

# **Meta-analytic evidence for downregulation of the amygdala during working memory maintenance**

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Words in abstract: 229

Words in introduction: 709

Words in discussion: 2172

Figures: 3

Tables: 4

Keywords: meta-analysis, amygdala, working memory, functional MRI, emotion regulation

## **Abstract**

The amygdala is a region critically implicated in affective processes. Downregulation of the amygdala is therefore one of the hallmarks of successful emotion regulation. Downregulation is thought to be established through top-down control of the executive control network over the amygdala. Such a reciprocal relationship, however, is not exclusive to cognitive regulation of emotion. It has recently been noted that any cognitively demanding task may downregulate the amygdala, including a standard working memory task. Here, using a coordinate-based meta-analysis based on an activation likelihood estimation (ALE), we examined whether a standard working memory task (i.e., a 2-back task) downregulates the amygdala similarly to a cognitive reappraisal task. Following the PRISMA guidelines, we included a total of 66 studies using a 2-back working memory task and 65 studies using a cognitive reappraisal task. We found that a standard 2-back working memory task indeed systematically downregulates the amygdala, and that deactivated clusters strongly overlap with those observed during a cognitive reappraisal task. This finding has important consequences for the interpretation of the underlying mechanism of the effects of cognitive reappraisal on amygdala activity: downregulation of amygdala during cognitive reappraisal might be due to the cognitively demanding nature of the task and not per se by the act of the reappraisal itself. Moreover, it raises the possibility of applying working memory tasks in a clinical setting as an alternative emotion regulation strategy.

## Introduction

Downregulation of the amygdala, a region critically implicated in threat detection (LeDoux, 1996; Öhman, 2005), is one of the hallmarks of successful emotion regulation. Cognitive regulation of emotion is accompanied by activation in the dorsolateral prefrontal cortex (dlPFC), a region that is part of the executive control network (Seeley et al., 2007), and downregulation of the amygdala (Buhle et al., 2014). Since there are little or no direct connections between the dlPFC and the amygdala (Amaral et al., 1992), it is commonly thought that downregulation may occur indirectly, via the ventromedial prefrontal cortex (Buhle et al., 2014).

However, this opposing interplay between the executive control network and the amygdala is not specific for emotion regulation. It has recently been noted that *any* cognitively demanding task that activates the executive control network may potentially downregulate the amygdala (de Voogd et al., 2018a). Indeed, a downregulation of the amygdala has been observed during the execution of a standard working memory task (de Voogd et al., 2018a, 2018b), with more cognitive load leading to a stronger downregulation (de Voogd, Hermans, et al., 2018). This suggests cognitive demand may play a role in the downregulation of the amygdala that is observed during emotion regulation.

Cognitively demanding tasks have been shown to be accompanied by a downregulation of defensive responses to threat. When participants perform a standard n-back working memory paradigm while simultaneously undergoing a threat conditioning paradigm, conditioned responses have been shown to be reduced (Carter et al., 2003). Moreover, threat-potentiated startle responses are decreased when participants perform a working memory paradigm (King and Schaefer, 2011; Vytal et al., 2012). Reductions in these threat-potentiated startle responses are stronger when the cognitive demand is increased (Vytal et al., 2012). Finally, also subjective reports of state anxiety were shown to decrease with increasing cognitive load of a working memory task (Balderston et al., 2016; Vytal et al., 2012).

Lesion studies in humans have indicated that such defensive responses to threat are (partly) dependent on the amygdala (Bechara et al., 1995; Klumpers et al., 2015; LaBar et al., 1995). Therefore, a cognitively demanding task may offer a non-invasive way to impact defensive responses to threat via downregulation of the amygdala. Indeed, threat-induced amygdala responses were shown to be attenuated during the execution of a cognitively

demanding task (McRae et al., 2010; Price et al., 2013). Even though the general interpretation of such findings is that an initial amygdala activation, in response to the threat, can be downregulated by a cognitively demanding task, other findings show amygdala downregulation can also be observed without the presence of a threat-induced amygdala response (de Voogd et al., 2018a, 2018b). Thus, performing a working memory task alone is sufficient to downregulate the amygdala.

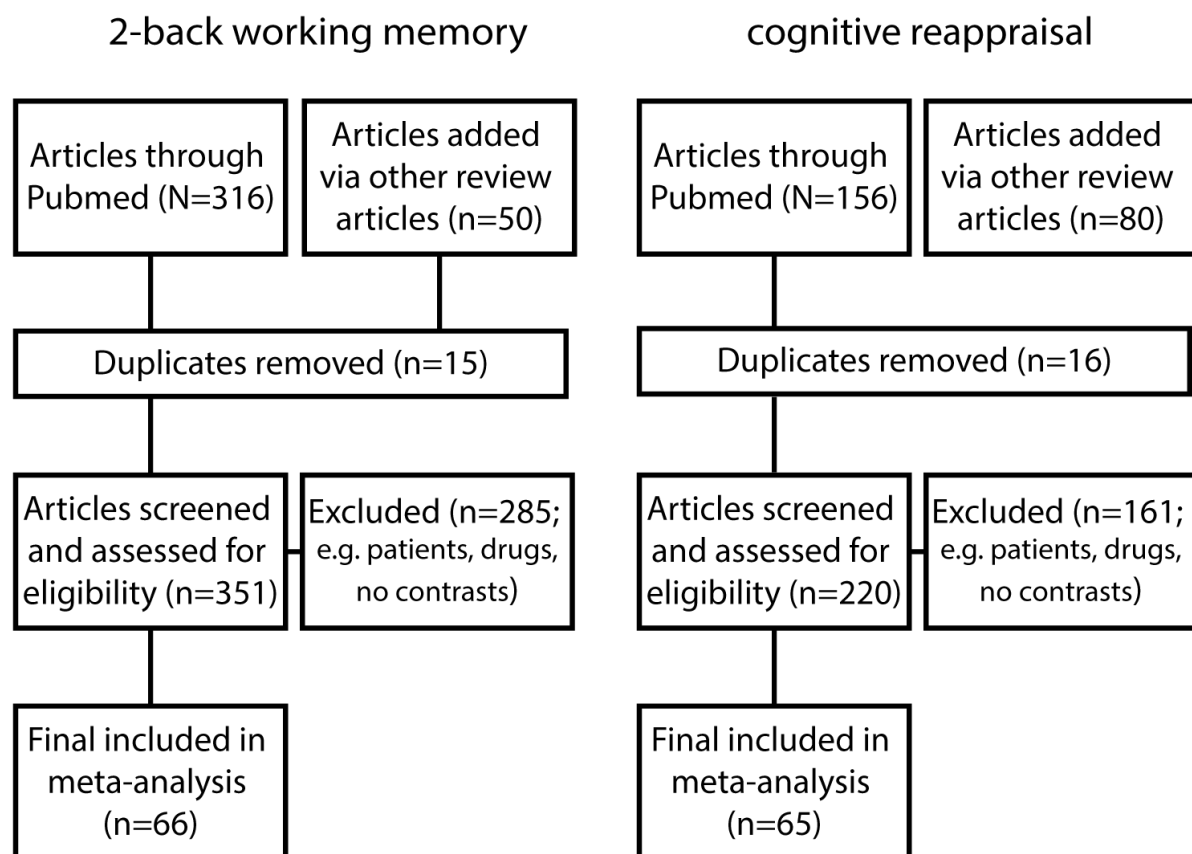
If a working memory task establishes a downregulation of the amygdala and defensive response to threat, it raises the question whether the effects of cognitive reappraisal on the amygdala are driven by cognitive demand. It has been proposed that through a reinterpretation of the threatening situation, with the explicit goal to change the affective impact of the threat, threat-related responses and amygdala reactivity is reduced (Buhle et al., 2014). Alternatively, a downregulation of amygdala during cognitive reappraisal might be due to the cognitively demanding nature of the task and not per se by the act of the reappraisal itself (de Voogd et al., 2018a). It remains unclear, however, whether downregulation of the amygdala is a consistent finding across studies on working memory. More importantly, it is unknown whether there is a systematic difference in amygdala downregulation between a working memory task and cognitive reappraisal.

The aim of this study is therefore to investigate, using a meta-analytic approach, whether working memory tasks downregulate the amygdala, and whether this downregulation is similar to cognitive reappraisal. As a standard working memory task, we opted for a “2-back” working memory task, as there are many studies available that have previously reported an activation (2-back > control) contrast (Lee and Xue, 2018). To test whether a working memory task downregulates the amygdala similar to a cognitive reappraisal task, we conducted an ALE coordinate-based meta-analysis (Eickhoff et al., 2009). We predicted a reduced BOLD signal during a standard 2-back working memory task that would overlap with the reduction in BOLD signal during cognitive reappraisal.

## Methods

### *Study and data selection for the ALE meta-analysis*

We performed the ALE meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2016). For the PRISMA flow diagram see **Fig 1**.



**Figure 1** – A flow chart describing the steps used to identify the articles that were included in the ALE meta-analysis.

Eligibility criteria: Peer-reviewed fMRI articles including healthy adult volunteers which included a 2-back working memory or a cognitive reappraisal experiment.

Information sources: The PubMed database (<https://www.ncbi.nlm.nih.gov>) and other meta-analyses (Buhle et al., 2014; Kohn et al., 2014; Lee and Xue, 2018; Ochsner et al., 2012).

Search: 1) ((2-back [Title/Abstract]) AND fmri) NOT review [Publication Type], and 2) ((cognitive reappraisal [Title/Abstract]) AND fmri) NOT review [Publication Type]. The search was performed on April 01 2020.

Study selection: Articles were included based on the following criteria: 1) healthy human adult volunteers (range between 18-45 mean years old). Articles including patient studies with a separate analysis of the control group were included, 2) whole-brain analysis, 3) Region of interest(ROI)-based analysis were excluded, except for the amygdala, 4) reporting of standardized coordinates for activation foci in Montreal Neurological Institute (MNI) or Talairach space, 5) working memory studies including a 2-back condition: the specific modality is reported (see **Table 1**) OR emotion regulation strategy that involved cognitive reappraisal: the specific technique such as reinterpretation or distancing is reported (See **Table 2**) 6) general linear model analysis (GLM) involving a 2-back < > control analysis: the control condition such as rest or 0-back is reported (see **Table 3 and Table 4**) OR GLM analysis involving a Reappraisal < > control analysis: the specific instruction such as view, watch, or attend is reported (See **Table 3 and Table 4**).

Data collection process: We performed an analysis on 66 working memory studies and 65 emotion regulation studies (See **Table 1 and 2**). All studies reported an activation contrast (2-back: 954 foci, 80 experiments; cognitive reappraisal: 799 foci, 76 experiments), but 16 (165 foci, 19 experiments) 2-back working memory studies and 29 (289 foci, 34 experiments) emotion regulation studies reported a deactivation contrast. Two 2-back studies included emotional faces as stimuli (See **Table 1**). Since these can be considered as potentially threatening stimuli, we reran the analysis without these 2 studies to ensure our findings were not driven by these two studies. The results and conclusions remained the same and we therefore included those studies in the final analysis. None of the studies reported a deactivation contrast without an activation contrast.

Data items: We collected the peak coordinates of the selected contrasts for analysis. The focus of this study are the deactivation contrasts (Control > 2-back and Control > Reappraise). We also included the activation contrasts, mainly for comparison purposes to several other meta-analyses as a validation of our procedure. See **Table 1 and Table 2** for the articles included in the ALE meta-analysis.

**Table 1 – An overview of the working memory studies included in the meta-analysis**

Author	N participants (N Females)	Source	Space	A/D	Age M (SD) or range	Domain	Stimuli	Activation contrast	Deactivation contrast
Allen et al., 2006	10 (2F)	Table 2	Tal	A	23–35 range	Visual	Letters	Sham condition (2-back > 0-back)	
Barch et al., 2007	120 (70F)	Table 4	Tal	A	27.2 (10.8)	Verbal, Nonverbal	Words, Faces	Working Memory > Encoding	
Binder et al., 2006	12 (5F)	Table 2	Tal	A	23.52 (2.52)	Verbal	Letters	2-back > 0-back	
	12 (5F)	Table 3	Tal	A	23.52 (2.52)	Nonverbal	Abstract texture patterns	2-back > 0-back	
Bleich-Cohen et al., 2014	20 (8F)	Table							
		2a	Tal	A	26.4 (2.7)	Visual	Achromatic numbers	2-back > 0-back	
Blokland, et al. 2011	319(174F)	S1	MNI	A	23.6(1.8)	Spatial	Numbers	2-back > 0-back	
Bustamante et al. 2011	15(0F)	Table 2	Tal	A	32.40 (7.56)	Auditory	Letters	2-back > 0-back	
Carlson et al. 1998	7(3F)	Table 1	Tal	A	21.1	Visuospatial	White squares	2-back > 0-back	
Chang et al. 2004	10(0F)	Table 2	Tal	A	14.4(3.2)	Visuospatial	Letter O	2-back > 0-back	
Chang et al., 2010	21 (0F)	Table 3	MNI	A	49.7 (4.3)	Visual	Letters (symbols from the Korean alphabet)	2-back > rest	
Deckersbach et al., 2008	17 (17F)	Table 3	MNI	A	25.6 (5.9)	Visual	Letters	N-back > Fixation (sad/neutral)	
Dehghan et al., 2019	24(12F)	Tabel 5	MNI	A/D	23 (2.69)	Visual	Letters	2-back > 0-back	0-back > 2-back
de Voogd et al. 2018	24(12F)	Table 1	MNI	A/D	26.95(3.6)	Visual	Numbers	2-back > fixation	fixation > 2-back
Dima et al., 2014	40 (20F)	Table II	MNI	A	31.5 (10.4)	Visual	Letters	2-back > 0-back	
Dores et al. 2017	10(4F)	Table 2	Tal	A	27.10(2.89)	Visuospatial	Grid	2 back > fixation	
Drapier et al., 2008	20 (10F)	Table 2	Tal	A	41.9 (11.6)	Visual	Letters	2-back > 0-back	
Drobyshevsky et al., 2006	31 (15F)	Table 2	Tal	A	41 (15.3)	Visual	Letters	2-back > 0-back	
Fernandez-Corcuera et al., 2013	41(17F)	Tabel 2	MNI	A/D	40.27(9.8)	Visual	Letters	2 back > baseline	baseline > 2-back
Ford et al. 2018	32(20F)	Table 3	MNI	A	30-65	Visual	Faces/places/tools/body parts	2-back > 0-back	
Garrett et al., 2011	19 (6F)	Table 3	Tal	A	34.85 (12.54)	Visual	Letters	2-back > 0-back	
González-Garrido et al., 2019	18 (7F)	Table 4	MNI	A	21.11 (4.65)	Visual	Neutral Faces	2-back > rest	
	18 (7F)	Table 5	MNI	A	21.11 (4.65)	Visual	Happy Faces	2-back > rest	
	18 (7F)	Table 6	MNI	A	21.11 (4.65)	Visual	Fear Faces	2-back > rest	
Goikolea et al. 2019	31(15F)	Table 2	Tal	A/D	31.06 (8.76)	Visual	Letters	2-back > baseline	Baseline > 2-back
		Table							
Guimond et al. 2018	20(5F)	1S	MNI	A/D	25.05(4.05)	Visual	Faces	2-back > 0-back	0-back > 2-back
Habel et al. 2007	22(0F)	Table 4	MNI	A	30.77(9.65)	Visual	Letters	2-back > 0-back	
Harding et al. 2016	25(11F)	Tabel 1	MNI	A	25.5(4.4)	Visual	Numbers	2-back > 0-back	
Honey et al., 2000	20 (0F)	Table 1	Tal	A	39.3 (13.6)	Visual	Letters	2-back > 0-back	
Honey et al., 2003	27 (6F)	Table 3	Tal	A	35.1 (9.9)	Visual	Letters	2-back > 0-back	
Johannsen et al., 2013	12 (8F)	Table 1	MNI	A	26.1 (4.7)	Visual	Letters	2-back > 0-back	
Joseph et al., 2012	8 (8F)	Table 1	MNI	A	25 (6.4)	Visual	Letters	2-back > 0-back	
	8 (8F)	Table 1	MNI	A	25 (6.4)	Visual	Letters	2-back > 0-back	
Keresztes et al., 2004	29(20F)	Table 1	MNI	A	22.93(2.26)	Visual	Letters	2-back > 0-back	
Kwon et al. 2001	15(15F)	Table 3	Tal	A	15.05(4.58)	Visual	Letters	2-back > 0-back	
Koppelstaetter et al., 2008	15(0F)	Table 2	Tal	A	25–47(5.58)	Visual	Letters	2-back > 0-back	

		Table							
Li et al., 2014	15(15F)	S1	MNI	A	19.45(1.38)	Visual	Letters	2-back > Rest	
Luo et al., 2014	25(0F)	Table 1	MNI	A/D	23.14(1.83)	Visual	Faces	2-back > 0-back	0-back > 2-back
Lycke et al., 2008	26 (14)	Table 1	Tal (from MNI)	A	23.4 (2.4)	Auditory	Letters	2 back > rest	
	26 (14)	Table 1	Tal (from MNI)	A	23.4 (2.4)	Visuospatial	Letters	2 back > rest	
Matsuo et al., 2007	15(10F)	Table 2	Tal	A	37.77(12.1)	Visual	Numbers	2-back > 0-back	
Meisenzahl et al., 2006	12(1F)	Table 3	Tal	A	33.58 (9.27)	Visual	Letters	2-back > 0-back	
	12(1F)	Table 3	Tal	A	33.58 (9.27)	Visual	Letters	2 back > 0 back (degraded)	
Monks et al., 2004	12 (0F)	Table 1	Tal	A	45.6 (3.52)	Visual	Letters	2-back > 0-back	
Oflaz et al., 2014	9 (2F)	Table 3	MNI	A	44.6 (10.2)	Visual	Letters	2-back > 0-back	
		Table 4-							
Park et al., 2011	10 (0F)	6	MNI	A/D	23.7 (0.95)	Sound	Word	2-back > 0-back	0-back > 2-back
		Table 4-							
	10 (0F)	6	MNI	A/D	23.7 (0.95)	Sound	Pitch	2-back > 0-back	0-back > 2-back
		Table 4-							
	10 (0F)	6	MNI	A/D	23.7 (0.95)	Sound	Location	2-back > 0-back	0-back > 2-back
Paskavitz et al. 2010	17(9F)	Tabel 1	Tal	A	35.08(13.73)	Visual	Letters	2-back > 0-back	
Pfefferbaum et al., 2001	10(0F)	Table 2	Tal	A/D	60.2(12.8)	Visual	Letters	2 back > rest	rest > 2-back
		Table							
Philip et al., 2016	13(9F)	3B	Tal	A	30(9)	Visual	Letters	2 back > baseline	
		Table							
Quidé et al., 2013	28 (14F)	2A	MNI	A	32.96 (10.97)	Visual	N/A	2-back > 0-back	
Ragland et al., 2002	11(5F)	Table 2	Tal	A	32.2	Visual	Letters	2-back > 0-back	
	11(5F)	Table 2	Tal	A	32.2	Visual	Fractals	2-back > 0-back	
Rämä et al., 2001	8(8F)	Table 1	Tal	A	22	Auditory	Connotation	2-back > 0-back	
Reuter et al., 2008	49 (30F)	Table 1	MNI	A	27.4 (6.3)	Visual	Numbers	2 back > 0 back	
Rodriguez-Jimenez et al. 2009	13(6F)	Table 1	Tal (from MNI)	A	30(8.19)	Auditory and Visual conjunction	Letters	2 back > 0 back	
	13(6F)	Table 1	Tal (from MNI)	A				2 back > 0 back	
Rudner et al., 2013	20 (15F)	Table 5	Tal (from MNI)	A	26.4 (5.6)	Visual	Pictures	2 back > baseline (Phonological)	
	20 (15F)	Table 5	Tal (from MNI)	A	26.4 (5.6)	Visual	Pictures	2 back > baseline (Orthographic)	
Salavert et al., 2018	41(13F)	Table 3	MNI	A/D	31.7 (9.6)	Visual	Letters	2 back > baseline	0-back > 2-back
Sanchez-Carrion et al., 2008	18 (7F)	Table 3	MNI	A	24.2 (4.7)	Visual	Numbers	2-back > 0-Back	
Scheuerecker et al., 2008	23 (4F)	Table 2	MNI	A	32.6 (9.9)	Visual	Letters	2-back > 0-back	
	23 (4F)	Table 2	MNI	A	32.6 (9.9)	Visual	Letters	2-back degraded > 0-back degraded	
Schneiders et al., 2011	48(26)	Table 1	Tal	A	23.67	Visual/Auditory	Pattens/ bird voice	2 back > 0 back pre-test	
	48(26)	Table 2	Tal	A	23.67	Visual/Auditory	Pattens/ bird voice	2 back > 0 back post-test	
Seo et al., 2012	22 (22F)	Table 2	MNI	A/D	38.27 (8.48)	Visual	Letters	2-back > 0-back	0-back > 2-back
Seo et al., 2014	34 (34F)	Table 2	MNI	A	59.3 (5.2)	Visual	Letters	2-back > 0-back	
Stoodley et al., 2012	9 (0F)	Table 2	MNI	A	25.5	Visual	Letters	2-back > 0-back	
									progressive
Stretton et al., 2012	15 (11F)	Table 2	MNI	A/D	27 (19-58 range)	Visuo-spatial	Location of dots	2-back > 0-back	deactivation



Suchan et al., 2005	13(8F)	Table 2	Tal	A	26	Visual/auditory	Pictures	2-back > 0-back	
Sumowski et al., 2010	18(15F)	Table 1	Tal	A/D	43.8(7)	Visual	Letters	2 back > rest	rest > 2-back
Sweet et al., 2010	12 (7F)	Table 1	Tal	A/D	38.67 (12.91)	Visual	Letters	2-back > 0-back	0-back > 2-back
Thermenos et al., 2011	10(5F)	Tabel 2	MNI	A/D	17.1 (1.4)	Visual	Letters	2-back > 0-back	0-back > 2-back
Thomas et al., 2005	16 (1F)	Table 3	Tal	A	37.6 (6.3)	Visual	Letters	2-back > 0-back	
Townsend et al., 2010	14 (8F)	Table 3	MNI	A	30.8 (6.0)	Visual	Letters	2-back > 0-back	
	14 (8F)	Table 3	MNI	A	30.8 (6.0)	Visual	Letters	2-back > 0-back	
Valera et al., 2005	20(8F)	Table 3	MNI	A	33(10.6)	Visual	Letters	2-back > 0-back	
Wu et al., 2017	45(21F)	Table 2	MNI	A/D	24.07(4.83)	Visual	Numbers	2-back > 0-back	0-back > 2-back
Yan et al., 2011	28(16F)	Table 1	Tal	A/D	20.4(1.4)	Visuospatial	White squares	2-back > 0-back (SL group)	0-back > 2-back
	28(16F)	Table 1	Tal	A/D	20.9(1.5)	Visuospatial	White squares	2-back > 0-back (HL group)	0-back > 2-back
Ziemus et al., 2008	9(4F)	Table2	Tal	A	44.2(9.6)	Visual	Letters	2-back > 0-back	

Notes: A= Activation, D=Deactivation

**Table 2 – An overview of the cognitive reappraisal studies included in the meta-analysis**

Author	N (Females)	Source	Space	A/D	Age M (SD)	Stimuli	Instruction	Activation contrast	Deactivation contrast
Albein-Urios et al. 2013	21(1F)	Table S2	MNI	A	31.00 (4.60)	Negative and neutral pictures	Reappraise	Suppress>Maintain	
Allard et al. 2014	34 (16F)	Table 2	Tal	A/D	23.40 (4.39)	Unpleasant film clips	Reappraise	Emotion regulation > Passive viewing	Passive viewing > Emotion regulation
Beauregard et al. 2001	10 (0F)	Table 2	Tal	A	23.5	Erotic movies	Decrease/Distance	Attempted inhibition condition > neutral	
Campbell-Sills et al. 2011	26 (22F)	Table 1	Tal	A	19.15 (1.83)	Negative pictures	Reappraise	Reduce > Maintain	
Che, 2015	29(15F)	Table 1	MNI	A	22.62(1.59)	Negative pictures	Reappraise/decrease	Reduce > maintain	
Corbalan et al. 2015	17 (9F)	Table 3 / text	MNI	A/D	41.4 (13.3)	Negative and neutral pictures	Reappraise	Decrease > Look	Look > Decrease
Cosme et al. 2018	33 (16F)	Table 3	MNI	A/D	18.12 (0.34)	Food pictures	Reappraise	Regulate > look	Look > regulate
de Wit et al. 2015	38 (20F)	Table 2	MNI	A	39.6 (11.4)	Fear, OCD related, neutral pictures	Reappraise	Attend > regulate	
Delgado et al. 2008	12 (6F)	Table 2	Tal	A/D	23.29 (3.31)	Conditioned stimulus with shock	Reappraise	Regulate CS+ > Attend CS+	Attend versus Regulate CS+ Trials
Denny et al. 2015	21 (11F)	Table S1	MNI	A	29 (6.71)	Negative and neutral pictures	Reappraise	Reappraise Cue > Look Cue	
	21 (11F)	Table S3	MNI	A	29 (6.71)	Negative and neutral pictures	Reappraise	Reappraise Negative > Look Negative	
Domes et al. 2010	33 (17F)	Table IV	MNI	A	m: 25.2 (1.9) f:24.6 (1.6)	Negative pictures	Reappraise	Decrease > Maintain	
Eippert et al. 2007	24 (24F)	Table II, III	MNI	A/D	23.3	Negative pictures	Reappraise/distance	Decrease > View	
Erk et al. 2010	17 (8F)	Table 2	MNI	A/D	43.9 (10.1)	Negative and neutral pictures	Reappraise	Regulation > No regulation	Negative no regulation > regulation
	17 (8F)	Table 2	MNI	A/D	43.9 (10.1)	Negative and neutral pictures	Reappraise		Negative no regulation > regulation
Fitzgerald et al. 2018	49 (67%F)	Table 2	MNI	A	25.24 (7.98)	Negative and neutral pictures	Reappraise	Reappraise>Look-Negative	
Giuliani et al. 2014	55 (33F)	Table 1	MNI	A/D	22.17 (2.36)	Food pictures	Reappraise	Regulate > Look	Look > Regulate
Goldin et al. 2008	17 (17F)	Table 2	Tal	A	22.7 (3.5)	Negative film clips	Reappraise	Reappraise > Watch-Negative (Early)	
Goldin et al. 2019	35(20F)	Table 3	Tal	A/D	32.2(8.9)	Autobiographical social situations	Reappraise	Reappraisal > React	React > Reappraisal
Golkar et al. 2012	58 (32F)	Table S1	MNI	A	24.02 (2.26)	Negative and neutral pictures	Reappraise	Reappraise > Attend	
Grecucci et al. 2012	21 (10F)	Table 2	MNI	A	23.5 (3.6)	Ultimate game / unfair offers	Reappraise	Unfair accepted Down > Look	

Hallam et al. 2015	20 (?F)	Table 3	Tal	A/D	20 (?)	Negative and neutral pictures	Reappraise	Implementation intention > goal intention	Goal intention > Implementation intention
Harenski and Hamman 2006	10 (10F)	Table 3	MNI	A	18-29	Moral and non-moral pictures	Reappraise	Decrease moral > odd-even baseline	
	10 (10F)	Table 3	MNI	A	18-29	Moral and non-moral pictures	Reappraise	Decrease non-moral > odd-even baseline	
Hayes et al. 2010	25 (11F)	Table 1,2	MNI	A/D	21.6 (2.5)	Negative pictures	Reappraise	Reappraise > View	View > reappraise
Hollmann et al. 2012	17 (17F)	Table 1	MNI	A	25.3 (3.1)	High-caloric food pictures	Reappraise	Regulate_tasty versus Admit_tasty	
Kanske et al. 2011	30 (17F)	Table 3	MNI	A/D	21.8 (2.1)	Negative and positive pictures	Reappraise	Reappraisal--view emotional	View emotional--reappraisal
Kanske et al. 2012	25 (18F)	ST2	MNI	A/D	43.88 (11.21)	Negative and positive pictures	Reappraise	reappraisal positive - view positive	view positive - reappraisal positive
	25 (18F)	ST2	MNI	A/D	43.88 (11.21)	Negative and positive pictures	Reappraise	reappraisal negative - view negative	view negative - reappraisal negative
Kim and Hamann 2007	10 (10F)	Table 3	MNI	A	20.7	Negative and positive pictures	Reappraise	Decrease > Watch Contrast for Negative Pictures	
	10 (10F)	Table 4	MNI	A	20.7	Negative and positive pictures	Reappraise	Decrease > Watch Contrast for Positive Pictures	
Koenigsberg et al., 2010	16(9F)	Table 1	MNI	A/D	31.8(7.7)	Negative and neutral pictures	Reappraise/distance	Distancing ≥ looking	Looking ≥ distancing
Korb et al. 2015	18 (10F)	Table 3	MNI	A/D	27	Angry prosody	Reappraise	Decrease > Feel Negative	Feel Negative > Decrease
Krendl et al. 2012	20 (10F)	Table 1	MNI	A/D	21.6	(Non)stigmatized negative pictures	Reappraise	Decrease IAPS > attend IAPS	Attend IAPS > decrease IAPS
Lang et al. 2012	15 (15F)	Table S3	MNI	A	24.73 (5.64)	Negative and neutral scripts	Reappraise/distance	Down vs. maintain	
Leiberg et al. 2012	24 (24F)	Table S2	MNI	A/D	24.1	Negative and neutral pictures	Reappraise/distance	Disengage-minus-view	View-minus-Disengage
Mak et al. 2009	12 (12F)	Table 1	MNI	A/D	24 (1.78)	Positive pictures	Reappraise	Regulate > view	View > Regulate
	12 (12F)	Table 1	MNI	A/D	24 (1.78)	Negative pictures	Reappraise	Regulate > view	View > Regulate
McRae et al. 2010	18	Tabel 3	MNI	A	24.4(3.5)	Negative and neutral pictures	Reappraise	Reappraise > Look	
McRae et al. 2008	25 (13F)	Table 1	MNI	A	m:20.36 f:20.6	Negative pictures	Reappraise	Decrease Negative > Look Negative	
Modinos et al. 2010	18 (7F)	Table 1	MNI	A	21.1 (2.8)	Negative and neutral pictures	Reappraise	Reappraisal > Negative	
Moodie et al. 2020	30(17F)	Table 2	MNI	A	24.3	Negative and neutral pictures	Reappraise	Reappraisal > Watch (Low)	Watch > Reappraisal (Low)
	30(17F)	Table 2	MNI	A	24.3	Negative and neutral pictures	Reappraise	Reappraisal > Watch (High)	Watch > Reappraisal (High)
Morawetz et al. 2017	23 (12F)	Table 2	Tal	A/D	25.70 (5.95)	Negative and neutral pictures	Reappraise/distance	Decrease > Look Negative	Look Negative > Decrease
Nelson et al. 2015	22 (11F)	Table 1	MNI	A	25.2 (5.8)	Negative and neutral pictures	Reappraise	Reappraise > Maintain	
New et al. 2009	14 (14F)	Table S3	MNI	A	31.7 (10.3)	Negative pictures	Reappraise	Diminish minus maintain	
Ochsner et al. 2002	15 (15F)	Table 1,2	MNI	A/D	21.9	Negative and neutral pictures	Reappraise	Reappraise > Attend	Attend > Reappraise
Ochsner et al. 2004	24 (24F)	Table 2,3	MNI	A/D	20.6	Negative pictures	Reappraise	Decrease > Look	Look > Decrease
Otto et al. 2014	26 (26F)	Table 1	Tal	A/D	24.9 (5.6)	Fearful faces + emotional information	Reappraise	reappraise versus look	look versus reappraise
Paret et al. 2011	21 (0F)	Table 1	MNI	A	28 (4)	Shock or no shock	Reappraise	Main effect of reappraisal (R–NR)	
Paschke et al. 2016	108 (55F)	Table S5 +			26.12 (3.7)	Negative and neutral pictures	Distance	RegulateNeg > WatchNeg	WatchNeg>RegulateNeg
		text	MNI	A/D					
Phan et al. (2005)	14(8)	Table 1	MNI	A/D	27.6(4.4)	Negative pictures	Reappraise	S > M	M > S
Price et al. 2013	11 (8F)	Table 2	Tal	A/D	22.2 (2.2)	Autobiographical Memories	Reappraise	Reappraisal > fixation	Fixation > reappraisal
Qu et al. 2017	29 (14F)	Table 1	MNI	A	19.2	Negative pictures	Reappraise	decrease-look (positive activation)	
	29 (14F)	Table 1	MNI	A	19.2	Negative pictures	Reappraise	decrease-look (negative activation)	
Sarkheil et al. 2015	14 (8F)	Table 2	Tal	A/D	range 20-27	Negative pictures	Reappraise	Reappraisal > view	View > reappraisal
Schardt et al. 2010	37 (37F)	Table 1	MNI	A/D	22.6 (2.2)	Fear, disgust, neural pictures	Reappraise	Regulation > perception	Perception>Regulation
Schienze et al. 2017	45F	Table 1	MNI	A	22.91 (3.21)	Disgusting and neutral pictures	Reappraise	Reappraisal > Passive Viewing	
Schulze et al. 2011	15F	Table S2	MNI	A/D	24.53 (2.85)	Negative and neutral pictures	Reappraise	decrease > maintain emotions HC	maintain > decrease emotions HC
Shermohammed et al. 2017	25(12F)	Table 3	MNI	A	20.89 (1.71)	Negative pictures	Reappraise	decrease-negative > look-negative	
Silvers et al. 2015	30 (13F)	Table 1	MNI	A	21.97	Negative and neutral pictures	Reappraise	Reappraise/low>Look/low	

	30 (13F)	Table 1	MNI	A	21.97	Negative and neutral pictures	Reappraise	Reappraise/high>Look/high	
Simsek et al. 2017	15	Table 3	MNI	A	22.53 (1.80)	Negative and neutral pictures	Reappraise	Reappraise Neg > Attend Negative	
Sokol-Hessner et al. (2013)	16	Table 1	Tal	A	19.8(3.1)	Monetary decisions	Reappraise	Regulate decision ME > Attend decision ME	
	14	Table S3	Tal	A/D	19.8(3.1)	Monetary decisions	Reappraise	Regulate Lose ME > Attend Lose ME	Attend Lose ME > Regulate Lose ME
Sripada et al. 2014	49 (23F)	Table 3	MNI	A/D	23.63 (1.3)	aversive or neutral pictures	reappraise	Reappraise > Maintain	Maintain > Reappraise
Staudinger et al. 2009	16 (8F)	In text	MNI	A	23.1 (3.1)	Reward anticipation	Reappraise/distance	Distance vs. Permit	
Staudinger et al. 2011	24 (13F)	Table 1	MNI	A	25.1 (2.8)	Reward anticipation	Reappraise/distance	Regulate > permit	
Van der Meer et al. 2014	20 (6F)	Table 3	MNI	A	35.5 (11.7)	Negative and neutral pictures	Reappraise	Reappraise > Attend negative HC	
Van der Velde et al. 2015	51 (?F)	Table S1	MNI	A	37.1 (10.3)	Negative and neutral pictures	reappraise	Reappraise > Attend negative	
Van der Velde et al. 2015	16 (8F)	Table S1	MNI	A	22.1 (3.6)	Negative and neutral pictures	Reappraise	Reappraise > Attend negative HC	
Vanderhasselt et al. 2013	42 (42F)	Table 1	MNI	A	21.26 (2.29)	Negative pictures	Reappraise	Target Reappraisal > Target Appraise	
Walter et al. 2009	18 (18F)	Table 1	MNI	A/D	24 (3)	Negative and neutral pictures	Reappraise	Regulation > no regulation	No regulation > regulation
Winecoff et al. 2013	31 (21F)	Tabe 1	MNI	A	25	Negative and positive pictures	Reappraise	Negative Regulate > Negative Experience (exp1)	
	31 (21F)	Table 1	MNI	A/D	25	Negative and positive pictures	Reappraise	Positive Regulate > Positive Experience (exp1)	Positive Experience > Positive Regulate
Ziv et al. 2013	27 (13F)	Table 2	Tal	A	32.6 (9.5)	Pictures of faces	Reappraise	HC only: Reappraise > React (faces task)	
	27 (13F)	Table 3	Tal	A	32.6 (9.5)	Pictures of faces	Reappraise	HC only: Reappraise > React (criticism task)	

Notes: A= Activation, D=Deactivation

### *The ALE meta-analysis procedure*

We performed the meta-analysis using the activation likelihood estimation (ALE) algorithm implemented in the software GingerALE version 3.0.2 (<http://www.brainmap.org/ale>; Eickhoff et al., 2012, 2009; Turkeltaub et al., 2012). ALE is a coordinate-based method used for performing meta-analyses of human brain imaging studies. A Full-Width Half-Maximum (FWHM) of the Gaussian function is used to blur the foci. The size of the gaussian is determined by the number of subjects in each experiment. An ALE image is created based on all coordinates. Significance is determined via a permutation procedure which we set to 1000 permutations. We used a cluster-forming voxel-level threshold of  $p < 0.001$  (uncorrected). Alpha was set at 0.05, whole-brain family-wise error (FWE) corrected at the cluster level. Before the analysis, we converted all coordinates in Talairach space to MNI space using the GingerALE foci converter tool. The analyses were done on the MNI coordinates.

In addition, we performed a comparison analysis on the deactivation contrasts (Control > 2-back and Control > Reappraise) including a conjunction and subtraction analysis. In the conjunction analysis, a conjunction image was created using the voxel-wise minimum value of the two contrast (Control > 2-back and Control > Reappraise) ALE maps. The conjunction output image shows the similarity in clusters between the two contrast maps. In the subtraction analysis, two contrast (Control > 2-back and Control > Reappraise) ALE maps are directly subtracted from each other. In addition, we performed a “pooled” analysis following the procedure described above, including the coordinates from both contrasts. The pooled data was subsequently used for permutation testing where the data was randomly assigned to one of the two contrasts and repeated 10,000 times. The subtraction maps were tested against this null distribution.

Anatomical labels provided by the GingerALE software are derived from the Talairach Daemon atlas ([talairach.org](http://talairach.org)). For the amygdala deactivation clusters, we reported the % of that cluster falling in the amygdala based on those labels.

## Results

### *ALE meta-analysis activation contrasts*

We first verified regions that were systematically activated during a 2-back working memory task or a cognitive reappraisal task compared to a control task (i.e., 2-back > Control and Reappraisal > Control). We found 10 clusters for the 2-back > Control contrast among which are located in the left [cluster #1,  $z = 9.34$ ,  $p = 4.95E-21$ ,  $mm3 = 23680$ ] and right [cluster #2,  $z = 8.44$ ,  $p = 6.53E-18$ ,  $mm3 = 18840$ ] dorsolateral prefrontal cortex (dlPFC), the left [cluster #3,  $z = 10.32$ ,  $p = 2.69E-25$ ,  $mm3 = 12440$ ] and right [cluster #4,  $z = 9.92$ ,  $p = 2.36E-19$ ,  $mm3 = 12296$ ] posterior parietal cortex (PPC), the left [cluster #1,  $z = 9.34$ ,  $p = 4.95E-21$ ,  $mm3 = 23680$ ] and right [cluster #2,  $z = 8.44$ ,  $p = 6.53E-18$ ,  $mm3 = 18840$  and cluster #6,  $z = 12.84$ ,  $p = 4.82E-38$ ,  $mm3 = 5104$ ] anterior insula, and the left/right [cluster #5,  $z = 8.03$ ,  $p = 5.03E-16$ ,  $mm3 = 9032$ ] dorsal anterior cingulate cortex (dACC). See **Table 3** for a full overview of the clusters and statistics.

We found 9 clusters for the Reappraisal > Control contrast among which are the left [cluster #3,  $z = 6.91$ ,  $p = 2.46E-12$ ,  $mm3 = 7320$ ] and right [cluster #8,  $z = 5.61$ ,  $p = 1.01E-08$ ,  $mm3 = 2.46E-12$ ] dorsolateral prefrontal cortex (dlPFC), the left [cluster #2,  $z = 8.10$ ,  $p = 2.81E-16$ ,  $mm3 = 9136$ ] and right [cluster #4,  $z = 8.44$ ,  $p = 6.53E-18$ ,  $mm3 = 18840$  and cluster #6,  $z = 7.69$ ,  $p = 7.60E-15$ ,  $mm3 = 6552$ ] anterior insula, and the left/right [cluster #1,  $z = 8.80$ ,  $p = 6.66E-19$ ,  $mm3 = 10880$ ] dorsal anterior cingulate cortex (dACC). See **Table 3** for a full overview of the clusters and statistics.

Together these findings are in line with previous meta-analyses' reports of activation patterns during working memory (Wager and Smith, 2003), a 2-back working memory task (Lee and Xue, 2018), and a cognitive reappraisal task (Buhle et al., 2014; Kohn et al., 2014; Lee and Xue, 2018).

### *ALE meta-analysis deactivation contrasts*

The main aim of this study was to investigate whether the amygdala is systematically downregulated during working memory in a similar fashion as it is during emotion regulation.

Indeed, for the Control > 2-Back working memory contrast we saw clusters in the left [cluster #3,  $z = 5.53$ ,  $p = 1.56E-08$ ,  $mm3 = 1952$ ] and right [cluster #4,  $z = 5.70$ ,  $p = 6.16E-09$ ,  $mm3 = 1160$ ] amygdala. These clusters fall for 82.6% within the left amygdala and 91.5% within

the right amygdala. We also observed a cluster in left/right [cluster #2,  $z=6.18$ ,  $p=3.27E-10$ ,  $mm3=5480$ ] ventral medial prefrontal cortex (vmPFC), and the left/right [cluster #1,  $z=6.63$ ,  $p=1.68E-11$ ,  $mm3=5568$ ] posterior cingulate cortex (PCC). See **Figure 2 and Table 4**.

For the Control > Reappraisal contrast we also observed clusters in the left [cluster #2,  $z=9.02$ ,  $p=9.55E-20$ ,  $mm3=2992$ ] and right [cluster #1,  $z=7.45$ ,  $p=4.70E-14$ ,  $mm3=3728$ ] amygdala, [cluster #3,  $z=5.75$ ,  $p=4.55E-09$ ,  $mm3=952$ ] which overlap with the amygdala clusters found during the Control > 2-Back contrast. These clusters falls for 75.8% within the left amygdala and 59.2% within the right amygdala. See **Figure 2 and Table 4**.

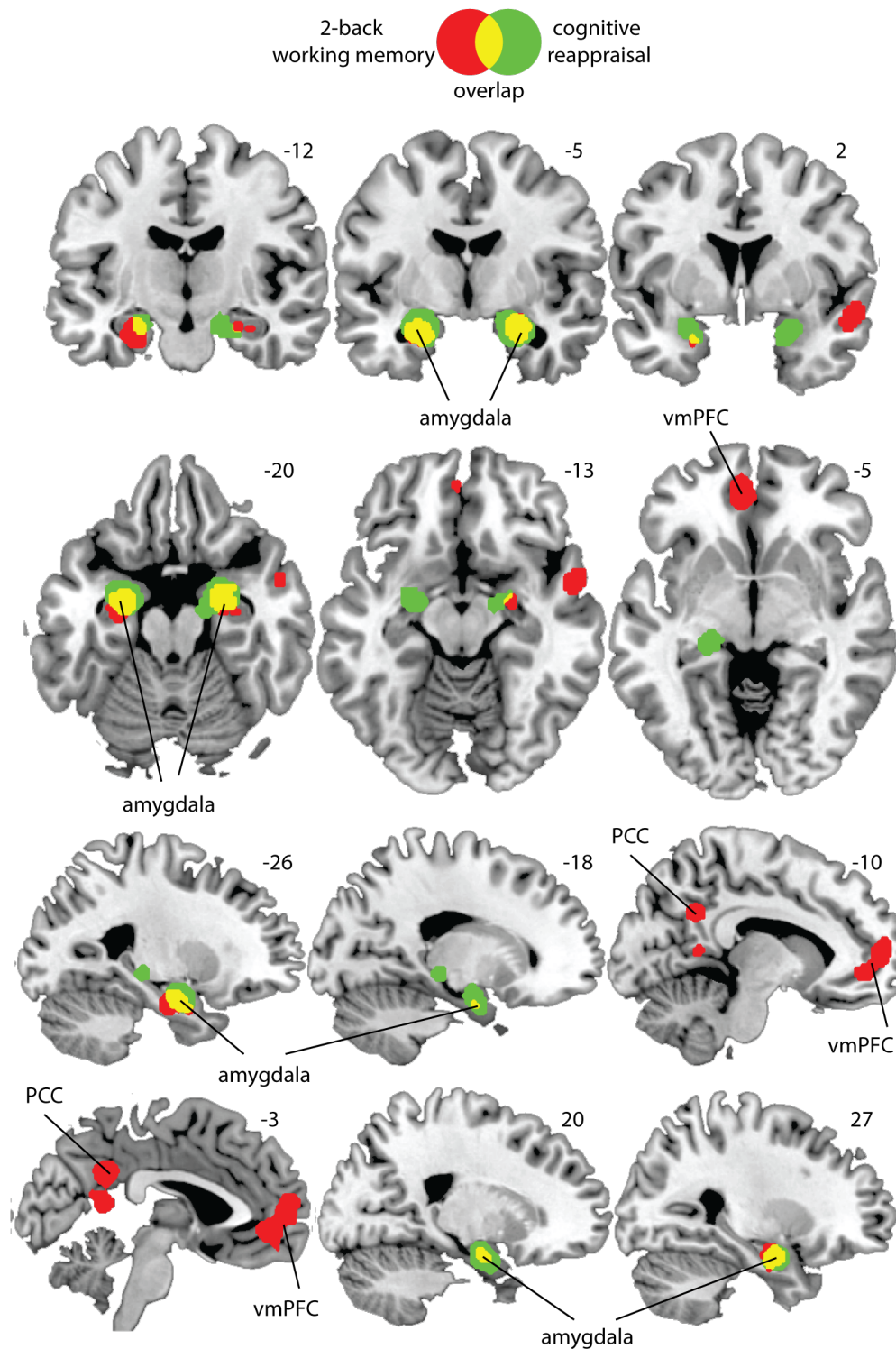
In sum, there is reduced amygdala activity during cognitive reappraisal compared to a control task, as has been shown before (Buhle et al., 2014). Critically, this is also the case during a 2-back working memory task compared to a control task.

#### *Comparison analysis of the deactivation contrasts*

Finally, we performed a comparison analysis between the deactivation contrasts (Control > 2-back and Control > Reappraise). The conjunction analysis revealed there is an overlap in deactivation patterns during cognitive reappraisal and the 2-back working memory task in the amygdala [left: 96.7% falls within the amygdala, right: 91.1% falls within the amygdala]. The subtraction analysis revealed that a cluster partly falling within the amygdala [left: 55% falls within the amygdala, 30% falls in the dorsal entorhinal cortex (BA34)] was present stronger for cognitive reappraisal compared to the 2-back working memory task, and a cluster partly falling within the amygdala [left: 5% falls in the amygdala, 90% falls in the hippocampus] was present for the 2-back working memory task compared to cognitive reappraisal.

In sum, both 2-back working memory and cognitive reappraisal tasks show bilateral clusters of common deactivation in the amygdala. The deactivation clusters associated with both tasks do differ somewhat in their topography, with stronger deactivation extending from (left) amygdala toward entorhinal cortex for cognitive reappraisal, and toward hippocampus for working memory. See **Figure 3 and Table 5**.

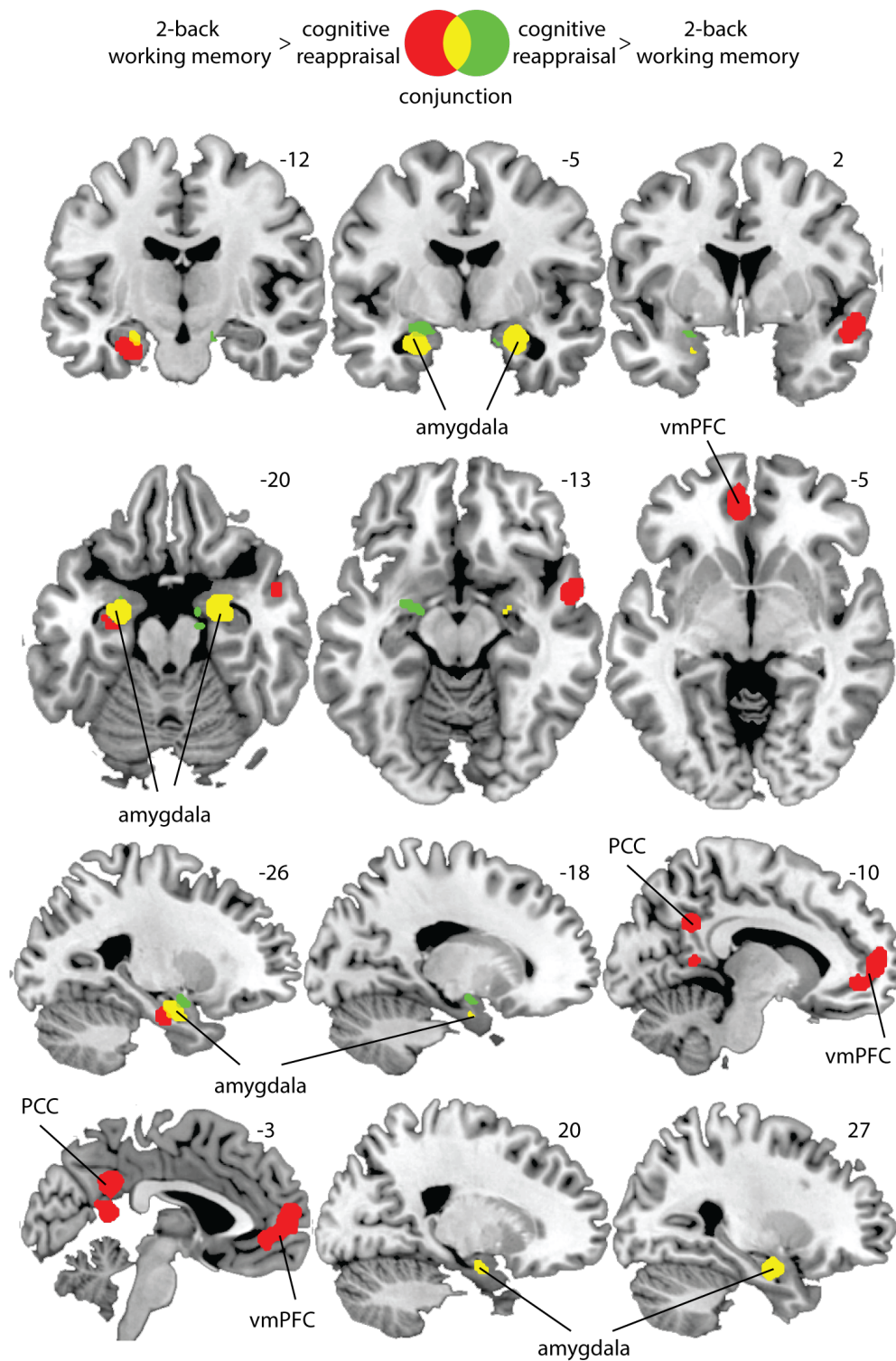
## ALE meta-analysis: deactivation



**Figure 2** – Display of the significant clusters for the ALE meta-analysis on the deactivation contrasts Control > 2-Back (red) and Control > Cognitive reappraisal (green) and the overlap (yellow).



## ALE meta-analysis: deactivation



**Figure 3** – Display of the significant clusters for the ALE meta-analysis on the differences in deactivation contrasts Control > 2-Back (red) and Control > Cognitive reappraisal (green) and the conjunction of the two where the show common activation (yellow).



**Table 3 – Significant clusters from the ALE meta-analysis showing an activation pattern**

Cluster #	Region	Side	X (mm)	Y (mm)	Z (mm)	mm <sup>3</sup>	ALE	P	Peak Z
<i>WM activation (2-back &gt; Control)</i>									
#1	anterior insula / dorsolateral prefrontal cortex (dlPFC)	L	-32	22	0	23680	0.078	4.95E-21	9.34
			-42	8	30		0.076	3.56E-20	9.13
			-40	-8	40		0.046	6.95E-11	6.42
			-28	-2	52		0.043	5.97E-10	6.08
			-30	-8	48		0.039	7.72E-09	5.66
			-36	38	24		0.034	1.90E-07	5.08
#2	anterior insula / dorsolateral prefrontal cortex (dlPFC)	R	30	6	58	18840	0.069	6.53E-18	8.54
			40	28	30		0.062	1.11E-15	7.93
			30	-2	48		0.057	6.43E-14	7.41
			32	38	22		0.042	1.63E-09	5.92
			32	46	20		0.039	1.08E-08	5.60
			36	6	32		0.039	1.09E-08	5.60
#3	posterior parietal cortex / angular gyrus	L	44	12	26	12440	0.029	2.67E-06	4.55
			22	-12	58		0.020	4.90E-04	3.30
			-42	-44	42		0.090	2.69E-25	10.33
			-28	-60	38		0.077	1.38E-20	9.23
			-34	-54	46		0.070	2.27E-18	8.66
			-20	-70	54		0.021	2.58E-04	3.47
#4	posterior parietal cortex / angular gyrus	R	30	-62	44	12296	0.073	2.36E-19	8.92
			40	-46	42		0.071	1.07E-18	8.75
#5	dorsal anterior cingulate cortex	L/R	-2	8	50	9032	0.063	5.03E-16	8.03
			8	26	32		0.029	3.54E-06	4.49
#6	anterior insula	R	32	22	-2	5104	0.123	4.82E-38	12.84
#7	cerebellum		30	-62	-32	3688	0.036	6.64E-08	5.28
			26	-60	-20		0.030	1.49E-06	4.67
			40	-62	-18		0.027	9.14E-06	4.28
#8	fusiform gyrus	L	-40	-60	-18	2240	0.032	7.37E-07	4.81
			-32	-64	-30		0.027	1.07E-05	4.25
#9	caudate / putamen	L	-16	-2	16	1464	0.034	1.53E-07	5.12
#10	middle frontal gyrus	L	-36	56	14	1456	0.037	3.24E-08	5.41
<i>CR activation (Reappraisal &gt; Control)</i>									
#1	dorsal anterior cingulate cortex	L/R	-6	14	62	10880	0.072	6.66E-19	8.80
			12	18	62		0.037	2.28E-08	5.47
			4	28	40		0.031	7.13E-07	4.82

			20	12	60		0.029	2.46E-06	4.57
			-6	24	44		0.024	2.70E-05	4.04
			-2	36	38		0.024	3.30E-05	3.99
			2	20	46		0.022	1.06E-04	3.70
#2	anterior insula	L	-46	28	-8	9136	0.063	2.81E-16	8.10
			-52	22	-2		0.045	1.06E-10	6.35
			-42	46	-6		0.037	1.92E-08	5.50
#3	dorsolateral prefrontal cortex (dlPFC)	L	-44	6	48	7320	0.051	2.46E-12	6.91
			-40	20	46		0.039	5.25E-09	5.72
#4	anterior insula	R	50	30	-8	6552	0.059	7.60E-15	7.69
			48	44	-10		0.035	4.38E-08	5.35
			50	18	-4		0.034	9.59E-08	5.21
			58	24	6		0.028	3.94E-06	4.47
			40	22	-12		0.021	1.59E-04	3.60
#5	middle temporal gyrus / angular gyrus	L	-42	-56	22	5488	0.039	5.08E-09	5.73
			-56	-52	44		0.036	4.20E-08	5.36
			-50	-64	42		0.034	8.50E-08	5.23
			-52	-62	34		0.032	3.04E-07	4.99
			-60	-52	20		0.023	7.03E-05	3.81
			-62	-50	32		0.023	7.37E-05	3.80
#6	middle temporal gyrus	L	-60	-38	-4	4768	0.063	5.24E-16	8.02
#7	angular gyrus	R	60	-54	38	3768	0.051	1.90E-12	6.94
#8	dorsolateral prefrontal cortex (dlPFC)	R	40	22	44	2712	0.038	1.01E-08	5.61
			50	6	46		0.027	7.55E-06	4.33
			44	12	44		0.024	2.76E-05	4.03
#9	middle cingulate cortex	L/R	-2	-22	28	1008	0.035	5.94E-08	5.30

Notes: All coordinates are defined in MNI152 space. All statistics listed are significant at  $p < 0.05$ , whole-brain FWE- corrected using a cluster forming threshold of  $p < .0001$  uncorrected, and a permutation test with 1000 permutations.

**Table 4 – Significant clusters from the ALE meta-analysis showing a deactivation pattern**

Cluster #	Region	Side	X (mm)	Y (mm)	Z (mm)	mm^3	ALE	P	Peak Z	
WM deactivation (Control > 2-back)										
#1	posterior cingulate cortex / precuneus	L/R	-4	-50	30	5568		0.031	1.68E-11	6.63
			-4	-52	12			0.019	6.18E-07	4.85
			4	-50	18			0.013	5.53E-05	3.87
			-6	-60	16			0.011	2.55E-04	3.48
			16	-56	30			0.011	3.67E-04	3.38
			8	-58	20			0.010	6.24E-04	3.23
#2	ventromedial prefrontal cortex (vmPFC)	L/R	-6	58	10	5480		0.028	3.27E-10	6.18
			-6	46	-4			0.020	3.88E-07	4.94
			4	62	14			0.016	4.97E-06	4.42
			-2	52	-16			0.010	6.57E-04	3.21
#3	amygdala / hippocampus	L	-24	-8	-22	1952		0.023	1.56E-08	5.53
#4	amygdala	R	24	-6	-20	1160		0.024	6.16E-09	5.70
#5	angular gyrus	L	-48	-64	28	1120		0.022	3.73E-08	5.38
#6	middle / superior temporal gyrus	R	54	4	-16	872		0.016	1.03E-05	4.26
			58	4	-12			0.015	1.88E-05	4.12
CR deactivation (Control > Reappraisal)										
#1	amygdala / dorsal entorhinal cortex (BA34)	R	26	-4	-20	3960		0.045	6.57E-15	7.70
			18	-8	-16			0.028	9.83E-09	5.62
#2	amygdala / dorsal entorhinal cortex (BA34)	L	-24	-6	-18	3000		0.058	1.78E-20	9.20
#3	thalamus / parahippocampal gyrus	L	-22	-28	-4	688		0.026	3.77E-08	5.38

*All coordinates are defined in MNI152 space. All statistics listed are significant at  $p < 0.05$ , whole-brain FWE- corrected using a cluster forming threshold of  $p < .0001$  uncorrected, and a permutation test with 1000 permutations.*

**Table 5 – Significant clusters from the ALE meta-analysis comparing the deactivation patterns**

Cluster #	Region	Side	X (mm)	Y (mm)	Z (mm)	mm <sup>3</sup>	ALE	P	Peak Z
<i>Conjunction</i>									
#1	amygdala	L	-24	-8	-22	1232		0.023	na
#2	amygdala	R	24	-6	-20	1064		0.024	na
<i>2-back &gt; reappraisal</i>									
#1	posterior cingulate cortex / precuneus	L/R	-1	-51	29	5048		na	> 0.001
			-6	-49	16			na	1.00E-04
			-4	-56	18			na	8.00E-04
			14	-56	28			na	0.001
#2	ventromedial prefrontal cortex (vmPFC)	L/R	-2	59	8	5008		na	> 0.001
#3	angular gyrus	L	-49	-66	30	1120		na	1.00E-04
			-49	-62	23			na	0.001
#4	middle temporal gyrus	R	53	3	-18	872		na	1.00E-04
			58	7	-14			na	3.00E-04
#5	amygdala / hippocampus	L	-30	-12	-24	560		na	0.006
#6	precuneus	R	8	-58	22	32		na	0.019
<i>reappraisal &gt; 2-back</i>									
#1	amygdala / dorsal entorhinal cortex (BA34)	L	-24	0	-14	616		na	0.004
#2	dorsal entorhinal cortex (BA34)	R	14	-6	-20	40		na	0.035

*All coordinates are defined in MNI152 space. All statistics listed are significant at  $p < 0.05$ .*

## Discussion

Using a meta-analytic approach, we investigated whether a standard working memory task would downregulate the amygdala similarly to a cognitive reappraisal task. Amygdala deactivation is widely considered as a key neural correlate of cognitive regulation of emotion, and has been documented previously in a meta-analysis of cognitive reappraisal studies (Buhle et al., 2014). We indeed replicate these findings, but critically reveal that a working memory task also robustly triggers deactivation in bilateral clusters in the amygdala, although the extent and topography of the deactivated clusters differed somewhat between the two tasks. Together, our findings suggest that the effects of cognitive reappraisal on the amygdala are driven by cognitive demand rather than the content of the reappraisal.

Downregulation of the amygdala during cognitive reappraisal has typically been interpreted as a top-down inhibition by prefrontal regions (e.g., Etkin et al., 2011). The amygdala is a region critically implicated in threat detection, as has been detailed in animal models (LeDoux, 1996). Indeed, functional MRI studies in humans have revealed activation of the amygdala related to processing of threatening or salient stimuli (Hariri et al., 2002; Morris et al., 1997; Vuilleumier et al., 2001). Via reinterpretation of the threatening situation, with the explicit goal to change the affective impact of the threat, such amygdala reactivity is thought to be reduced. Amygdala downregulation during cognitive reappraisal was furthermore shown to be enhanced by real-time fMRI neurofeedback based on dlPFC responsivity (Sarkheil et al., 2015). Since there are little or no direct connections between the dlPFC and the amygdala (Amaral et al., 1992), downregulation is thought to occur indirectly via the ventromedial prefrontal cortex (Buhle et al., 2014), a region involved in implicit forms of emotion regulation such as extinction learning (Hartley and Phelps, 2010). Thus, the commonly held view is that the act of cognitive reappraisal, through neural pathways that are shared with other emotion regulation strategies, leads to a downregulation of the amygdala reactivity to threat.

However, our findings demonstrate that a standard working memory task is also accompanied by a downregulation of the amygdala. This suggests that the content of the cognitive task may not be relevant. While at odds with theories of cognitive reappraisal, this notion is in line theories postulating a reciprocal relationship between large-scale neural systems encompassing dlPFC (the executive control network) and amygdala (the salience network; Hermans et al., 2014). For instance, acute threat is known to trigger activation of

the salience network, and this is accompanied by a loss of executive control network function (Hermans et al., 2014). Most evidence for this comes from studies that have investigated the impact of acute threat and arousal on executive functioning. For example, behavioral studies have shown that during high states of arousal, working memory performance is impaired (Elzinga and Roelofs, 2005; Lupien et al., 1999). This trade-off also occurs at the network level, namely, when participants perform a working memory task while under threat, BOLD signal in the executive control network is reduced compared to a non-threatening context (Van Ast et al., 2016). Furthermore, the dynamics between the salience network and the central executive control network was shown to change during acute threat (Young et al., 2017).

Our findings suggest that such a trade-off between the salience network and the executive control network may also occur the other way around. This idea is in line with previous studies indicating that defensive responses which have shown to be (partly) dependent on the amygdala (Bechara et al., 1995; Klumpers et al., 2015; LaBar et al., 1995), are reduced during cognitively demanding tasks. For instance, during working memory maintenance, threat conditioning is impaired (Carter et al., 2003), and threat-potentiated startle responses are decreased (Vytal et al., 2012). Other types of cognitively demanding tasks, apart from the 2-back working memory task we investigated here, also downregulate the amygdala. Examples are playing a game of Tetris (Price et al., 2013) or making goal-directed eye movements (de Voogd et al., 2018b; Jamadar et al., 2013). Cognitive demand may indeed lead to a competition between the executive control network and the salience network, where resources are allocated to the executive control network at the expense of the salience network (de Voogd et al., 2018a). Thus, the reduced BOLD signal found in the amygdala during cognitive reappraisal and working memory tasks is in line with a vast body of literature showing reciprocal relationships between large-scale neural systems.

If the executive control network and the salience network are reciprocally activated with respect to one another in both directions, an important question that remains to be answered is how this competitive allocation of resources is established. A first possibility is that resource allocation is established via active suppression. This may occur during a working memory task in a similar fashion as has been proposed for cognitive reappraisal. Namely, downregulation of the amygdala may occur indirectly via the vmPFC (Buhle et al., 2014). This mechanism is similar to the proposed working mechanism of implicit emotion regulation such as extinction learning (Hartley and Phelps, 2010), since during extinction, it has been shown

the amygdala is inhibited by the ventromedial prefrontal cortex (vmPFC), leading to a reduction in the expression of threat responses (Milad and Quirk, 2012). Indeed, it has been proposed that the vmPFC may serve as a common mechanism for reducing learned defensive responses to threat (Schiller and Delgado, 2010). This pathway may be activated via several pathways including those involved in high-order cognition such as the dlPFC, and our findings suggest that the specific content of the cognitive process may not be a critical factor.

It is worthwhile to also consider other potential explanations for the reciprocal relationship between dlPFC and amygdala as observed using functional MRI. One alternative possibility is that when one large-scale network activates, an increase in blood flow to those regions may deplete other neural systems from oxygenated blood, resulting in decreased BOLD-fMRI signal. Recent findings indicate that BOLD signal in specific functional brain networks may indeed be partly driven by vascular regulation (Bright et al., 2020). The fact that alterations in amygdala-dependent functions are seen during cognitively demanding tasks that elicit reduced BOLD in the amygdala (Carter et al., 2003; de Voogd et al., 2018a, 2018b; Fox et al., 2009; Hermans et al., 2014) appears to speak against the notion that this BOLD signal decrease is a purely vascular effect. However, it is also possible that depletion of oxygenated blood may itself affect neuronal activity. There is indeed evidence that vascular changes can influence neuronal activity (Croal et al., 2015; Hall et al., 2011). Future studies should therefore determine whether amygdala downregulation during cognitively demanding tasks is also observed using electrophysiological methods, which more directly measure neuronal activity.

If a cognitively demanding task can reduce threat-related processes (Carter et al., 2003; Vytal et al., 2012) via downregulation of the amygdala, this may have clinical implications. Interestingly, a cognitively demanding task that involves goal-directed attention may already be part of a therapy, namely, in the case of Eye Movement Desensitization and Reprocessing (EMDR; Shapiro, 1989). EMDR is an evidence-based therapy for treatment of fear and anxiety-related disorders (Bisson et al., 2013; Lee and Cuijpers, 2013). This therapy has been widely used in clinical populations, but a mechanistic understanding of the role of eye movements in this therapy is still largely unclear. Laboratory studies have shown that making cognitively demanding eye movements (de Voogd et al., 2018b) or a working memory task (de Voogd and Phelps, 2020; Loos et al., 2020) embedded during extinction learning reduces defensive responses to threat in healthy (de Voogd et al., 2018b; de Voogd and

Phelps, 2020) and phobic (Loos et al., 2020) participants. These cognitively demanding tasks during extinction learning were accompanied by downregulation of the amygdala (de Voogd et al., 2018b; Loos et al., 2020). It could therefore be the case that an additional inhibition of the amygdala during extinction can strengthen safety learning.

If indeed cognitive demand is the mechanism underlying cognitive reappraisal, then any task that is cognitively demanding may potentially be a suitable intervention to reduce defensive responses to threat, and potentially have added value in a clinical setting. An ideal intervention, however, should allow for the cognitive demand to be systematically increased to accommodate individual differences in cognitive capacity. The cognitive demand of a working memory task can be systematically increased and has a greater impact on the reduction of BOLD signal in the amygdala (de Voogd et al., 2018a). In comparison to cognitive reappraisal, which is one of the most common cognitive emotion regulation strategies translated to the clinic (Kredlow et al., 2020), compliance with task instructions and task performance in working memory tasks are easier to assess. Moreover, working memory tasks typically impair episodic memory for threatening events (Onderdonk and van den Hout, 2016), while cognitive reappraisal typically enhances episodic memory for threatening events (Dillon et al., 2007; Hayes et al., 2010), likely due to increased attention and encoding (Hayes et al., 2010). Since our findings indicate that they operate via similar neural pathways, working memory tasks may have benefits over cognitive reappraisal as a treatment intervention.

It has been argued that distraction during exposure may be counterproductive as it leads to avoidance. It may therefore be the case that performing a cognitively demanding task during treatment may induce distraction and thereby avoidance. However, empirical evidence suggest that in some cases, distraction may be more beneficial than focused exposure (see, for a review, Podinã et al., 2013). Moreover, goal-directed eye movements as used in EMDR could also be seen as distraction, but have been shown to have beneficial effects on threat-related symptoms compared to exposure or extinction alone (de Voogd et al., 2018b; de Voogd and Phelps, 2020; Lee and Cuijpers, 2013).

We observed that only a subset of the articles included in our meta-analysis reported a deactivation contrast. This was the case for the 2-back working memory studies (i.e., 16 out of 66 studies) and the cognitive reappraisal studies (i.e., 29 out of 65 studies). It is possible that underreporting of deactivation contrasts has consequences for the conclusion of our findings. We cannot rule out that a systematic bias has led to the decision to report or not to



report deactivation patterns. It may be that studies that have reported deactivation patterns may have done so because the results were in line with the expectation. This may be specifically true for cognitive reappraisal studies, as amygdala downregulation forms an important part of the mechanistic explanation of how reappraisal is established. Moreover, we observed that from the studies that contributed to the amygdala deactivation during cognitive reappraisal, 12 out of the 16 reported amygdala deactivations based on Small Volume Correction (SVC), while only one of the six studies that contributed to the amygdala deactivation during working memory reported amygdala deactivation based on SVC. It is therefore possible that this bias has led to an overrepresentation of amygdala deactivation for cognitive reappraisal. We propose that patterns of downregulation are meaningful and that it is therefore important to report BOLD deactivation patterns as well. This will ultimately contribute to a broader understanding of the role of network dynamics in the brain and its relation to function.

Although we observed a striking overlap in amygdala deactivation between working memory and cognitive reappraisal, we also observed that the overlap was not absolute. We observed two deactivation clusters in the left amygdala that were unique for either cognitive reappraisal or working memory. For cognitive reappraisal, this deactivation was located dorsally with respect to the conjunction deactivation, within the amygdala and Brodmann area 34. For working memory, the location of the deactivation was more ventral, within the amygdala and hippocampus. This can be interpreted in a few ways. First, it is possible that the deactivation across the two tasks is not identical and both lead to a deactivation pattern that is unique to the task that is being conducted. Second, an alternative explanation could be that the difference is due to a bias in reporting. Since the amygdala deactivation during cognitive reappraisal is largely based on an SVC, it is possible that this influences the location of the reported peak voxel (i.e., this would always lie within the amygdala). Several studies have shown that deactivation patterns during a working memory task are present in both amygdala and hippocampus (Cousijn et al., 2010; de Voogd et al., 2018b; Qin et al., 2009). It is therefore possible that with an SVC, the reporting of the peak value is more biased towards the hippocampus in working memory studies. To resolve this, a study directly comparing working memory and cognitive reappraisal would be necessary to investigate whether the deactivation patterns are similar or meaningfully distinct.

In conclusion, using meta-analytic evidence, we demonstrate that both cognitive reappraisal tasks and working memory tasks deactivate the amygdala, thus suggesting that the amygdala deactivation is driven by cognitive demand rather than the actual reinterpretation of a threatening stimulus. Our findings are in line with accounts of brain function in terms of reciprocal activation or competition between large-scale neural networks.

### **Acknowledgements**

We thank Lieke Martens, Habiba Schiller, and Zhiwei Zheng for their assistance. This work was supported by the European Research Council (ERC-2015- CoG 682591) awarded to EJH.

### **Conflict of interest**

The authors report no conflict of interest.

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