Compassion-based emotion regulation up-regulates experienced positive affect and associated neural networks

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Emotion regulation research has primarily focused on techniques that attenuate or modulate the impact of emotional stimuli. Recent evidence suggests that this mode regulation can be problematic in the context of regulation of emotion elicited by the suffering of others, resulting in reduced emotional connectedness. Here, we investigated the effects of an alternative emotion regulation technique based on the up-regulation of positive affect via Compassion-meditation on experiential and neural affective responses to depictions of individuals in distress, and compared these with the established emotion regulation strategy of Reappraisal. Using fMRI, we scanned 15 expert practitioners of Compassion-meditation either passively viewing, or using Compassion-meditation or Reappraisal to modulate their emotional reactions to film clips depicting people in distress. Both strategies effectively, but differentially regulated experienced affect, with Compassion primarily increasing positive and Reappraisal primarily decreasing negative affect. Imaging results showed that Compassion, relative to both passive-viewing and Reappraisal increased activation in regions involved in affiliation, positive affect and reward processing including ventral striatum and medial orbitofrontal cortex. This network was shown to be active prior to stimulus presentation, suggesting that the regulatory mechanism of Compassion is the stimulus-independent endogenous generation of positive affect.

Keywords: compassion; reappraisal; emotion regulation; fMRI

INTRODUCTION

Research has demonstrated that exposure to others' pain elicits negative affective responses on both an experiential and physiological level (Lamm *et al.*, 2011). Consequently, being confronted with the suffering of others can be a potent source of personal distress. Prolonged exposure to suffering can therefore have deleterious mental health effects. This is seen in the high stress levels and burnout rates often reported for professionals tasked with caring for suffering individuals, such as physicians (Shanafelt *et al.*, 2012) and nurses (Adriaenssens *et al.*, 2014). With this in mind, identifying effective emotion regulation strategies that can be employed to promote resilience for exposure to others' suffering is potentially of great help both for the individual and society at large.

One particularly effective strategy for regulating negative emotional responses involves the cognitive generation of alternate interpretations of an emotional event, thereby modulating their emotional meaning and impact (McRae *et al.*, 2012a). This strategy, most frequently called Reappraisal, has been shown to be effective across a wide range of different emotional stimuli and contexts (Gross, 2014). Furthermore, trait use of Reappraisal is a predictor of psychological well-being and resilience (McRae *et al.*, 2012b; Min *et al.*, 2013). As such, Reappraisal is as a strong candidate for an effective means of coping with exposure to the suffering of others. However, recent research has identified a potentially problematic side effect of using Reappraisal to regulate ones

affective reactions to the suffering of others: Cameron and Payne (2011) demonstrated that Reappraisal can lead to decreased concern and willingness to help, especially when multiple individuals are suffering, and when helping is costly. One explanation for this is that Reappraisal involves discounting negative information as it is perceived, and substituting a more positive interpretation. Although an effective panacea for personal distress, this mechanism in effect disconnects the Reappraiser from the communicated affective experience when applied to stimuli signaling others' suffering. Thus, Reappraisal might not be the optimal strategy in contexts where an inter-individual emotional connection is required.

One promising way to supplement traditional emotion regulation strategies is the use of meditation techniques. In the context of suffering, one particularly promising technique is Compassion-meditation. The emotional state of compassion[1] can be defined as the emotion one experiences when feeling concern for another's suffering and desiring to enhance that individual's welfare (Goetz *et al.*, 2010). Training in Compassion-meditation aims at enabling the individual to volitionally generate states of compassion, allowing them to encounter the suffering of others while maintaining a positive emotional state of benevolence, warmth and concern and a motivation to help (Lutz *et al.*, 2008; Klimecki *et al.*, 2013a; Kok *et al.*, 2013). Concretely, Compassion-meditation involves the initial generation of an emotional state of loving-kindness through directed imagery emphasizing positive emotional qualities of warmth, care and other-related concern. Once this emotional state is achieved it can then be applied to the suffering of others, turning the initial state of loving-kindness into one of compassion (Singer and Klimecki, 2014). Behavioral research has shown that short-term training of loving-kindness and compassion is associated with increases in daily positive affect (Kok *et al.*, 2013), prosocial behavior (Leiberg *et al.*, 2011; Weng *et al.*, 2013), resilience (Fredrickson *et al.*, 2008) and empathy (Mascaro *et al.*, 2013). Speaking to its potential efficacy as an explicit regulation strategy, Compassion training

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[1] In the following '''compassion''' refers to the emotional state, while the capitalized '''Compassion''' refers to the specific meditation technique employed in the current study.

has been shown to alter the emotional experience of the individual when confronted with the suffering of others, by specifically increasing positive affect related to experiences of warmth and concern (Klimecki et al., 2013a,b).

Interestingly, the neural mechanisms supporting Compassion appear to be markedly different from those reported for Reappraisal. Increases in positive affect through Compassion-training have been shown to be paralleled by an increase in brain regions associated with reward and affiliation, such as the ventral striatum (VS) including nucleus accumbens (NACC) and medial orbitofrontal cortex (mOFC), perigenual anterior cingulate (pgACC) and mid-insular cortices (Klimecki et al., 2013a,b). In contrast, Reappraisal has consistently been associated with activation of regions involved in selective attention, conflict monitoring and cognitive control, including dorsal anterior cingulate (dACC), ventrolateral prefrontal cortex (vlPFC), dorsolateral PFC (dlPFC) and supramarginal gyrus/temporoparietal junction (SMG/TPJ) (Ochsner et al., 2012; Buhle et al., 2014). As such, the neural implementation of Compassion and Reappraisal appears to mirror their conceptual differences, in that Compassion involves the volitional endogenous generation of an emotional and motivational state rather than alteration of exogenously triggered states through cognitive control and self-regulation, as seen in Reappraisal. These qualities suggest the appropriateness of Compassion as a regulation strategy in contexts where emotional connection is important since it does not involve the alteration of ones emotional reactions to stressors directly, but rather the counter-generation of a positive affective state.

In this study, we tested this hypothesis by investigating how explicit employment of Compassion as an emotion regulation strategy modulates both subjective and neural reactions to emotional stimuli depicting individuals in distress, and how this compares to the modulatory effects of Reappraisal. From previous work (Klimecki et al., 2013a,b) we know that the default response pattern to such stimuli is negative affect, presumably stemming from empathic distress reactions (Condon and Feldman Barrett, 2013), and that training is needed in order to generate loving-kindness and compassion when confronted with others' suffering. We therefore recruited a cohort of expert Compassion meditators who had undergone extensive instruction in a Buddhist tradition focusing on altruism and compassion. Further, all meditators had participated in at least one 3-year full-time retreat at the same institution, in which they practiced these techniques and underwent instruction by the same teachers. This ensured homogenous and expert implementation of Compassion allowing us to describe the workings of the technique at its optimum.

We tested our hypotheses specifically in the context of negative emotion caused by exposure to the suffering of others by adapting the socio-affective video task (SoVT; (Klimecki et al., 2014). This task has previously been successfully used in previous Compassion research and is optimized to elicit extended negative affect of a social nature. We adapted the SoVT to an emotion-regulation setting by including explicit instructions for the participants to modulate their emotional reactions to the film clips, yielding a design similar to previous studies aimed at differentiating emotion regulation strategies (e.g. Goldin et al., 2008).

We hypothesized that Compassion and Reappraisal should be differentiable in terms of their effects on experienced affect. Provided that Compassion involves the direct generation of positive affect, we expected it to be particularly effective at increasing positive affect. Conversely, as Reappraisal involves re-interpreting the negative aspects of external emotion eliciting stimuli, we expected this to be more effective at decreasing negative affect. Neurally, we expected Compassion to rely less on lateral prefrontal regions thought to be important in top-down cognitive regulation of emotion (Buhle et al., 2014). Rather,

we expected Compassion to engage networks known to be associated with affiliation and positive affect in general, including basal ganglia and VS/NACC, mOFC, peri- and subgenual ACC (sgACC/pgACC) and mid-insula (Bartels and Zeki, 2004; Schultz, 2006; Vrtička et al., 2008; Kringelbach and Berridge, 2009; Strathearn et al., 2009; Rangel and Hare, 2010; Berridge and Kringelbach, 2013). Following our hypothesis that Compassion centrally involves the endogenous generation of positive affect, we expected to find evidence of activation of this network independently of stimulus presentation. Mirroring our behavioral hypotheses, we expected that Compassion and Reappraisal would be differentiable in terms of their impact on core affective processing regions such as the amygdala and VS/NACC. As the regulation of affect through Reappraisal has been shown to be particularly noticeable by its influence on the amygdala (Buhle et al., 2014), we expected lower levels of amygdala activation during Reappraisal than Compassion. Conversely, given the focus of Compassion the generation of positive affect we expected to see higher activation of NACC/VS, a key region in positive affect, during Compassion relative to Reappraisal.

METHODS

Participants

In total, 18 long-term practitioners of meditation in the Nyingma tradition of Tibetan Buddhism were recruited. This tradition is known for specifically focusing on the cultivation of loving-kindness, altruism and compassion. Participants were included only if they had participated in a full-time meditation retreat of at least 3 years at the Songsen Chanteloube retreat center in Dordogne, France. Of these 15 (five Women; age range = 45–62 years, age mean ± s.d. = 56.1 ± 4.6 years) completed the current experiment. All participants were Western European Caucasians. Meditation experience was assessed through semi-structured interviews, showing an estimated cumulative total of 40 000 ± 9000 h of meditation (range = 10 000–62 000 h). Written and informed consent was obtained from all participants. The study was approved by the Ethics Committee of the University of Leipzig and was carried out in compliance with the Declaration of Helsinki. All participants gave written informed consent, were economically compensated, and debriefed after the study was completed.

MRI acquisition

Structural MRI data were acquired on a 3 T Siemens Verio Scanner (Siemens Medical Systems, Erlangen, Germany) using a 32-channel head-coil. High-resolution structural images were acquired using a T1-weighted 3D-MPRAGE sequence (TR = 2300 ms, TE = 2.98 ms, TI = 900 ms, flip angle = 7°, iPat = 2; 176 sagittal slices, FOV = 256 mm, matrix size = 240 × 256, 1^3 mm voxels; total acquisition time = 5.10 min). Functional volumes were collected using a 12-channel head-coil. We employed a T2*-weighted gradient EPI sequence that was optimized (Nichols et al., 2006) to minimize distortions in medial orbital and anterior temporal regions (TR = 2000 ms, TE = 27 ms, flip angle = 90°, iPat = 2; 37 slices tilted at ~30° from the AC/PC axial plane, FOV = 210 mm, matrix size = 70 × 70, 3^3 mm voxels, 1 mm gap; 700 volumes per session).

Stimuli

The stimuli were short film clips (10–12 s in length; 40 negative and 20 neutral stimuli) taken from the previously validated SoVT stimulus set (for details see Klimecki et al., 2013a). The negative film clips depicted people in distress, such as scenes from documentaries and newscasts of, e.g. starving children, crying mothers or hospitalized individuals. The matched neutral film clips depicted similar individuals in non-distressing situations doing everyday activities. The stimuli were

back-projected using a mirror setup. Eyesight was corrected using goggles where appropriate.

Procedure

Prior to testing, subjects were sent short written descriptions of each of the conditions that they were requested to read and reflect upon. Immediately, prior to scanning subjects were reminded of this text before they underwent a guided training session. In this session, the different strategies were explained and discussed before the subjects performed a training session of six trials, allowing them to experience and practice each strategy employed in the experiment (Watch-Neutral, Watch-Negative, Reappraisal, Compassion, Distraction and Open-Presence). The Distraction and Open-Presence conditions will be the focus of another forthcoming article and do not figure in the current study. Subjects were instructed to start implementing the strategies immediately upon receipt of instruction. To ensure homogeneity in strategy execution, subjects were asked to describe each strategy in their own words prior to the start of training and to describe in detail exactly how they implemented the strategy after each practice trial, with misunderstandings corrected when apparent. For the Compassion condition subjects were asked to employ their Compassion-meditation technique, so as to generate a warm feeling of positive affect and caring towards the individuals depicted in the film. For Reappraisal, subjects were asked to reinterpret the clips by thinking about what was occurring in a way in which the narrative ended more positive than was immediately apparent, i.e. to employ a Reappraisal technique with positive emphasis (cf. Wager et al., 2008). We chose to use positive Reappraisal to ensure comparability of with Compassion in terms of regulatory goal. For the Watch conditions, subjects were asked to respond naturally without trying to alter their reactions.

The subjects underwent two sessions of scanning. Emotion regulation strategies (Reappraisal and Distraction) and meditation techniques (Compassion and Open-Presence) were implemented in separate sessions. Each session consisted of four conditions [Session A: (Reappraisal, Distraction, Watch-Negative, Watch-Neutral), Session B: (Compassion, Open-Presence, Watch-Negative, Watch-Neutral)]. Ten trials of each condition were performed in each session for a total of 40 trials. Stimulus and session order were counterbalanced across subjects. Within each session condition order was pseudo-randomized with the constraint that no more than two consecutive iterations of any condition could occur. Each trial (Figure 1A) consisted of (i) 10 s instruction, (ii) 10–12 s film clip presentation, (iii) 10 s rating of experienced positive emotion, (iv) 10 s rating of experienced negative emotion and (v) 5 s fixation cross. Ratings were given using a button box to move a cursor on a 600-point visual analogue scale (VAS) ranging from 'Not at all' to 'Extremely'. Subjects were instructed to rate their affect as it was at the moment of report rather than how they remembered it to be during the film clip.

fMRI preprocessing

Preprocessing was done using SPM8 (r5236, Wellcome Trust) and included slice time correction, combined realignment and field-map based unwarping, DARTEL-based normalization (Ashburner, 2007) and smoothing with an isotropic Gaussian kernel with FWHM of 8 mm. As controlled breathing is a key component of meditation, we accounted for potential respiratory artifacts and confounds by despiking the data using the ArtRepair toolbox (version 4, http://cibsr.stanford.edu/tools/human-brain-project/artrepair-software.html) and removing the run-specific global signal for each voxel (Macey et al., 2004) in line with previous work (e.g. Farb et al., 2013).

fMRI analysis

To ensure robustness of the analyses in the face of potential differences in temporal dynamics of the conditions, a finite impulse response deconvolution approach was used. Single subject models included both runs, and included regressors coding the onset of instruction in each trial and the following fourteen 2 s time bins for each condition. Separate, non-orthogonalized parametric regressors for positive and negative affect ratings were included, as well as seven nuisance regressors coding movement and linear temporal trend. Models were high-pass filtered at 0.005 Hz and temporal autocorrelations were modeled using an AR(1) process. Group repeated-measures analyses were performed using GLMFlex (http://mrtools.mgh.harvard.edu/) and constrained to voxels within a grey matter mask derived from the MNI-projected DARTEL-generated template, created using the optimized thresholding algorithm included in the Masking toolbox (Ridgway et al., 2009). Inference was performed on truncated AUC estimates of BOLD signal, with separate t-contrasts performed for the Preparation (0–10 s) and Implementation (10–22 s) phases of the trial. Multiple comparisons were controlled for using cluster-level FWE correction at $\alpha < 0.05$ (T > 3.36, $P = 0.001$, $k > 30$) as determined by AFNI's AlphaSim Monte Carlo simulation method. Cortical surface renderings were created using NeuroElf, while subcortical renderings were made using scripts provided by Tor Wager and colleagues (available at http://wagerlab.colorado.edu/tools). Anatomical labels were determined using a combination of the TD client implemented in NeuroElf, the Anatomy toolbox (Eickhoff et al., 2005) and stereotactic atlases (Duvernoy, 1999; Naidich et al., 2009; Duvernoy et al., 2013).

ROI analyses were done using the MarsBar toolbox (http://marsbar.sourceforge.net). To test our a priori hypotheses that Reappraisal and Compassion should differ in terms of their temporal profiles and their effects on the neural substrates of positive and negative affect, we focused our analyses on subregions of the NACC/VS and amygdala in which activation varied as a function of reported positive and negative affect, respectively (see Supplementary Materials for details on the ROI selection procedure).

RESULTS

Behavioral results

Figure 1B shows the differences in subjective ratings as a function of employed strategy. Positive and negative emotion ratings were analyzed separately using linear mixed modeling (LMM) as implemented in SPSS 21, with Condition (Compassion, Reappraisal, Watch-Negative, Watch-Neutral) as a fixed effect and subject-level random intercepts. This revealed a significant main effect of Condition for both Positive [$F(3, 882) = 26.66$, $P < 0.001$] and Negative [$F(3, 882) = 176.10$, $P < 0.001$] ratings. Post-hoc comparisons were corrected for multiple comparisons using the sequential Bonferroni method. These revealed that the Negative-Watch condition elicited significantly more negative [$\mu = 191.19$, SE $= 8.47$, $t(882) = 22.58$, $P < 0.001$] and significantly less positive [$\mu = -54.74$, SE $= 9.71$, $t(882) = -5.64$, $P < 0.001$] affect than the Neutral-Watch condition, demonstrating successful emotion induction. Further comparisons revealed that both Compassion and Reappraisal decreased negative [Compassion: ($\mu = -56.13$, SE $= 10.37$), $t(882) = -5.41$, $P < 0.001$); Reappraisal: ($\mu = -54.74$, SE $= 9.71$), $t(882) = -5.64$, $P < 0.001$] and increased positive affect [Compassion: ($\mu = 101$, SE $= 11,89$), $t(882) = 8.50$, $P < 0.001$; Reappraisal: $\mu = -97.82$, SE $= 10.37$), $t(882) = -9.43$, $P < 0.001$] relative to the Negative-Watch condition, demonstrating their efficacy at regulating affective states. Importantly, direct comparison of Compassion and Reappraisal revealed that Compassion was associated with significantly higher positive affect [$\mu = 50.29$, SE $= 13.73$), $t(882) = 3.66$, $P < 0.005$], while Reappraisal
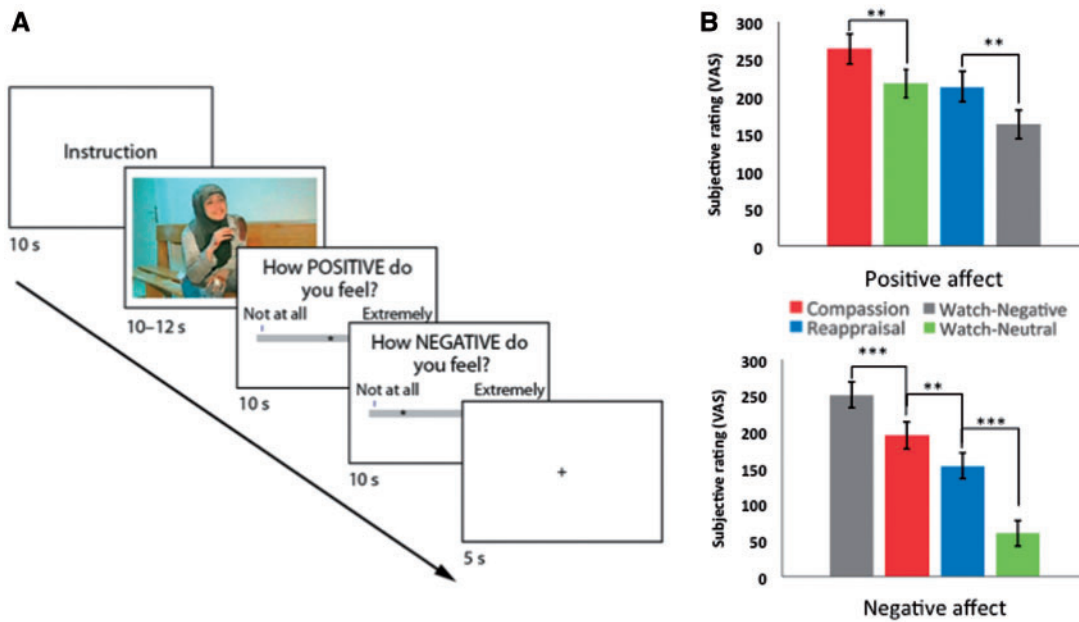
Fig. 1 (**A**) Schematic of a single trial. Although being scanned, subjects were first instructed which strategy to employ, then they viewed a 10–12 s film clip while employing the strategy, whereupon they rated their experienced positive and negative affect on two serially presented scales. (**B**) Behavioral results of experienced affect in each of the four conditions. Compassion was associated with significantly higher positive affect than all other conditions, while Reappraisal was associated with significantly higher positive affect than the Watch-Negative condition. Both compassion and Reappraisal decreased negative affect, though Reappraisal did so significantly more. **, $P < 0.01$; ***, $P < 0.001$. All P-values Bonferroni corrected.

was associated with significantly lower negative affect [$\mu = -54.74$, SE = 9.71), $t(882) = -5.64$, $P < 0.001$]. Furthermore, only Compassion increased positive affect above the Watch-Neutral condition [Compassion: ($\mu = 46.28$, SE = 11.89), $t(882) = 3.89$, $P < 0.001$; Reappraisal: ($\mu = -4.01$, SE = 11.89), $t(882) = -0.34$, $P > 0.1$], supporting the notion that Compassion is uniquely associated with an increase of positive affect, whereas Reappraisal occasioned a return to baseline positive affect.

fMRI results

Validation contrasts

In order to establish the efficacy of the emotion induction procedure used and the comparability of the Reappraisal implementation to previous work, several validation contrasts were performed (Reappraisal > Watch-Negative, Watch-Negative > Watch-Neutral). These contrasts are reported in Supplementary Tables S1 and S2. The Watch-Negative > Watch-Neutral contrast served as a validation contrast for successful emotion induction, and showed increased activation of core affective processing regions such as amygdala and insula, in addition to widespread activation of regions associated with both cognitive and perceptual components of affect. The Reappraisal > Watch-Negative contrast served to validate the implementation of Reappraisal in this study and establish comparability to previous studies. This revealed a pattern of results closely resembling previous work (e.g. Goldin *et al.*, 2008; Buhle *et al.*, 2014), including fronto-parietal activation and deactivation of amygdala (Supplementary Figure S1).

Compassion vs Watch-Negative

The contrast of Compassion over Watch-Negative assessed the neural correlates of the active employment of Compassion when preparing for and actively implementing Compassion to regulate ones affective response to negative stimuli. Results from these contrasts are reported in Table 1. As we had no specific hypotheses regarding deactivations these were not interpreted, but are reported in Supplementary Table S3.

In the preparation phase (Figure 2A), activations were observed laterally in frontal regions, including middle frontal gyrus (MFG) and triangular/orbital junction of the inferior frontal gyrus (IFG), supplementary motor area (SMA), as well as superior and inferor parietal lobules. Medially, activations were observed in frontopolar and mOFC and ventromedial PFC (vmPFC), pgACC/sgACC and posterior cingulate cortex (PCC). Subcortical activations were observed in pulvinar and medial nuclei of the thalamus, hypothalamus, VS, superior and inferior parietal lobules. Additionally, large portions of the cerebellum were activated.

In the Implementation phase (Figure 2B), substantial activations were observed in medial PFC, including vmPFC and mOFC, as well as genual ACC and SMA. Left dorsolateral and ventrolateral prefrontal activations were again observed, including middle and superior frontal gyrii (SFG), as well as the orbital portion of the triangular and orbital IFG. Further activations were observed in SMG/TPJ and posterior cingulate, as well as middle and inferior temporal gyrii, and portions of the cerebellum. Subcortical activations were observed in VS including NACC, globus pallidus, caudate, putamen, hypothalamus and superficial portions of the right amygdala.

Compassion vs Reappraisal

The direct contrast of Compassion and Reappraisal over the course of the Preparation and Implementation phases was performed to identify differences in the neural underpinnings of Compassion and Reappraisal, as well as their temporal dynamics. The results from these contrasts are reported in Table 2.

In the Preparation phase (Figure 3A), higher activation was found for the Compassion condition primarily in medial frontal regions, including vmPFC/gyrus rectus, pgACC, sgACC, dorsal ACC/SMA, precuneus. Additional activations were observed in bilateral superior temporal gyrus (STG) and right IFG/operculum ranging into mid-insula. In contrast, higher activation for the Reappraisal condition was found

Table 1 Brain regions activated during Compassion relative to the Watch-Negative baseline

Region	Side	Extent	t	t	MNI			Label/BA
		(voxel)	(max)	(avg)	x	y	z	
Compassion>Watch-negative								
Preparation phase								
Precuneus	**L**	**313**	**9.44**	**3.90**	**−12**	**−70**	**51**	**7**
Precuneus	L	161	9.44	4.20	−12	−70	51	7
Superior parietal lobule	L	77	5.98	3.78	−33	−70	44	7
Inferior parietal lobule	L	31	4.43	2.96	−39	−46	39	19
Cerebellum	L	1164	8.66	4.21	−6	−67	−11	**Declive**
Cerebellum	L	161	8.66	4.92	−6	−67	−11	Declive
Cerebellum	R	138	8.30	4.84	6	−73	−26	Pyramis
Cerebellum	R	151	7.94	4.30	25	−74	−15	Declive
Cerebellum	L	129	7.26	4.25	−19	−64	−15	Declive
Cerebellum	R	57	6.93	4.28	41	−76	−40	Inferior semi-lunar lobule
Cerebellum	R	119	6.56	4.12	38	−66	−20	Declive
Cerebellum	R	92	6.36	4.30	20	−83	−29	Tuber
Cerebellum	R	86	5.56	3.85	12	−81	−14	Declive
Cerebellum	L	51	5.06	3.38	−10	−84	−11	Lingual gyrus
Cerebellum	R	46	4.98	3.63	46	−67	−28	Tuber
Cerebellum	L	39	4.78	3.12	−23	−84	−14	Declive
Cerebellum	L	45	4.65	3.34	−45	−70	−22	Declive
Thalamus	**L**	**93**	**8.12**	**3.86**	**0**	**−27**	**2**	**Pulvinar**
Thalamus	L	38	8.12	4.45	0	−27	2	Pulvinar
Thalamus	L	31	5.66	3.46	0	−14	12	Lateral-dorsal
IFG	**L**	**58**	**7.70**	**4.20**	**−42**	**30**	**−15**	**47**
Superior frontal gyrus	**R**	**107**	**6.87**	**3.55**	**3**	**8**	**60**	**6**
Superior frontal gyrus	R	34	6.87	3.71	3	8	60	6
Superior frontal gyrus	L	53	5.27	3.31	−8	0	67	6
IFG	**L**	**50**	**6.87**	**3.89**	**−53**	**12**	**1**	**45**
Precentral gyrus	**L**	**50**	**6.50**	**3.51**	**−19**	**−23**	**71**	**6**
MTG	**L**	**55**	**6.43**	**3.90**	**−61**	**−20**	**−9**	**21**
Posterior cingulate	**L**	**51**	**6.43**	**3.90**	**0**	**−38**	**22**	**Posterior cingulate**
Precentral gyrus	**R**	**65**	**6.03**	**3.73**	**60**	**0**	**7**	**Precentral gyrus**
Orbital gyrus	**L**	**264**	**5.91**	**3.68**	**0**	**39**	**−20**	**11**
Orbital gyrus	L	68	5.91	3.81	0	39	−20	11
Medial frontal gyrus	L	46	5.77	3.94	−12	58	9	10
Anterior cingulate	L	58	5.17	3.37	0	32	−2	24
Medial frontal gyrus	R	39	4.94	3.34	4	52	−2	10
IFG	**L**	**53**	**5.21**	**3.41**	**−53**	**10**	**33**	**9**
Caudate	**L**	**77**	**4.88**	**3.42**	**0**	**4**	**1**	**Head**
Implementation phase								
Anterior cingulate	**L**	**1651**	**10.59**	**4.40**	**−4**	**54**	**−2**	**10**
Anterior cingulate	L	125	10.59	5.80	−4	54	−2	10
Medial frontal gyrus	L	130	10.00	5.93	−12	55	9	10
Anterior cingulate	L	103	7.74	4.91	−6	26	−3	24
MFG	L	47	7.62	3.95	−25	45	−11	11
Anterior cingulate	R	171	7.59	4.62	4	31	−10	32
IFG	L	48	7.31	4.39	−24	33	−9	47
Superior frontal gyrus	L	36	6.77	4.29	−25	57	−1	10
Anterior cingulate	R	97	6.71	4.11	11	33	9	32
Lentiform nucleus	L	74	6.67	4.27	−16	13	2	Putamen
VS	L	58	6.47	3.97	−13	13	−6	NACC
Medial frontal gyrus	R	45	6.43	4.29	15	54	1	10
MFG	L	99	6.33	4.16	−29	41	20	10
Medial frontal gyrus	L	126	6.26	4.19	−8	42	16	9
Medial frontal gyrus	R	96	6.08	3.88	12	44	19	9
Caudate	L	61	5.75	4.29	−16	23	3	Caudate
Medial frontal gyrus	R	38	5.50	4.06	8	55	15	10
Lentiform nucleus	L	47	5.46	3.62	−23	5	19	Putamen
MFG	L	33	5.45	3.72	−35	42	10	10
Hypothalamus	R	64	5.17	3.47	6	−3	−3	Anterior
Caudate	R	38	4.87	3.37	13	20	8	Caudate body
Anterior cingulate	L	34	4.75	3.58	−7	33	9	24
Cerebellum	**R**	**1466**	**9.98**	**4.43**	**36**	**−47**	**−29**	**Culmen**
Cerebellum	R	88	9.98	5.42	36	−47	−29	Culmen
Cerebellum	R	120	8.94	5.21	45	−64	−28	Tuber
Cerebellum	R	99	8.84	4.55	6	−73	−26	Pyramis
Cerebellum	L	127	8.44	5.07	0	−64	−26	Pyramis
Cerebellum	R	84	7.36	4.57	6	−53	−23	Anterior lobe dentate
Cerebellum	R	63	7.22	4.83	26	−81	−30	Tuber
Cerebellum	R	158	6.99	4.75	28	−65	−23	Uvula

Table 1 Continued

Region	Side	Extent	t	t	MNI			Label/BA
		(voxel)	(max)	(avg)	x	y	z	
Cerebellum	L	87	6.49	4.27	−6	−68	−9	Culmen
Cerebellum	R	115	6.27	4.76	19	−71	−30	Pyramis
Cerebellum	R	68	6.25	3.92	14	−54	−43	Cerebellar tonsil
Cerebellum	R	39	5.91	3.49	20	−34	−19	Culmen
Cerebellum	R	54	5.90	4.26	25	−77	−15	Declive
Cerebellum	L	70	5.45	3.54	−13	−42	−34	Cerebellar tonsil
Cerebellum	L	37	5.19	3.17	−22	−31	−17	Culmen
Cerebellum	R	60	5.15	4.01	33	−77	−39	Inferior semi-lunar lobule
Cerebellum	L	71	5.13	3.73	−5	−48	−34	Cerebellar tonsil
Cerebellum	L	60	4.87	3.41	−18	−64	−17	Declive
Cerebellum	L	35	4.47	3.27	−17	−48	−19	Culmen
IFG	**L**	**81**	**8.90**	**3.77**	**−32**	**18**	**−17**	**47**
IFG	L	32	7.64	4.34	−48	23	−8	47
Precentral gyrus	L	357	6.82	3.67	−19	−23	71	4
Precentral gyrus	L	103	6.82	3.97	−19	−23	71	4
Medial frontal gyrus	R	55	6.43	3.99	7	5	61	6
MFG	L	50	5.85	3.46	−24	2	60	6
Precentral gyrus	L	33	5.56	3.48	−20	−18	62	6
Medial frontal gyrus	L	58	5.31	3.65	−8	−3	55	6
Precuneus	L	73	6.61	3.08	−15	−70	51	7
Precuneus	L	42	6.61	3.28	−15	−70	51	7
Precuneus	L	31	4.28	2.81	−12	−53	58	7
MFG	**L**	**238**	**6.51**	**4.00**	**−49**	**2**	**40**	**6**
MFG	L	209	6.51	4.12	−49	2	40	6
Posterior cingulate	**L**	**120**	**6.40**	**3.69**	**−3**	**−42**	**19**	**29**
Posterior cingulate	L	70	6.40	4.02	−3	−42	19	29
Precuneus	L	50	4.45	3.23	0	−56	30	7
MTG	**L**	**73**	**6.14**	**3.70**	**−59**	**−8**	**−6**	**21**
Erebellum	**L**	**90**	**5.57**	**3.68**	**−37**	**−57**	**−23**	**Culmen**
Cerebellum	L	53	5.57	3.62	−37	−57	−23	Culmen
Cerebellum	L	37	5.30	3.78	−42	−67	−23	Tuber
SMG	**L**	**173**	**5.39**	**3.47**	**−53**	**−52**	**23**	**40**
Precentral gyrus	**L**	**61**	**5.31**	**3.35**	**−44**	**6**	**11**	**44**
Precentral gyrus	L	45	5.31	3.47	−44	6	11	44

Cluster maxima are reported in bold. Local maxima (unbolded) denote subclusters within a cluster found to be not connected to the already considered (central) mass in a higher-values-first watershed searching algorithm implemented in NeuroElf (i.e. the *splitclustercoords* function). Multiple comparisons were controlled for using cluster-level FWE correction at $\alpha < 0.05$ ($T > 3.36$, $P = 0.001$, $k > 30$) as determined by AFNI's AlphaSim Monte Carlo simulation method. For consistency, subclusters smaller than the respective cluster thresholds are not reported.
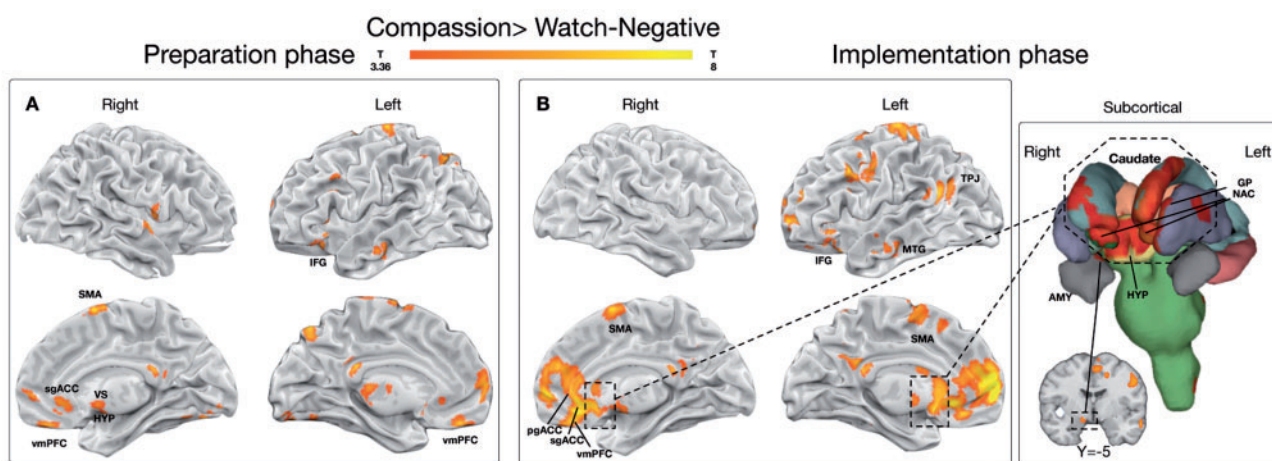

Fig. 2 Results from the whole brain contrast of Compassion > Watch-negative presented separately for the Preparation and Implementation phases. All results thresholded at FWEc $\alpha < 0.05$ as determined by AFNI's AlphaSim ($P < 0.001$, extent threshold = 30 voxels).

in posterior and polar middle temporal gyrus (MTG), posterior cingulate/precuneus and cerebellum.

For the Implementation phase (Figure 3B), increased activation was found for the Compassion condition in medial PFC, including vmPFC, mOFC, sgACC, pgACC, frontopolar cortex, bilateral SMA and

mid-cingulate. Laterally, activations were observed in bilateral operculum/mid-insula, STG, precuneus and right fusiform gyrus. Subcortically, activations were observed in NACC/VS, bilateral amygdala, hypothalamus, caudate, globus pallidus, putamen, right hippocampus and ventral anterior portions of the thalamus. For Reappraisal,

Table 2 Brain regions differentially activated in Compassion and Reappraisal

Region	Side	Extent (voxel)	t (max)	t (avg)	MNI x	MNI y	MNI z	Label/BA
Compassion>Reappraisal								
Preparation phase								
Rectal gyrus	**R**	**702**	**11.79**	**4.47**	**11**	**32**	**−21**	**11**
Rectal gyrus	R	173	11.79	5.52	11	32	−21	11
Superior orbital gyrus	L	91	9.20	4.45	−13	30	−20	11
Superior medial gyrus	L	143	6.95	4.34	−4	52	4	10
Anterior cingulate	R	149	6.44	4.04	4	32	−8	32
Middle orbital gyrus	L	79	6.09	3.97	−21	41	−16	11
SMA	**R**	**237**	**8.47**	**4.04**	**3**	**8**	**58**	**6**
SMA	R	55	8.47	4.71	3	8	58	6
Superior medial gyrus	L	57	7.58	4.19	0	52	26	9
Superior medial gyrus	L	54	5.67	3.67	−4	40	43	8
Precuneus	**L**	**302**	**7.43**	**4.37**	**−3**	**−70**	**42**	**7A**
Precuneus	L	192	7.43	4.57	−3	−70	42	7A
Precuneus	L	66	6.67	4.35	0	−44	59	5M
STG	R	150	6.97	4.01	60	0	4	22
Implementation phase								
Rectal gyrus	**R**	**2631**	**11.04**	**4.32**	**11**	**32**	**−21**	**11**
Rectal gyrus	R	181	11.04	5.84	11	32	−21	11
Superior orbital gyrus	L	102	9.94	5.55	−13	30	−20	11
Anterior cingulate	R	212	8.95	5.61	4	32	−8	32
Anterior cingulate	R	153	8.05	4.75	4	41	−1	32
STG	R	101	7.61	4.51	60	0	4	22
Postcentral gyrus	R	86	7.12	3.83	43	−14	32	3A
Superior medial gyrus	L	163	7.05	4.81	−11	55	4	10
Claustrum	L	160	7.04	4.44	−23	22	3	Claustrum
Superior orbital gyrus	L	119	6.90	4.40	−14	44	−18	11
Rolandic operculum	R	78	6.90	3.96	54	−12	13	43
Anterior cingulate	R	94	5.94	4.00	7	27	5	24
Insula	R	107	5.90	4.08	41	11	−2	13
Thalamus	R	64	5.73	3.73	24	−31	11	Pulvinar
Lentiform nucleus	L	106	5.73	3.65	−19	5	12	Putamen
Anterior cingulate	R	107	5.61	4.07	18	41	0	10
Anterior cingulate	L	74	5.51	3.88	−22	43	3	10
STG	R	47	5.38	3.86	50	10	−4	22
Anterior cingulate	L	84	5.17	4.00	−3	27	7	24
Lentiform nucleus	R	53	5.10	3.36	23	6	15	Putamen
Superior frontal gyrus	R	52	5.05	3.42	22	54	−1	10
Claustrum	R	51	4.36	3.56	27	25	3	Claustrum
Thalamus	**L**	**96**	**8.01**	**4.34**	**−3**	**−8**	**2**	**Ventral anterior nucleus**
Thalamus	L	73	8.01	4.71	−3	−8	2	Ventral anterior nucleus
Precentral gyrus	**L**	**93**	**6.60**	**3.63**	**−22**	**−23**	**68**	**6/4A**
Fusiform gyrus	**R**	**175**	**6.49**	**3.67**	**29**	**−33**	**−17**	**Fusiform gyrus**
Fusiform gyrus	R	58	6.49	3.99	29	−33	−17	Fusiform gyrus
STG	**L**	**421**	**6.26**	**3.95**	**−49**	**4**	**−4**	**22**
STG	L	86	6.26	4.11	−49	4	−4	22
Rolandic operculum	L	112	6.17	4.22	−54	0	4	22
IFG	L	73	6.11	4.05	−47	6	6	44
Amygdala	L	47	5.29	3.73	−22	1	−15	Superficial
Insula	L	47	4.05	3.21	−35	1	3	Mid
Precuneus	**L**	**220**	**5.93**	**3.58**	**−6**	**−56**	**52**	**7P**
Precuneus	L	153	5.93	3.67	−6	−56	52	7P
Cingulate gyrus	**L**	**88**	**5.47**	**3.63**	**−22**	**−43**	**26**	**31**
Cingulate gyrus	L	77	5.47	3.64	−22	−43	26	31
Reappraisal > Compassion								
Preparation phase								
Cerebellum	**R**	**1099**	**9.24**	**4.46**	**11**	**−40**	**−46**	**Cerebellar tonsil**
Cerebellum	R	111	9.24	5.15	11	−40	−46	Cerebellar tonsil
Cerebellum	L	92	7.97	4.93	−2	−54	−51	Cerebellar tonsil
Cerebellum	L	49	7.86	6.06	−10	−43	−48	Cerebellar tonsil
Brainstem	R	137	7.36	4.88	1	−35	−37	Medulla
Cerebellum	R	116	7.28	4.29	12	−70	−37	Inferior semi-lunar lobule
Cerebellum	L	63	7.12	4.74	−15	−40	−39	Cerebellar tonsil
Cerebellum	R	124	6.47	4.59	6	−62	−26	Nodule
Cerebellum	L	92	6.11	4.35	−16	−52	−49	Cerebellar tonsil
Cerebellum	R	60	4.92	3.65	16	−42	−29	Anterior lobe
Cerebellum	L	170	4.86	3.69	−10	−54	−31	Cerebellar tonsil
Cerebellum	R	55	4.54	3.64	23	−58	−51	Cerebellar tonsil

(continued)

Table 2 Continued

Region	Side	Extent (voxel)	t (max)	t (avg)	MNI x	y	z	Label/BA
MTG	R	92	5.89	3.81	49	0	−17	21
IFG	L	95	5.37	3.50	−38	36	3	46
Posterior cingulate	L	99	4.89	3.44	−9	−47	8	29
Implementation phase								
IFG	L	136	7.83	4.26	−51	25	25	45/44
IFG	R	93	7.20	4.26	49	25	20	45
Cerebellum	L	232	7.07	3.99	−20	−78	−37	**Inferior semi-lunar lobule**
Cerebellum	L	60	7.07	4.72	−20	−78	−37	Inferior semi-lunar lobule
Cerebellum	L	72	5.52	3.73	−20	−81	−26	Uvula
Cerebellum	L	67	5.22	3.74	−26	−70	−33	Pyramis
MTG	L	245	6.97	3.94	−53	−34	−2	39
MTG	L	61	6.97	4.42	−53	−34	−2	39
MTG	L	63	5.79	4.00	−58	−57	7	21
MTG	L	55	5.23	3.62	−60	−43	3	22
Medial temporal gyrus	R	133	6.68	4.20	53	5	−16	21
Calcarine gyrus	L	95	6.66	3.77	−3	−57	4	17
IFG	L	123	6.61	4.13	−45	49	−3	45
Superior medial gyrus	L	90	5.47	3.88	−4	26	39	8
Angular gyrus	R	117	5.07	3.59	56	−58	24	39

Cluster maxima are reported in bold. Local maxima (unbolded) denote subclusters within a cluster found to be not connected to the already considered (central) mass in a higher-values-first watershed searching algorithm implemented in NeuroElf (i.e. the *splitclustercoords* function). Multiple comparisons were controlled for using cluster-level FWE correction at $\alpha < 0.05$ ($T > 3.36$, $P = 0.001$, $k > 30$) as determined by AFNI's AlphaSim Monte Carlo simulation method. For consistency, subclusters smaller than the respective cluster thresholds are not reported.
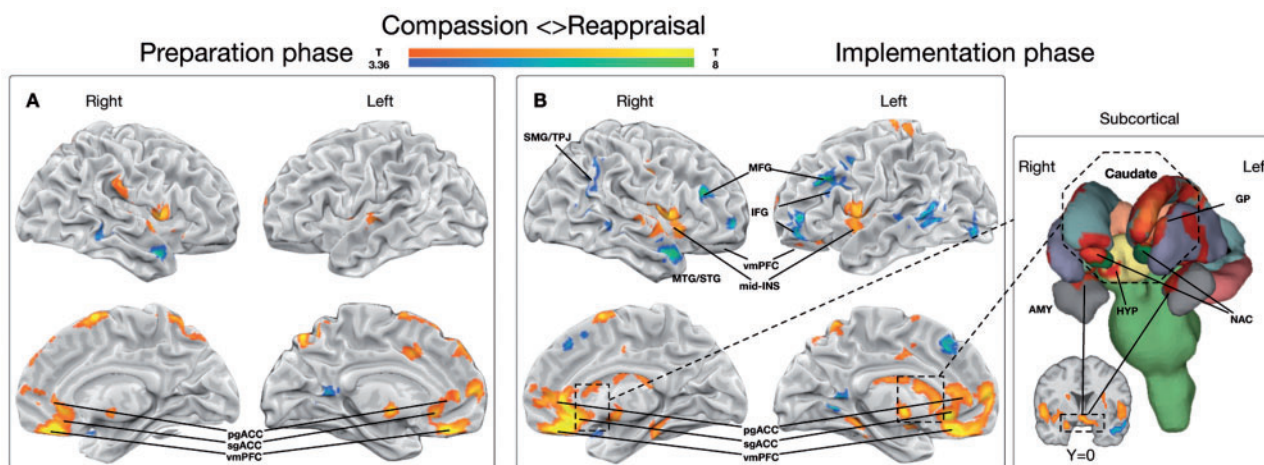

Fig. 3 Results from the whole brain contrast of Compassion > Reappraisal and Reappraisal > Compassion presented separately for the Preparation and Implementation phases. Red-scaled blobs denote regions of significantly higher activation during Compassion than Reappraisal, while blue-scaled blobs denote regions with higher activation during Reappraisal than Compassion. All results thresholded at FWEc $\alpha < 0.05$ as determined by AFNI's AlphaSim ($P < 0.001$, extent threshold = 30 voxels).

increased activation was observed in dlPFC, including bilateral MFG and left IFG, pre-SMA/medial SFG, right SMG/TPJ, right anterior MTG/STG and left posterior MTG, left calcarine gyrus and cerebellum.

Temporal dynamics of compassion and reappraisal in regions tracking subjective affect

To test our hypotheses that Reappraisal and Compassion would differ in terms of dynamics of core affective regions, we extracted the condition-wise time courses of regions in the NACC/VS and amygdala associated with trial-wise reported positive and negative affect (Figure 4). First, we established the efficacy of Reappraisal and Compassion in modulating activity in these regions by submitting the extracted time series for these conditions and their respective Watch-Negative baselines to LMM analysis. Analyses were shifted to allow for hemodynamic lag by excluding the three first time points,

corresponding to the 0–4 s following Instruction onset. The remaining time points were averaged for the Preparation (five time points, 6–16 s following Instruction onset) and Implementation (six time points, 16–28 s following Instruction onset) phases. Separate models were fitted for each technique and region, consisting of fixed factors for Condition (2 levels; Reappraisal/Compassion, Watch-Negative) and Period (2 levels; Preparation, Implementation) with subject-level random intercepts.

For the Compassion condition, these analyses revealed a main effect of Condition in both VS/NAC [$F(1, 312) = 10.52$, $P < 0.001$] and amygdala [$F(1, 312) = 4.50$, $P < 0.05$] ROIs. Follow-up t-tests showed that this effect consisted of higher signal in the VS/NAC [$t(312) = 3.32$, $P = < 0.001$] and lower signal [$t(342) = −2.17$, $P = < 0.05$] in the amygdala ROIs relative to the Watch-Negative condition. For the Reappraisal condition, only a main effect of Condition in the amygdala
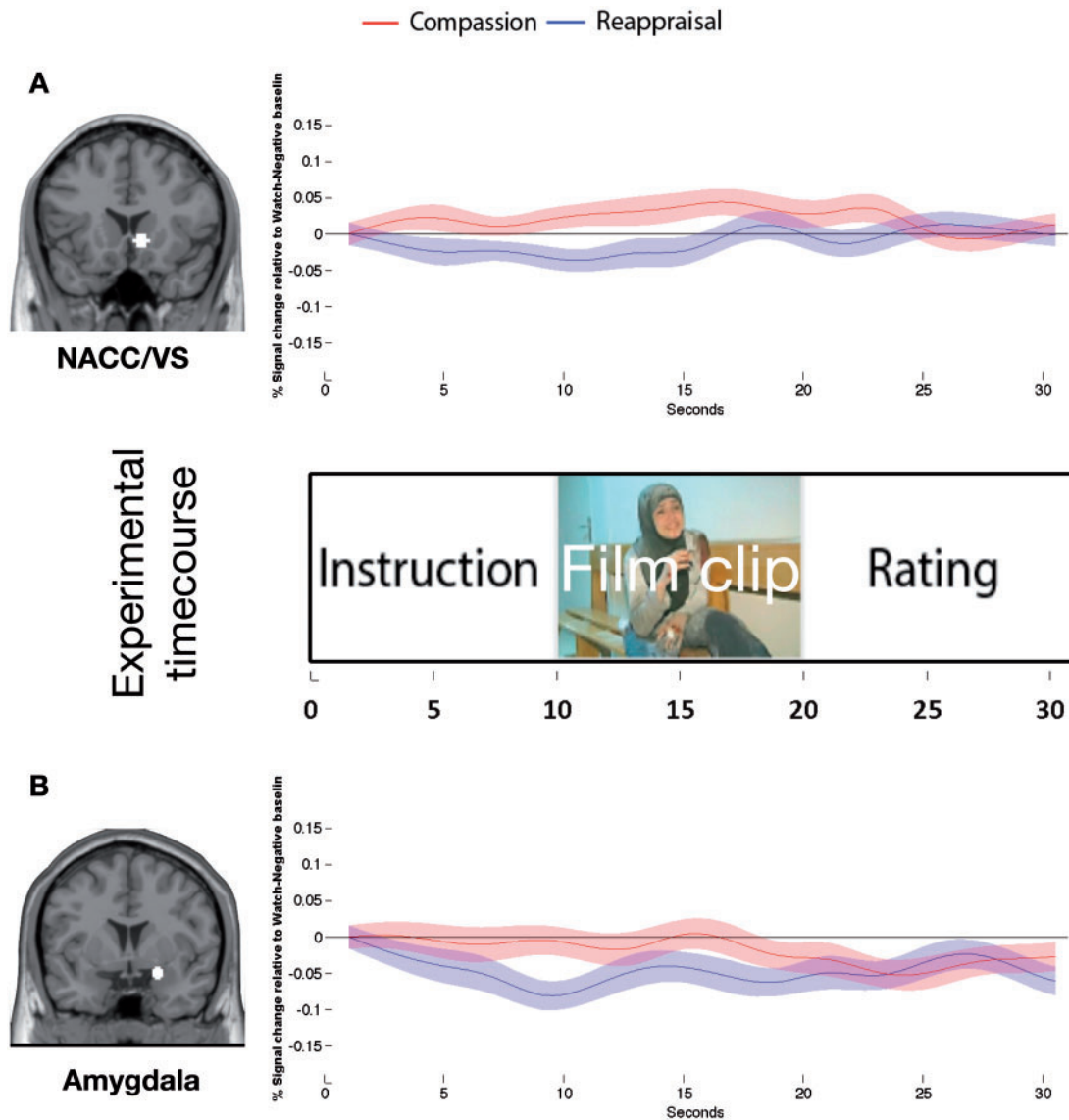
Fig. 4 Event-related time-courses in amygdala and NACC/VS ROIs for Compassion (red) and Reappraisal (blue), subtracted from their respective Watch-Negative baselines. Shaded areas denote within-subject standard errors (Loftus and Masson, 1994). Time points where shaded area does not overlap the abscissa denote significant effects relative to Watch-Negative baseline. Time courses are plotted relative to actual timing of experiment and have been interpolated for presentation purposes only.

$[F(1, 312) = 28.83, P < 0.001]$, ROI was observed. Follow-up t-tests showing these effects consisted of lower signal overall in the amygdala $[t(312) = -5.4, P = < 0.001]$ in Reappraisal relative to the Watch-Negative condition. Thus, while both Compassion and Reappraisal was shown to decrease activation of amygdala relative to Watch-Negative, only Compassion was shown to increase activation of VS/NAC.

To enable direct comparison of modulatory effects, we subtracted their respective Watch-Negative baselines from the Compassion and Reappraisal time-courses and submitted these to LMM analysis separately for each region using the same model as above. Figure 4A and B show time series of this subtraction for the NACC/VS and amygdala ROIs, respectively. For the VS/NAC, this revealed a main effect of Condition, $[F(1, 312) = 11.16, P < 0.001]$ as well as a Condition* Period interaction effect $[F(1, 312) = 3.96, P < 0.05]$. For the amygdala, only a main effect of Condition was observed $[F(1, 312) = 5.84, P < 0.05]$. Follow-up t-tests revealed that these effects consisted of

higher signal in the VS/NAC for Compassion relative to Reappraisal specifically during the Implementation period [Preparation: $t(134) = 3.79, P = < 0.0001$; Implementation: $t(164) = 0.97, P = > 0.1$] and overall lower signal in the amygdala for Reappraisal than Compassion $[t(312) = -2.42, P = < 0.05]$.

In summary, these results show that Compassion and Reappraisal are differentiable in terms of their modulatory effects on the neural correlates of subjective positive (VS/NAC) and negative (amygdala) affect.

DISCUSSION

In this study, we sought to identify the subjective and neuronal signatures of Compassion-meditation when employed to regulate emotional reactions to depictions of others' suffering and compare the mechanisms and effects of Compassion to those of the established emotion regulation strategy of Reappraisal. Behaviorally, we expected that the main regulatory effect of Compassion should be increased positive

affect, reflecting the direct generation of positive affect hypothesized to underlie its regulatory effects. This in contradistinction to Reappraisal, which we expected to have a more pronounced effect on negative affect on account of its focus on altering the affective meaning of the stimuli. Neurally, we expected to find evidence of increased activation of core positive affect regions during Compassion. Further, consistent with our hypothesis that the regulatory mechanism of Compassion is the endogenous generation of positive affect we expected engagement of this network independent of stimulus presentation. This effect should also be distinguishable from the modulatory mechanisms of Reappraisal, as Compassion to a lesser degree should down-regulate core negative affective regions, and not engage cognitive control regions shown to be important in regulating negative affect.

On the subjective level, we found that Compassion was associated with increased positive affect relative to Watch-Neutral, Watch-Negative and Reappraisal. Thus, Compassion was more effective at increasing positive affect than Reappraisal. Importantly, unlike Reappraisal, Compassion occasioned an increase of positive affect relative to baseline levels of positivity (Watch-Neutral). Mirroring these behavioral effects, our fMRI analyses revealed that Compassion, relative to both Watch-Negative and Reappraisal, was associated with increased activation in subcortical structures associated with positive affect, such as VS/NACC and globus pallidus as well as midline cortical structures such as vmPFC, rgACC and pgACC (Figures 2 and 3). These regions have all previously been associated with positive affect, motivation and reward (Kringelbach and Berridge, 2009; Rangel and Hare, 2010; Schultz, 2010), and affiliation (Strathearn et al., 2009; Vrtička et al., 2008). Overall, these results are consistent with previous findings (Klimecki et al., 2013a,b), demonstrating that Compassion is an effective regulation strategy and that a key mechanism underlying these regulatory effects is the engagement of neural systems associated with positive affect.

This interpretation is strengthened by the direct comparison between Reappraisal and Compassion: in line with previous work (Buhle et al., 2014), Reappraisal was characterized by activation of a fronto-parietal network, including ventral and dorsal PFC, dACC and TPJ/SMG, regions known to be associated with cognitive control, attention regulation and working memory (Ochsner et al., 2012). Contrary to this, Compassion was shown to rely primarily on activation of the aforementioned medial and subcortical systems, with the strongest differentiation observable in mOFC and VS/NACC (Figure 3). Additionally, Compassion was shown to specifically increase activation in bilateral mid-insula, a region previously associated with specifically affiliative types of positive affect, such as maternal love (Bartels and Zeki, 2004). These different activation patterns appear to reflect the conceptual difference between Reappraisal and Compassion: Reappraisal involves the employment of cognitive control to modulate affective influences, whereas Compassion involves the generation of positive affect, without altering the processing of negative stimuli. In line with this, we found differential effects of Compassion and Reappraisal in regions specifically tracking experienced positive (VS/NACC) and negative (amygdala) affect: Compassion showed evidence for increased activation of VS/NACC compared to both Reappraisal and passive-viewing. Critically, this modulation was apparent prior stimulus presentation consistent with Compassion involving the endogenous generation of positive affect in a stimulus-independent fashion. Furthermore, Compassion was associated with overall higher amygdala activity than Reappraisal, suggesting that Compassion to a lesser degree modulated the primary affective processing of the negative stimulus material. Overall, these findings are in line with a view that the underlying mechanism of Compassion-based emotion regulation is the volitional and stimulus-independent engagement of neural systems supporting the endogenous generation of positive affect.

Our findings are largely consistent with earlier work on short-term effects of Compassion training by Klimecki et al. (2013a,b). However, unlike these studies, we found that Compassion had a small but significant regulatory effect on subjectively experienced negative affect. One possible explanation for this difference is the level of experience between the expert practitioners in our study and those subjects tested in the Klimecki studies, which had only 1 week of practice in Compassion. It is possible that extensive experience in Compassion affords a concomitant decrease in negative affect. Another, complementary, possibility is that these differences stem from the current design explicitly instructing participants to generate Compassion prior to exposure to the stimuli. It could be that proactive generation of Compassion is particularly effective at dampening negative affect, presumably by providing a buffer of positive affect (Garland et al., 2010). The current design does not allow a direct test of this hypothesis, but future research could address this by comparing differences in Compassion efficacy as a function of whether it is generated proactively or reactively, as this has been shown to be an important determinant of the efficacy of other regulation strategies (Sheppes and Gross, 2011).

The capacity to be employed independently of specific stimuli and an underlying mechanism not involving attenuation or alteration of negative emotional responses potentially affords Compassion some unique advantages as an emotion regulation strategy. In the context of others' suffering, Compassion affords maintenance of an empathic connection while counteracting empathic distress (Singer and Klimecki, 2014). Thus, employment of Compassion as a regulation strategy could avoid of the decreased sensitivity and empathy reported when employing cognitive emotion regulation strategies to cope with others' suffering (Cameron and Payne, 2011). Furthermore, Compassion has been shown to be associated with an increase in prosocial motivation and helping (Leiberg et al., 2011; Weng et al., 2013) suggesting an additional beneficial effect if used as coping strategy in helping professions as it would not only increase resilience but also increase their willingness to assist individuals in need.

CONCLUSION

In this study, we showed that Compassion can be employed as an effective emotion regulation strategy outside of its traditional meditative context, and that both experientially and neurally, it is associated with the endogenous generation of positive affect. Although the generalizability of our findings, especially with regards to the relative efficacy of Reappraisal and Compassion, is limited by the fact that our subjects had extensive experience in generating Compassion, recent work demonstrates that it is possible to elicit similar neural and behavioral effects to what we observe here with short-term training (Leiberg et al., 2011; Klimecki et al., 2014; Weng et al., 2013). This suggests that Compassion might be an effective means to promote resilience to others' suffering also in the general population while at the same time promoting emotional connectedness and pro-sociality.

SUPPLEMENTARY DATA

Supplementary data are available at SCAN online

Conflict of Interest

The authors declare that they have no conflicts of interest.

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