6, 12, 66	3.844	0.000428557	13.73%
				Left SFG (dmPFC) (↑Dist, ↓Ext)	−2, 28, 58	3.267	0.002287567	43.34%
	Right parieto-temporal	1807	0.155	Angular gyrus (↑Dist)	50, -58, 32	4.997	0.000005364	56.69%
				MTG (↑Dist)	58, -58, 20	4.995	0.000005364	20.30%
				STG (↑Dist)	62, -54, 20	4.989	0.000005484	14.51%
				Supramarginal gyrus (↑Dist)	64, -38, 42	4.551	0.000034571	0%
	Left parietal	1638	0.338	Supramarginal gyrus (↑Dist, ↓Ext)	−60, -54, 24	5.002	˜0	18.40%
				Angular gyrus (↑Dist, ↓Ext)	−58, -56, 32	4.999	0.000005364	34.81%
	Right PFC	1359	0.723	IFG (vlPFC) (↑Dist, ↓Ext)	46, 40, -10	5.000	0.000005364	38.78%
				MFG (↑Dist)	36, 54, -2	4.579	0.000030994	1.39%
				SFG (dmPFC) (↑Dist)	20, 60, 12	4.113	0.000173807	0%
	Left MTG	580	0.338	MTG (↑Dist)	−64, -46, 2	4.814	0.000012100	20.92%
	Left vlPFC	500	0.055	IFG (↑Dist, ↓Ext)	−50, 34, 0	4.721	0.000018060	17.87%

Abbreviations: Ke cluster extent; MNI Montreal Neurological Institute; SDM Signed Differential Mapping; P p-value; I2 percentage of variance attributable to study heterogeneity.

a. Regions of difference stemming from a larger activation in Reinterpretation are indicated by ↑Reint, while regions stemming from a larger deactivation in Extinction are indicated by ↓Ext.

b. Regions of difference stemming from a larger activation in Extinction are indicated by ↑Ext, while regions stemming from a larger deactivation in Distancing are indicated by ↓Dist.

c. Regions of difference stemming from a larger activation in Distancing are indicated by ↑Dist, while regions stemming from a larger deactivation in Extinction are indicated by ↓Ext.

responses, including defensive responses to threats, and its activity is typically reduced via emotion regulation processes (Ochsner et al., 2004; Phelps and LeDoux, 2005). Since distancing involves emotionally detaching from stimuli, its effects in decreasing negative affect should be considerably faster when compared to extinction, which, as discussed, should require maintaining the focus of attention toward emotional stimuli in order to facilitate learning. Similarly, reinterpretation strategies may also less efficiently regulate amygdala deactivation since individuals have to keep the emotional stimuli online (i.e., working memory) in order to reappraise its representation. In this regard, novel paradigms controlling for time effects could probably be informative about the differences across emotion regulation strategies in downregulating amygdala activity at the short and the long-term.

Finally, we were not able to detect consistent vmPFC activation for extinction or reappraisal, which is at odds with Diekhof et al. (2011) who stressed the role of the vmPFC as a common brain region involved in the general regulation of negative affect. However, in contrast to ours, that meta-analysis included both extinction learning and extinction recall studies, and vmPFC activation seems to be more characteristic of extinction recall (see Fullana et al., 2018). Moreover, activation of the vmPFC has not been consistently reported across cognitive reappraisal studies (Buhle et al., 2013; Kohn et al., 2014). Recent work also suggests that this region may be preferentially engaged in the valuation stage of emotional processing rather than in its regulation (Ochsner and Gross, 2014).

This study has some limitations. Firstly, we focused on extinction and cognitive reappraisal as representing implicit and explicit emotion regulation strategies, although other emotion regulation strategies could have been included (see the meta-analyses by Langner et al. (2018) or Morawetz et al. (2017)). Secondly, we only included extinction studies with reported evidence of extinction at a behavioral level and this was not a requisite for reappraisal studies (because these studies rarely incorporate such a measurement). Lastly, we have not been able to compare early and late extinction phases, which, as discussed, could have allowed a deeper understanding of the differences between emotion regulation processes at the short- and the long-term. In this sense, such distinction between early and late phases could also be of interest for cognitive reappraisal studies, although this has been rarely studied. Moreover, emotion regulation in general, and extinction and reappraisal in particular, are complex constructs that involve a number of different processes (perceptive, attentional, affective, regulatory, etc). The goal of our meta-analysis was to offer a broad perspective on the neural commonalities/differences between two specific forms of emotional regulation. The assessment of potential differences in the neural correlates of the specific processes engaged by these strategies awaits future research. Strengths of the current study include the use of a very large number of studies with methodologically homogenous and comparable protocols as well as the use of a meta-analytic approach combining the positive features of standard (i.e., non-neuroimaging) meta-analytic methods (i.e., the inclusion of full information from a given study, represented here by the original brain maps) with those of neuroimaging coordinate approaches.

In conclusion, our results indicate that implicit and explicit emotion regulation strategies, represented here by extinction learning and cognitive reappraisal, are associated with common and differential activations in several brain regions. While they share a common core, encompassing the dACC and the AIC, they also involve distinct regions, allegedly supporting the use of different psychological processes. The dACC and the AIC seem to play a role in the general control feedback loop involved in self-regulation across different domains. By contrast, the brain activation pattern associated with extinction reflects an increased need for active perceptual processing of emotional stimuli, whereas the pattern associated with reappraisal reflects the increased demand of high order cognitive resources posed by these strategies. Finally, reinterpretation and distancing appear to differ as compared to extinction not in their cognitive load, but in its effectiveness to decrease activity in areas important for processing of emotional stimuli and generation of emotional responses, being distancing more effective in this sense. Our results can provide a framework for future studies contrasting the use of these strategies in populations (e.g. patients with mental disorders) characterized by a maladaptive/inefficient use of emotion regulation strategies, or after interventions aimed at improving such strategies. Likewise, our findings point to the existence of emotion regulatory hubs, which may be preferentially targeted by neuromodulation techniques.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neubiorev.2019.06.029.

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