Neuroscience and Biobehavioral Reviews 108 (2020) 112–123

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

The neurophysiological basis of compassion: An fMRI meta-analysis of compassion and its related neural processes

Jeffrey J. Kim[a,b,*], Ross Cunnington[a,b,c], James N. Kirby[a,b]

[a] School of Psychology, The University of Queensland, Brisbane, Queensland, Australia
[b] Compassionate Mind Research Group, The University of Queensland, Brisbane, Queensland, Australia
[c] Queensland Brain Institute, The University of Queensland, Brisbane, Queensland, Australia

ARTICLE INFO

Keywords:
Compassion
Salience
Basal-ganglia
PAG
fMRI
Review

ABSTRACT

Theoretical and neurophysiological investigations into compassion are burgeoning, yet the putative neural mechanisms which underpin such processes are less well understood. Therefore, we have conducted an Activation-Likelihood Estimate meta-analysis in order to ascertain the shared neural processes consistently identified as relevant to compassion. Our analysis of sixteen fMRI studies revealed activation across seven broad regions, with the largest peaks localized to the Periaqueductal Grey, Anterior Insula, Anterior Cingulate, and Inferior Frontal Gyrus. Overall, we identified a tendency for studies to operationalize compassion in one of three ways, as driven either 'top-down', 'bottom-up', or modified by target context. We failed to identify regions purportedly common to compassion such as the DLPFC, OFC, and Amygdala, possibly due to a small number of studies which used Loving-Kindness meditation. We argue future research in compassion science continue a multi-modal approach to examine links between neural activity and actual prosocial behavior, and recommend the application of fMRI paradigms on compassion with clinically diagnosed populations to parallel current trends in psychotherapy such as Compassion Focused Therapy.

1. Introduction

Compassion is the motive to detect and approach suffering, with a commitment to try and alleviate or prevent it (Gilbert, 2019). Compassion likely emerged from our mammalian care-giving neurophysiology (Brown and Brown, 2015; Marsh, 2019; Mayseless, 2016), and is evidenced to facilitate connection, care and improved social functioning (Ferrari et al., 2019; Seppälä et al., 2017; Kirby et al., 2017a,b; Kirby, 2017; Strauss et al., 2016). As compassion is inherently prosocial, however, it has been conflated with conceptually similar processes such as empathy and sympathy (Klimecki and Singer, 2017). Although compassion includes sympathetic and empathic processes as informants to help in the engagement and reduction of suffering (Stevens and Woodruff, 2018; Klimecki and Singer, 2017), compassion can include other factors such as care for well-being, being sensitive to another's needs, the ability to tolerate emotional distress, and non-judgement (Ashar et al., 2017; Gilbert, 2019; Gonzalez-Liencres et al., 2013; Weng et al., 2018).

The key distinction of compassionate motivation when compared to competencies such as empathy and sympathy, is that the motivation of compassion is to reduce suffering (Ashar et al., 2016b; Gilbert, 2019; Heyes, 2018).

The motivation of compassion likely emerged from mammalian caregiving, which requires parental investment to be attentive to the distress and needs of another (i.e., offspring/infant), and then turn towards and approach distress signals in order to help alleviate the distress, whether it be via protection if threatened, feeding if hungry, rescue if distant, or soothing if distressed (Bowlby, 1969; Gilbert, 2019; Porges, 2007). Human compassion emerges from this basic mammalian caring motivation and combines complex cognitive competencies that have evolved over the last two million years (Dunbar and Shultz, 2017; Gilbert, 2019). These include the social intelligences of knowing awareness (i.e., ability to mentalize and engage in mindfulness, have mental time travel, symbolic thinking); empathic awareness (i.e., insight into why we feel/think/act the way we do, and that of others); and knowing intentionality (i.e., deliberately choosing to cultivate specific motives and develop specific skills to enact the motive) (Dunbar and Shultz, 2017; Gilbert, 2019; Kirby and Gilbert, 2017; Suddendorf, 2018). These social cognitive competences enables the compassionate motive to be strengthened, through cultivation and training, and thus compassion can be applied beyond just offspring or kinship groups and extend towards others (Gilbert, 2019; Kirby et al., 2019). Importantly these competencies can also be applied to other motives such as

* Corresponding author at: School of Psychology, The University of Queensland, St Lucia, 4072, Brisbane, Qld, Australia.
E-mail address: Jeffrey.kim@uqconnect.edu.au (J.J. Kim).

https://doi.org/10.1016/j.neubiorev.2019.10.023
Received 7 August 2019; Received in revised form 24 October 2019; Accepted 30 October 2019
Available online 04 November 2019
0149-7634/

competitive or sexual motivations (e.g., Gilbert, 2019). Whilst the field of compassion science has disagreed about how to best define and measure compassion, which has caused some problems for the field (Goetz et al., 2010; Kirby, 2017; Kirby et al., 2017a,b; Strauss et al., 2016), investigation into the neuroscientific (i.e., fMRI) and physiological basis (i.e., heart-rate variability, HRV) of compassion has grown steadily (e.g., Petrocchi and Chelli, 2019).

Indeed, functional imaging in compassion has historically drawn upon numerous techniques and/or perspectives within the literature (Seppälä et al., 2017). This underscores that compassion is not a single process mediated by a single brain network, but rather is multi-faceted and associated with numerous processes. Elucidation of this complexity is therefore critical to understand compassion, as this can provide evidence to support theoretical accounts of compassion and it's correlates, and perhaps establish a neural basis for compassion as distinct from processes such as sympathy or empathy (Klimecki and Singer, 2017; Stevens and Woodruff, 2018). Here, this may reveal compassion as a unique motive poised to confront and reduce suffering, in order to promote individual wellbeing and social flourishing.

We have conducted an Activation-Likelihood Estimate (ALE) meta-analysis on previous fMRI studies of compassion, which will for the first time synthesize the existing literature via coordinates-based analysis, in order to provide insight into which brain networks are most consistently reported to be associated with compassion. Crucially, in identifying studies for the meta-analysis, we selected all papers with activation foci that the authors interpreted as reflecting compassion-related activation. This allowed us to first identify the brain regions that have been most commonly attributed to compassion-related processes. We then reviewed details of the authors' operationalization of compassion and the experimental paradigms used within these studies, and discuss differences within the overall networks of brain areas associated with different aspects of compassion.

2. Materials and methods

2.1. Literature search and exclusion criteria

PUBMED and the Web of Science databases were searched using the keywords 'Compassion' AND 'fMRI'. As of December 2018, this search revealed 651 published, peer-reviewed papers. The inclusion criteria for our analyses were as follows:

1. Studies that explicitly mentioned compassion and fMRI within title, abstract and/or keywords were included, whereas those that did not were excluded. Two hundred and fifty-eight (258) of the 651 papers met this criterion.
2. Studies which utilized fMRI were included, whereas those that employed other techniques (i.e., Electroencephalography (EEG), Transcranial Magnetic Stimulation (TMS), behavioral measures and review articles) were excluded. Our study was restricted to fMRI data as we wanted to have approximately comparable temporal and spatial resolution for the ALE analyses. Twenty-six (26) of the remaining 258 papers met this criterion.
3. Studies that failed to include whole-brain analyses were excluded. Primarily, this step removed studies that only reported activation results using a region-of-interest approach. After deletion of duplicate articles, Sixteen (16) of the remaining twenty-six papers remained for analysis.

2.2. Selection of activated voxels

From the 16 studies which passed the criteria listed above, we included all voxels that the authors explicitly interpreted as reflecting significant compassion-related activity. If studies reported original voxels in Talairach space, we then transformed them into MNI space using the mni2tal algorithm (Lancaster et al., 2007) within the Ginger Ale software (Eickhoff et al., 2009). In total, 309 foci were included in the overall analysis. If studies incorporated additional comparisons which pertain to compassion (i.e., interaction terms) these were also included.

2.3. Activation Likelihood Estimation (ALE)

In order to identify regions of consistent activation between studies, we performed an ALE analysis using the GingerALE software (Eickhoff et al., 2009, Version 2.3.6). An advantage of this current version (2.3.6) over pre-existing algorithms is that it permits random-effects interference, by assessing for above-chance clustering of foci between experiments (Laird et al., 2005; Turkeltaub et al., 2012). We corrected for multiple comparisons using the false-discovery rate (FDR) at $p < 0.05$, and utilized a 0mm^3 volume to define a cluster. The thresholded maps of the ALE values were superimposed on a canonical T1-weighted structural scan using Mango (http://ric.uthscsa.edu/mango/). The ALE analysis included additional output which provides information of cluster-size, location, and anatomical labels (Table 1).

3. Results

Table 1 displays our ALE-activation from seven distinct regions – Middle Frontal Gyrus, Bilateral Inferior Frontal Gyrus, Bilateral Insula, Anterior Cingulate, Medial Frontal Gyrus, Basal Ganglia/Thalamus circuitry, and Other. Fig. 1 depicts numerous regions of interest superimposed on a canonical T1-weighted structural scan. Table 2Table 2A synthesizes the studies we have included in our ALE analysis into three broad operationalizations, 'stimulus', 'mindset', or modulated by 'target' characteristics. We decided upon this framework by reporting how studies have conducted experimental contrasts. For example, 'stimulus' describes emotional-neutral contrasts, which isolate an effect of negative emotion, 'mindset' describes any study which investigated as part of their task a top-down generation, mindset, or cultivation of compassion, and 'target' considers an interaction between affect and properties of stimuli (i.e., attractiveness vs unattractiveness, guilt vs innocence).

3.1. Anatomical specificity

In order to establish valid and consistent anatomical labels and terminology throughout the remainder of this paper, we compared our coordinates of ALE activation with published reviews, meta-analyses, and experimental data.

3.2. Bilateral Insula

First, our ALE revealed consistent activation within Bilateral Anterior Insula. Overall, the Insula are thought to be involved in processing visceral and autonomic responses, such as awareness of internal bodily sensations and a subjective experience of emotions (Menon, 2015), and comprise anterior, middle and posterior subdivisions (Uddin et al., 2017). Coordinates in our ALE activation appear to correspond most closely with the anterior subdivision, supported from coordinates reported in other studies attributed to this sub-region (Menon, 2015).

3.3. Cingulate Cortex

Second, our ALE revealed consistent activation in the Cingulate Cortex. Overall, the Cingulate is a central "hub" responsible for the integration of sensory, motor, cognitive, and emotional information (Bush et al., 2000), and is evidenced to comprise general cognitive and

Table 1
Regions and cluster information elicited from our ALE-based analysis. Coordinates are listed in MNI space.

Region	ALE Label	Size	X	Y	Z
Middle Frontal Gyrus	Middle Frontal Gyrus	32	52	22	18
Bilateral Inferior Frontal Gyrus	Left Inferior Frontal Gyrus	376	−44	22	−16
	…	184	−44	22	−4
	…	8	−32	16	−18
	Right Inferior Frontal Gyrus	160	38	24	−16
	…		42	22	−20
Bilateral Insula	Left Insula	808	−50	10	−2
	Right Insula	536	46	20	0
Cingulate Cortex	Anterior Cingulate	584	−4	16	48
	Subcallosal Cingulate	224	−4	24	−18
	…	16	0	32	−4
Medial Frontal Gyrus	Medial Frontal Gyrus	88	−6	−16	52
	…	64	2	−2	58
Basal Ganglia/Thalamic Circuitry	Substania Nigra/ Periaqueductal Grey (PAG)	1056	−12	−14	−16
	…		−8	−26	−18
	Left Caudate Head	368	2	12	−6
	Right Red Nucleus	288	8	−20	−12
	Left Putamen	264	−16	12	4
	Left Thalamus/Medial Dorsal Nucleus	144	−4	−18	14
	Left Thalamus		0	−16	14
	Left Thalamus/Ventral Anterior Nucleus	80	−10	−2	6
	Left Lentiform Nucleus/Putamen	48	−34	−12	0
Other	Left Claustrum	104	−38	−4	−2
	Right Declive	88	10	−82	−10
	Right Culmen	16	6	−52	−24

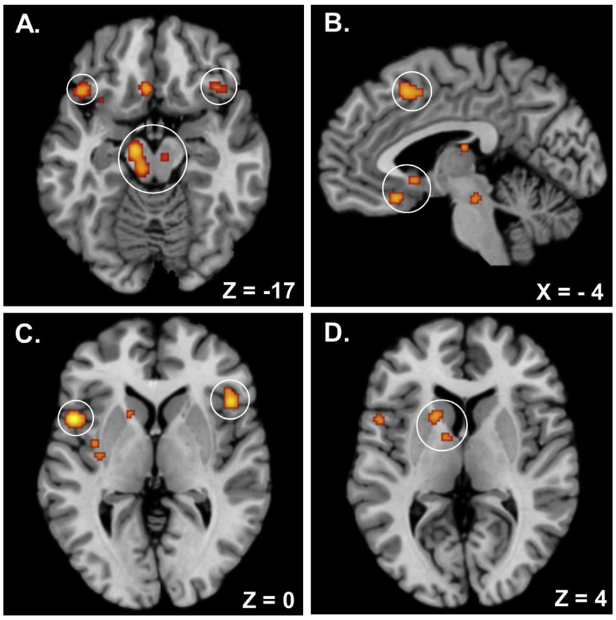

Fig. 1. Common regions of activation identified from our ALE-analysis of 16 fMRI studies on compassion. **a.** Bilateral Inferior Frontal Gyri (top) and Substantia Nigra/Periaqueductal Grey (bottom), **b.** Anterior Cingulate (top) and Subcallosal Cingulate (bottom), **c.** Bilateral Anterior Insula, **d.** Left Putamen and Left Thalamus. Peak activation thresholded at FDR, $p < 0.05$, and coordinates reported in MNI-space. Z- and X-values correspond to Axial and Sagittal planes, respectively.

affective subdivisions (Vogt, 2005), which are indicative of the anterior vs ventral portions, respectively (Bush et al., 2000). Coordinates in our ALE activation appear to correspond most closely with the cognitive than affective division of the cingulate, supported from coordinates in other studies attributed to this sub-region (Bush et al., 2000). Furthermore, our analysis also identified clusters of activation in the limbic section of the cingulate, in accordance with coordinates attributed to this area reported in previous research (Menon, 2015), and a functional and anatomical review of the limbic system (Catani et al., 2013).

3.4. Inferior, Medial, and Middle Frontal Gyri

Third, our ALE identified consistent activation in the Inferior Frontal Gyrus (IFG). Coordinates in our ALE activation appear to correspond most closely with bilateral IFG, supported from coordinates reported in other studies attributed to this sub-region (Hampshire et al., 2010; Swick et al., 2008).

We also observed consistent activation in the Medial Frontal Gyrus. Overall, the Medial Frontal Gyrus is thought to be involved in both performance monitoring (van Noordt and Segalowitz, 2012v) and social cognition (Amodio and Frith, 2006; Molenberghs et al., 2016). Coordinates in our ALE activation appear to correspond most closely with ventral and anterior portions, as assessed from coordinates outlined in previous research attributed to this sub-region (Amodio and Frith, 2006).

In addition, our analysis revealed consistent activation in the Middle Frontal Gyrus. Coordinates in our ALE activation appear to correspond most closely with cingulum subdivisions, which have been associated with greater activation toward temporal or "when" information, and suppression of spatial or "where" information, respectively, in other studies which reported coordinates attributed to this sub-region (Talati and Hirsch, 2005).

Table 2
Compassion as driven from experimental contrasts researchers performed, whether **2.A** stimulus, **2.B** mindset, **2.C** target characteristics, or **2.D** multi-level model. Authors which reported multiple contrasts which spanned categories are listed in applicable tables. We report substania nigra/PAG activation as separate to basal ganglia/thalamus given its importance in contemporary models of compassion.

A. Compassion driven from affective stimuli (negative – neutral contrasts).

Author	*Definition*	*ALE Network(s) Contribution*
Weng et al. (2018)	Affect/Feeling/Motive	N/A
Laneri et al. (2017)	Emotion	Frontal Salience Basal Ganglia/Thalamus
Mercadillo et al. (2015)	Emotion	Frontal Basal Ganglia/Thalamus Other
Jankowiak-Siuda et al. (2015)	Empathic Concern	Salience Basal Ganglia/Thalamus Substantia Nigra/PAG
Mascaro et al. (2013) (NeuroImage)	Feeling, Behaviour, "Universal Sense"	Frontal Salience Thalamus
Mascaro et al. (2013) (SCAN)	Feeling	Frontal Salience Thalamus Substantia Nigra/PAG
Mercadillo et al. (2011)	Emotion	Frontal Salience
Simon-Thomas et al. (2012)	Emotion	Substantia Nigra/PAG

B. Compassion driven from mindset/active strategy.

Author	*Definition*	*ALE Network(s) Contribution*
Engen and Singer (2015)	Emotion	Frontal Salience Basal Ganglia/Thalamus
Klimecki et al. (2014)	Emotion/Motive	Frontal Basal Ganglia/Thalamus
Longe et al. (2010)	Reassurance/Resilience	Salience
Kim et al. (2009)	Emotion/Response	Frontal Salience Substantia Nigra/PAG

C. Compassion driven by target characteristics.

Author	*Definition*	*ALE Network(s) Contribution*
Jankowiak-Siuda et al. (2015)	Empathic Concern	Frontal Salience Thalamus Other
Fehse et al. (2014).	Cognition/Affect/Behaviour/Urge	Frontal Salience
Weng et al. (2013)	Emotional Response	N/A
Mercadillo et al. (2011).	Emotion	Basal Ganglia/Thalamus Substantia Nigra/PAG Other
Immordino-Yang et al. (2009)	Motive	Salience
Kim et al. (2009)	Emotion/Response	Substantia Nigra/PAG

D. Compassion analyzed with a multi-level model (MLM).

Author	*Definition*	*ALE Network(s) Contribution*
Engen et al. (2018)	Motive/Wish	N/A

3.5. Basal Ganglia/Thalamus

Fourth, our ALE revealed consistent activation in the Basal Ganglia/Thalamus. The basal ganglia/thalamus network comprises distinct subdivisions, with unique circuitry for motor, oculomotor, prefrontal and limbic pathways (DeLong and Wichmann, 2010). Coordinates in our ALE activation appear to correspond most closely with ventral-anterior and medial-dorsal left thalamic nuclei, in accordance with coordinates reported in other studies attributed to this sub-region (DeLong and Wichmann, 2010). These sub-regions have been suggested to be functionally connected with pre-frontal and limbic/motor regions, respectively (DeLong and Wichmann, 2010).

4. Discussion

As can be seen in Table 2A and Appendix A, it is apparent that varied definitions of compassion have been provided by each set of authors. Furthermore, as can be seen in Table 3, there is inconsistency in instructions provided to participants, stimuli sets used in experiments, and only one experiment incorporated a behavioral measure of compassion or prosocial behavior. However, as can be seen in Appendix A, there is considerable evidence for three main operationalizations of compassion as governed by the experimental contrasts researchers performed. For example, eight studies considered compassion to be driven from affective neural responses via conducting an emotional minus neutral contrast (Table 2A). Next, four studies considered compassion to be an active mindset, driven 'top-down', typically measured in conjunction with a negative – neutral contrast (Table 2B). Last, six studies considered compassion to be attenuated by certain target or contextual attributes (i.e., interaction between target manipulation and negative – neutral contrast) (Table 2C). Specifically, this third approach recognizes certain stimulus or target characteristics (i.e., innocence vs guilt, attractiveness vs non-attractiveness) may facilitate or inhibit compassion-based responding. One study was unique in modelling their data within a multi-level model (Table 2D), and therefore deserves its own sub-category. We note this approach allowed the authors to model group, state, and group * state interactions, and believe an adoption of similar methodologies within future compassion neuroscience research will allow better approximation of the fixed and random factors within multi-modal compassion fMRI experiments (for methods, refer to Friston et al., 2005; Chen et al., 2013).

We note that despite these experimental contrasts and analysis strategies, neural activation of particular regions or networks do not appear to depend upon either one of these three approaches (i.e., Table 2A). Furthermore, we note our ALE-analysis identified activation localized to frontal lobes and subcortical regions, with no parietal or occipital components (i.e., Table 1).

4.1. Contribution of salience-network activation to compassion

First, we identified significant activation across two key regions, the anterior cingulate cortex and anterior insula (Greicius et al., 2009; Menon, 2015; Uddin et al., 2017). These regions are nodes in the Salience network, a network which is typically active in paradigms which measure neural responses to experienced or observed pain (Cao et al., 2015, 2017; Lamm et al., 2007, 2011). Functionally, dorsal, anterior insula sub-regions have been suggested to be involved in elements of executive function, as this sub-region sends and receives projections related to cognitive control regions such as frontal-parietal areas and the anterior cingulate (Uddin et al., 2017). In addition, dorsal, anterior divisions of the cingulate have been associated with cognitively demanding working memory and response conflict tasks such as stroop, divided attention or motor-response paradigms (Bush et al., 2000b). We also observed common activation amongst orbitofrontal/limbic sections of the cingulate, reputed to be involved in functions such as behavioral inhibition, memory, multi-modal sensory integration, and reward association learning (Catani et al., 2013).

The role of the salience network in compassion indicates a strong effect of processing negative emotion toward observed or experienced suffering or pain. Given the salience network responds preferentially toward stimuli which are affective or painful (Menon, 2015), it is possible the salience network is not necessarily coupled with compassion, but rather commonly active due to the processing of affective, emotional stimuli, an operationalization which has dominated the field to date. Certainly, only very few studies within our included sample (e.g. Engen et al., 2018) examined neural correlates of compassion in contexts which are markedly non-visceral or non-affective. However, additional studies have implicated the salience network in paradigms which were not restricted to negative-neutral contrasts alone, to consider factors such as mindset and/or active attention toward suffering or pain (i.e., Kim et al., 2009; Klimecki et al., 2014; Engen et al., 2018). Therefore, our original conceptualization of compassion we reported within the introduction - to attend to and hold a desire to reduce the suffering of another – might naturally incorporate functional activation of the salience network, in order to process and/or attend towards stimuli which encompasses suffering.

4.2. Contribution of Basal Ganglia/Thalamus to compassion

Second, our ALE-analysis also identified common activation in the basal ganglia and thalamus. Basal ganglia and/or thalamus dysfunction have been associated with deficits in emotional expression and processing, the inability to associate emotion with behaviour (Levy and Dubois, 2006), and the inability to detect salient emotional cues (Paulmann et al., 2013). Furthermore, convergent evidence from stroke-patient models has established basal ganglia impairment is associated with significantly greater affective (i.e., apathy, depression) and cognitive deficits than controls (Onoda et al., 2010; Paradiso et al., 2013). We believe more fine-grained analyses in future work may allow us to delineate the exact contribution of each of these regions' subcomponents in relation to compassion.

4.3. Contribution of other frontal regions to compassion

Third, our ALE-analysis also identified common activation in frontal regions which include inferior, medial and middle gyri. Taken together, these frontal regions are associated with a wide range of diverse functions which include language (Katzev and Tu, 2013; Poldrack et al., 1999), executive functions such as attention (Japee et al., 2015), and the capacity to monitor emotion and valence (Amodio and Frith, 2006). Interestingly, studies which have operationalized compassion as a 'top down' mindset could likely recruit frontal regions preferentially, and yet we identified this manipulation was not associated with activation solely from frontal regions (i.e., Table 2A). Indeed, frontal regions were

Table 3
Description of Task Instructions, Stimuli Sets, and checks for Prosocial Response of the 16 fMRI studies on compassion.

Author	Instruction	Stimuli Set	Pro-social Behaviour Measured?
Engen et al. (2018)	Generate Loving Kindness meditation.	No stimuli (i.e., picture, video) presented. This session asked participants to engage in the loving kindness practice and focus on individuals close to them.	No
Weng et al. (2018)	Generate Loving Kindness meditation.	Images depicting human suffering (Negative) or non-suffering (Neutral) from the International Affective Picture System (IAPS) (Lang et al., 1997).	No
Laneri et al. (2017)	Participants were asked to evaluate the intensity of the social target's experience of embarrassment during the preceding situation after each stimulus presentation.	Stimuli set of 20 previously validated hand-drawn sketches depicting embarrassing situations and 10 neutral sketches (NEUT) serving as control situations. The embarrassment situations displayed a social target while he or she was violating a social norm in public and threatened his or her social integrity	No
Engen and Singer (2015)	Generate Loving Kindness meditation.	Socio-affective video task (SoVT) stimulus set. As described in Klimecki et al. (2014), SoVT comprises three parallel video sets matched for valence, arousal and empathy at Each set contained 12 high emotion (HE) videos and 12 low emotion (LE) videos. Video scenes were taken from footage cast for news or documentaries and depict men, women and children. LE videos showed everyday scenes, whereas HE videos depicted people who were suffering (e.g. due to injuries or natural disasters).	No
Mercadillo et al. (2015)	Participants were asked to press a button with their index finger if they experienced compassion and a button with their left index finger in the absence of compassion while viewing each picture.	Compassion eliciting pictures (suffering) from the IAPS contrasted with neutral objects or social scenes (Lang et al., 1997).	No
Jankowiak-Siuda et al. (2015)	Participants were asked to imagine the emotions of the person in the movie. After the film, participants rated the intensity of compassion felt.	A series of 6 second videoclips depicting pain-inducing situations. The actors Sex (Male, Female) and attractiveness (More Attractiveness, Less Attractiveness) were manipulated.	No
Fehse et al. (2014)	Participants were asked to view the innocent vs responsible actors within these scenarios and button press if they felt compassion.	Written stimuli based on everyday life events that potentially arouse compassion, for example, a fatal car accident. Innocence verses responsibility of the actor within these scenarios were counterbalanced.	No
Klimecki et al. (2014)	After presentation of the videos participants rated how much empathy, positive affect and negative affect they had experienced while seeing the video.	SoVT videoset (Klimecki et al. (2014).	No
Mascaro et al. (2013a)	First, subjects completed the Self pain task, in which they received moderately painful and nonpainful stimulations to the inside of their wrist. Following the Selfpain task, subjects completed the Other pain task, in which they saw the previously described video clips of other people anticipating and receiving the same stimuli that they received.	Either self receive moderately painful or non-painful shock or view videoclips of other people receive a painful shock.	No
Mascaro et al. (2013b)	Participants were asked to view black and white photographs depicting the eye region of an equal number of male and female Caucasian adults. Participants had to judge what the person in the photograph was thinking or feeling.	Reading the Mind in the Eye Test (RMET) (Baron-Cohen et al., 2001).	No
Weng et al. (2013)	Generate Loving Kindness Meditation.	Images depicting suffering from the IAPS (Lang et al., 1997).	Yes (money donation)
Mercadillo et al. (2011)	Participants were asked to view the stimuli. Half the number of participants were asked to button press if they experienced a compassionate versus non-compassionate experience (counterbalanced).	Compassion- and non-compassion-evoking stimuli (i.e, suffering vs selected from the IAPS (Lang et al., 1997).	No
Simon-Thomas et al. (2012)	Participants viewed pictures and rated on intensity and quality-of-emotion their authentic emotional experience.	Images designed to elicit compassion or pride. Compassion slides featured depictions of vulnerable suffering and harm. Slides were drawn from a previous study (Oveis et al., 2010), IAPSs (Lang et al., 1997)., and the internet.	No
Longe et al. (2010)	Engage in either self-reassurance or self-criticism to written vignettes.	Written stimuli describing a personal mistake, setback or failure.	No
Kim et al. (2009)	Participants were asked to view sad vs neutral affective facial pictures from the perspective of either compassion or neutrality.	Negative or neutral facial pictures.	No
Immordino-Yang et al. (2009)	After a preparation session, participants were presented with pre-viewed written stories and asked to induce a similar emotion they experienced before scanning. Participants were asked to rate the strength of their current feelings within the scanner.	Written narratives designed to elicit admiration or compassion.	No

equally as likely to be recruited in studies which considered compassion to be stimulus and/or target driven (i.e., Tables 2A and 2B). Whilst research has begun to understand the functional role of these individual regions, however, we are unsure of the direct relevance of medial and middle frontal gyri toward compassion. However, a patient lesion model has supported a role for inferior frontal gyri in prosocial motivation, or “the desire to help”, a concept similar to compassion (Shdo et al., 2018).

4.4. Contribution of Midbrain/PAG regions to compassion

Fourth, Midbrain Periaqueductal regions are circuits which govern pain modulation, anxiety, reproductive behavior, and integrate autonomic function (Behbehani, 1995; Faull et al., 2019; Linnman et al., 2013). Furthermore, functional activation of human PAG and Midbrain Nuclei have also been implicated in cognitive control mechanisms, such as working memory response under cognitive load (Kragel et al., 2019). In humans, deep brain stimulation of ventral PAG regions is associated with parasympathetic-mediated outflow to the heart, and correlated with a reduction in pain (Pereira et al., 2010). Taken together, these outcomes were argued to indicate analgesic efficacy of the PAG (Pereira et al., 2010). Furthermore, there is considerable evidence for PAG circuits and corresponding hormones (i.e., oxytocin, oestrogen, prolactin, and vasopressin) to underlie mammalian nurturance or ‘care’ systems (Panksepp, 2011). Yet, neuropeptides such as oxytocin are also context dependent in circumstances such as defensive and/or maternal aggression (Bosch et al., 2005; Nephew et al., 2010; Bosch, 2013). Recognition of the neurophysiological basis of these evolved mechanisms for mammalian care (i.e., Panksepp, 2011) have informed numerous contemporary models of compassion, such as Compassion Focused Therapy (CFT) and Compassionate Mind Training (CMT) (Gilbert, 2017, 2019).

From our ALE-analysis, however, it is apparent only four studies report functional activation in the Midbrain/PAG (i.e., Table 2A), and yet this cluster formed the largest from all foci (i.e., Fig. 1a), followed by the Insula (i.e., Fig. 1c). Therefore, whilst compassion may not necessarily encompass functional activation of Midbrain/PAG circuits in theory, it is evident this region has been implicated strongly across extant compassion neuroscience paradigms to date. We believe this finding may complement Gilbert’s models of compassion (2017, 2019) to underscore compassion can build upon pre-existing care circuits, yet is ultimately contextual and may not be beholden toward PAG functional activation.

4.5. Areas outside ALE

Three studies in our meta-analysis did not contribute foci to our final ALE output. As reported natively within these individual studies, these regions comprised left fronto-polar cortex (Engen et al., 2018), right orbito-frontal cortex and perigenual cingulate cortex (Weng et al., 2018), and right dorsolateral prefrontal cortex and inferior parietal cortex (Weng et al., 2013). What is common between these studies are the use of Loving-Kindness Meditations (LKM), which has a slightly different focus than compassion. In LKM the focus is on the wellbeing, happiness and flourishing of others, whereas, compassion is focused on the suffering of others with a wish to see it alleviated (Wallace, 1999). Thus, LKM does not require one to stay focused on suffering. Despite this slightly different motivational focus many compassion training programs (e.g., Compassion Cultivation Training) include LKM, and this could be partly due to Buddhist influence of the four immeasurables, which include compassion, loving-kindness, equanimity, and appreciative joy (Wallace, 1999). Given this manipulation is unique to only a few studies included in our overall meta-analysis, it is apparent these foci may not have been identified as common given a lack of studies with a comparable methodology and results.

Critically, recent research has found kindness and compassion differ significantly in terms of eliciting self-reported emotional responses (Gilbert et al., 2019). To further examine the differential impact compassion may exhibit compared to kindness would be of interest, as we predict this would indicate different neural mechanisms. For example, might compassion be associated with greater functional activation of the PAG and related nuclei compared to a kindness manipulation, to facilitate up-regulation of care-circuitry? Certainly, this is an empirical question to test.

4.6. Regions of interest approach

In conjunction with whole-brain analyses, however, compassion science has frequently utilized a region-of-interest approach to reveal a crucial role of the amygdala for modulating and/or driving compassionate processes (Desbordes et al., 2012; Lamm et al., 2007; Leung et al., 2017; Lutz et al., 2008; Mascaro et al., 2013a,b; Weng et al., 2018). However, we had to exclude these studies from our ALE-analysis given they did not report relevant whole-brain results, and therefore failed to meet our entry criteria. Furthermore, if studies did report significant whole-brain amygdala activation, however, upon ALE-analysis we failed to find this region commonly active. Therefore, we can infer that if there is activation in the amygdala, it is likely to be inconsistent between studies to date, and operates at a weaker threshold than whole-brain results.

4.7. Future directions

Given the diversity evident throughout compassion neuroimaging research to date, we argue the future of this field would benefit from much greater specificity, clarity, and experimental innovation, in order to better approximate both compassionate motivation and action. We propose five main considerations to help guide future work. First, whilst difficult, we recommend future neuroimaging research seek to establish links between neural data and actual concrete behavior outside the scanner, such as prosocial or altruistic acts. For example, an inclusion of a donation paradigm to examine whether individuals act prosocially by giving to identified targets who are suffering (e.g., Ashar et al., 2016a). Alternatively, the inclusion of virtual reality technologies might also offer unique opportunities to examine brain activation in contexts where suffering is urgent (e.g., somebody in a burning house), to examine both brain region activation and the behavioral actions of the participant (e.g., Patil et al., 2018).

Second, we recommend future neuroimaging research consider studying clinical populations such as those with depression and/or anxiety, to parallel current trends in therapy (Kirby, 2017; Kirby et al., 2017b). Third, we reiterate Ashar et al.'s (2016b) recommendation for future compassion neuroimaging research to consider a systems and/or computational neuroscience approach (i.e., Bassett et al., 2018; Farrell and Lewandowsky, 2010), such as effective connectivity (Friston et al., 2003, 2019). The effective connectivity approach (Friston et al., 2003, 2019) models underlying neural function from traditional fMRI data, and can consider relationships between interacting regions in a network given experimental perturbations (Stephan et al., 2010; Friston et al., 2019). We believe an adoption of this method may allow a deeper understanding of compassionate motivation and it's ability to predict objective behavior. For example, Weng et al. (2013) (included in our ALE-analysis) conducted such an approach, and identified greater coupling of the dorsolateral prefrontal cortex and nucleus accumbens after compassion training predicted greater levels of helping behavior, measured as monetary donations.

Fourth, when we measure and assess compassion in research we recommend using various methods, such as neuroimaging, physiology (e.g., heart rate variability; Matos et al., 2017; Kirby et al., 2017a,b), behavioral paradigms, and self-report. Collectively these various measurement tools help provide insights and estimates as to what is compassionate engagement and behavior. When studies assessing compassion rely on only one form of assessment, particularly self-report measures, there are risks that compassion is conflated with competencies such as empathy, mindfulness, or kindness (Gilbert et al., 2019). Fifth, to respond to the call for "compassion training programs that teach skills for staying engaged with others' suffering without becoming overwhelmed or overly distressed, [which] might reduce the fear of feeling compassion and help sustain compassion in difficult situations" (Ashar et al., 2019, *BioRxiv Preprint*), we believe current and emerging approaches such as Compassion Focused Therapy and Compassionate Mind Training are ideal candidates for the neurosciences moving forward. Taken together, we believe these five recommendations to consider objective behavior, clinical samples, systems or computational methods, multi-modal designs, and validated therapeutic approaches, will aid neuroscience to identify more concretely compassionate motivation and related behavior.

5. Conclusion

We have conducted the first meta-analysis on compassion-related neuroimaging, and identified seven distinct regions associated with compassion localized to frontal and subcortical regions. We also identified numerous regions which, reputed to be key to compassion (i.e., DLPFC, OFC, Amygdala), failed to be revealed as commonly active between the studies included in our ALE-analysis - likely due to a small number of studies which utilized a specific manipulation (Loving-Kindness Meditation). In addition, we report three broad traditions of operationalizing compassion through experimental contrasts, which consider compassion as an emotional response to negative stimuli, compassion as an active mindset, or as a modulated by specific target attributes. We believe future research which can link neural data to objective behavior, consider clinical samples and computational methods, will push the frontiers of compassion science, to more fully approximate how the neuroscience of compassion can predict compassionate motivation and action within the real world.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

The authors have no competing interests to declare.

Acknowledgements

We wish to thank Dr. David Cowan and Dr. Stan Steindl for helpful feedback and discussion on a manuscript draft.

Appendix A

See Table A1

Table A1
Definitions of compassion, Experimental Contrasts, and Contributions to our ALE-activation. Note: individual foci identified within each study not revealed as commonly active from our ALE-analysis were not reported here.

Author	*Definition*	*Experimental Contrast*	*ALE Contribution*
Engen et al. (2018)	Training of loving-kindness meditation involves the active generation of feelings of warmth, love, kindness, and prosocial motivation for others; confronted with the suffering of others, loving-kindness may furthermore become compassion, associated with a wish to alleviate the suffering.	Linear mixed effects models to compare differences in amplitude between loving-kindness and resting-state conditions within LTMs and to study the interaction between this contrast and our study groups. The model included subject as a random effect and age, sex, group, state, as well as a group * state interaction as fixed effects [Multi-level Model]	N/A
Weng et al. (2018)	Compassion involves affective, cognitive, as well as motivational responses to suffering, where the person who witnesses suffering feels a sense of caring for and wanting to help others experiencing suffering.	Training Group * Looking Time conducted on post-training data (Negative-Neutral Contrast). [mindset]	N/A
Laneri et al. (2017)	… The practice of mindfulness encourages the development of compassionate emotions … some Buddhist traditions support the idea that compassion emerges from or is a synonym of pure awareness.	Empathic embarrassment > neutral. [stimulus]	Middle Frontal Gyrus, AI, Thalamus, Left Putamen
Engen and Singer (2015)	The emotional state of compassion can be defined as the emotion one experiences when feeling concern for another's suffering and desiring to enhance that individual's welfare.	Compassion > watch-negative [mindset]	Thalamus, IFG, Anterior Cingulate, Lentiform Nucleus, Medial Frontal Gyrus
		Compassion > reappraisal [mindset]	Anterior Cingulate, Anterior Insula, IFG
Mercadillo et al. (2015)	Compassion can be considered a prototypical moral emotion involving feelings of affliction elicited by perceiving suffering in others that motivates one to alleviate the suffering and to maintain social bonds.	Compassion evoking images (IAPS) > object images [stimulus] Compassion evoking images (IAPS) > landscapes/neutral [stimulus]	Middle Frontal Gyrus, Left Lentiform Nucleus, Declive, Culmen
Jankowiak-Siuda et al. (2015)	Compassion, also referred to as empathic concern, is a respondent's feeling of warmth and concern for others. As a consequence is associated with motivation to help others.	Pain > no pain [stimulus]	Thalamus, Anterior Insula, Anterior Cingulate, Declive, Substantia Nigra
		Attractiveness * sex, pain > no pain [target]	Thalamus, IFG, Anterior Insula, Thalamus
Fehse et al. (2014)	Compassion (than empathy) more strongly implies an integration of cognitive, affective, and behavioral aspects because it adds the urge to exhibit pro-social behavior.	Innocent > responsible, suffering [target]	ACC
		Responsible > innocent, suffering [target]	N/A
Klimecki et al. (2014)	Compassion is defined as a feeling of concern for the suffering of others that is associated with the motivation to help.	Compassion training (time 2 change) for high emotion stimuli > Memory training (time 2 change score) for high emotion stimuli [mindset]	Medial frontal gyrus, IFG
Mascaro et al. (2013) Neuroimage	No definition provided, but training protocol – Cognitive Behavioral Cultivation Training (CBCT) - designed to enhance interpersonal equanimity, increase feelings of gratitude toward others, and finally to induce strong feelings of empathy for all people.	Other pain (other pain > other no pain) [stimulus]	Anterior Insula
Weng et al. (2013)	Compassion is the emotional response of caring for and wanting to help those who are suffering.	Group * redistribution rank [target]	N/A
Mascaro et al. (2013) SCAN	Meditative techniques … (can) promote empathic feelings and behaviors toward others as initial steps toward developing a sense of universal compassion for all people. While little is known regarding whether meditation training actually enhances empathic behavior in daily life, increasing evidence suggests that meditation may positively impact a	Emotion > Gender [stimulus]	IFG, Anterior Cingulate, Thalamus, Substantia Nigra/Midbrain

(*continued on next page*)

Table A1 (*continued*)

Author	*Definition*	*Experimental Contrast*	*ALE Contribution*
	range of factors that while not sufficient for compassionate behavior in and of themselves are nonetheless known to impact empathic mental processes and their underlying neural correlates.		
Mercadillo et al. (2011)	Because it is strongly related to social cooperation … compassion can be considered a moral emotion usually elicited by witnessing the suffering of others and resulting in a motivation to alleviate their perceived affliction.	All subjects: Compassion evoking images (IAPS) > social images [stimulus]	IFG, Insula, Culmen, Declive
		Men: Compassion evoking images [target]	Substantia Nigra
		Women: [target]	Insula, Thalamus, Culmen, Declive
		Women vs Men: [target]	Thalamus
		Men vs Women: [target]	N/A
Simon-Thomas et al. (2012)	Compassion is an other-oriented emotional response to perceived suffering that involves wanting to care for those in need.	Compassion slides > neutral [stimulus]	Midbrain/PAG
Longe et al. (2010)	Self-compassion (or self-reassurance) is negatively linked to psycho- pathology, believed to be the result of both temperament and early attachment experiences, and results in resilience.	Self-reassuring > neutral scenarios [mindset]	Anterior Insula
Kim et al. (2009)	Compassion is an essential human quality that allows one to feel, understand, and respond to the suffering of others.	Main effect compassion [mindset]	Midbrain/PAG, Medial Frontal Gyrus, Insula, Lentiform Nucleus, IFG, AI
		Main effect sad facial affect [mindset]	Midbrain/PAG
		Interaction of compassionate attitude by sad facial effect [target]	Substantia Nigra
Immordino-Yang et al. (2009)	Compassion motivates us to remedy the circumstances of another person. Compassion can be evoked by witnessing situations of personal loss and social deprivation or by witnessing bodily injury.	Admiration for virtue AND compassion for social pain > admiration for skill AND compassion for physical pain [target]	Anterior Insula, Anterior Cingulate

References

Amodio, D.M., Frith, C.D., 2006. Meeting of minds: the medial frontal cortex and social cognition. Nat. Rev. Neurosci. 7 (April), 268–277. https://doi.org/10.1038/nrn1884.

Ashar, Y.K., Andrews-Hanna, J.R., Yarkoni, T., Sills, J., Halifax, J., Dimidjian, S., Wager, T.D., 2016a. Effects of compassion meditation on a psychological model of charitable donation. Emotion 16 (5), 691–705. https://doi.org/10.1037/emo0000119.

Ashar, Y.K., Andrews-Hanna, J.R., Dimidjian, S., Wager, T.D., 2017. Empathic care and distress: predictive brain markers and dissociable brain systems. Neuron 94 (6), 1263–1273. https://doi.org/10.1016/j.neuron.2017.05.014. e4.

Ashar, Y.K., Andrews-Hanna, J., Wager, T.D., Dimidjian, S., 2016b. Towards a neurosciences of compassion: a brain systems-based model and research agenda. In: Greene, Joshua D., Morrison, India, Seligman, Martin E.P. (Eds.), Positive Neuroscience, 1st ed. Oxford University Press, New York, pp. 1–256.

Ashar, Y.K., Andrews-Hanna, J., Halifax, J., Dimidjian, S., Wager, T., 2019. Effects of compassion training on brain responses to suffering others. bioRxivorg 1–26. https://doi.org/10.1101/616029.

Baron-Cohen, S., Wheelwright, S., Hill, J., Raste, Y., Plumb, I., 2001. The “reading the mind in the eyes” test revised version: a study with normal adults, and adults with Asperger syndrome or high-functioning autism. J. Child Psychol. Psychiatry 42 (2), 241–251. https://doi.org/10.1111/1469-7610.00715.

Bassett, D.S., Zurn, P., Gold, J.I., 2018. On the nature and use of models in network neuroscience. Nat. Rev. Neurosci. 19 (9), 566–578. https://doi.org/10.1038/s41583-018-0038-8.

Behbehani, M.M., 1995. Functional characteristics of the midbrain periaqueductal gray. Prog. Neurobiol. 46 (6), 575–605. https://doi.org/10.1016/0301-0082(95)00009-K.

Bowlby, J., 1969. Attachment and Loss: Volume 1, Attachment, 2nd ed. Basic Books, New York.

Bosch, O.J., Meddle, S.L., Beiderbeck, D.I., Douglas, A.J., Neumann, I.D., 2005. Brain oxytocin correlates with maternal aggression: link to anxiety. J. Neurosci. 25 (29), 6807–6815. https://doi.org/10.1523/JNEUROSCI.1342-05.2005.

Bosch, O.J., 2013. Maternal aggression in rodents: brain oxytocin and vasopressin mediate pup defence. Philos. Trans. Biol. Sci. 368 (1631), 1–11. https://doi.org/10.1098/rstb.2013.0085.

Brown, S.L., Brown, R.M., 2015. Connecting prosocial behaviour to improved physical health: contributions from the neurobiology of parenting. Neurosci. Biobehav. Rev. 55, 1–17. https://doi.org/10.1016/j.neubiorev.2015.04.004.

Bush, G., Luu, P., Posner, M.I., 2000. Cognitive and emotional influence in anterior cingulate cortex. Trends Cogn. Sci. 4 (6), 215–222. https://doi.org/10.1016/S1364-6613(00)01483-2.

Cao, Y., Contreras-Huerta, L.S., McFadyen, J., Cunnington, R., 2015. Racial bias in neural response to others’ pain is reduced with other-race contact. Cortex 70, 68–78. https://doi.org/10.1016/j.cortex.2015.02.010.

Cao, Y., Dingle, G., Chan, G.C.K., Cunnington, R., 2017. Low mood leads to increased empathic distress at seeing others’ pain. Front. Psychol. 8, 1–8. https://doi.org/10.3389/fpsyg.2017.02024.

Catani, M., Dell’Acqua, F., Thiebaut de Schotten, M., 2013. A revised limbic system model for memory, emotion and behaviour. Neurosci. Biobehav. Rev. 37, 1724–1737. https://doi.org/10.1016/j.neubiorev.2013.07.001.

Chen, G., Saad, Z.S., Britton, J.C., Pine, D.S., Cox, R.W., 2013. Linear mixed-effects modelling approach to fMRI group analysis. NeuroImage 73, 176–190. https://doi.org/10.1016/j.neuroimage.2013.01.047.

DeLong, M., Wichmann, T., 2010. Changing views of basal ganglia circuits and circuit disorders. Clin. EEG Neurosci. 41 (2), 61–67. https://doi.org/10.1177/155005941004100204.

Desbordes, G., Negi, L.T., Pace, T.W.W., Wallace, B.A., Raison, C.L., Schwartz, E.L., 2012. Effects of mindful-attention and compassion meditation training on amygdala response to emotional stimuli in an ordinary, non-meditative state. Front. Hum. Neurosci. 6 (292), 1–15. https://doi.org/10.3389/fnhum.2012.00292.

Dunbar, R.I.M., Shultz, S., 2017. Why are there so many explanations for primate brain evolution? Philos. Trans. Biol. Sci. https://doi.org/10.1098/rstb.2016.0244.

Engen, H.G., Singer, T., 2015. Compassion-based emotion regulation up-regulates experienced positive affect and associated neural networks. Soc. Cogn. Affect. Neurosci. 10 (9), 1291–1301. https://doi.org/10.1093/scan/nsv008.

Engen, H.G., Bernhard, B.C., Skottnik, L., Ricard, M., Singer, T., 2018. Structural changes in socio-affective networks: multi-modal MRI findings in long-term meditation practitioners. Neuropsychologica 116, 26–33. https://doi.org/10.1016/j.neuropsychologia.2017.08.024.

Eickhoff, S.B., Laird, A.R., Grefkes, C., Wang, L.E., Zilles, K., Fox, P.T., 2009. Coordinate-based activation likelihood estimation meta-analysis of neuroimaging data: a random-effects approach based on empirical estimates of spatial uncertainty. Hum. Brain Mapp. 30 (9), 2907–2926. https://doi.org/10.1002/hbm.20718.

Farrell, S., Lewandowsky, S., 2010. Computational models as aids to better reasoning in psychology. Curr. Direct. Psychol. 19 (5), 329–335. https://doi.org/10.1177/0963721410386677.

Ferrari, M., Hunt, C., Harrysunker, A., Abbott, M.J., Beath, A.P., Einstein, D.A., 2019. Self-compassion interventions and psychosocial outcomes: a meta-analysis of RCTs. Mindfulness 10 (8), 1455–1473. https://doi.org/10.1007/s12671-019-01134-6.

Faull, O.K., Subramanian, H.H., Ezra, M., Pattinson, K.T.S., 2019. The midbrain periaqueductal gray as an integrative and interoceptive neural structure for breathing. Neurosci. Biobehav. Rev. 98, 135–144. https://doi.org/10.1016/j.neubiorev.2018.12.020.

Fehse, K., Silveira, S., Elvers, K., Blautzik, J., 2014. Compassion, guilt and innocence: an fMRI study of responses to victims who are responsible for their fate. Soc. Neurosci. 10 (3), 243–252. https://doi.org/10.1080/17470919.2014.980587.

Friston, K.J., Harrison, L., Penny, W., 2003. Dynamic causal modelling. NeuroImage 19 (4), 1273–1302. https://doi.org/10.1016/S1053-8119(03)00202-7.

Friston, K.J., Stephan, K.E., Lund, T.E., Morcom, A., Kiebel, S., 2005. Mixed-effects and fMRI studies. NeuroImage 24, 244–252. https://doi.org/10.1016/j.neuroimage.2004.08.055.

Friston, K.J., Preller, K.H., Mathys, C., Cagnan, H., Heinzle, J., Razi, A., Zeidman, P., 2019. Dynamic causal modelling revisited. NeuroImage 199, 730–744. https://doi.org/10.1016/j.neuroimage.2017.02.045.

Gilbert, P., 2017. A brief outline of the evolutionary approach for compassion focused therapy. EC Psychol. Psychiatry 3, 218–227. Retrieved from. https://pdfs.semanticscholar.org/1661/f7202e1c8f844db6c0a0dcfbe957bcfae092.pdf.

Gilbert, P., 2019. Explorations into the nature and function of compassion. Curr. Opin. Psychol. 28, 108–114. https://doi.org/10.1016/j.copsyc.2018.12.002.

Gilbert, P., Basran, J., MacArthus, M., Kirby, J.N., 2019. Differences in semantics of prosocial words: an exploration of compassion and kindness. Mindfulness 1–13. https://doi.org/10.1007/s12671-019-01191-x.

Goetz, J.L., Keltner, D., Simon-Thomas, E., 2010. Compassion: an evolutionary analysis and empirical review. Psychol. Bull. 136 (3), 351–374. https://doi.org/10.1037/a0018807.

Gonzalez-Liencres, C., Shamay-Tsoory, S.G., Brüne, M., 2013. Towards a Neuroscience of empathy: ontogeny, phylogeny, brain mechanisms, context, and psychopathology. Neurosci. Biobehav. Rev. 37 (8), 1537–1548. https://doi.org/10.1016/j.neubiorev.2013.05.001.

Greicius, M.D., Supekar, K., Menon, V., Dougherty, R.F., 2009. Resting-state functional connectivity reflects structural connectivity in the default mode network. Cereb. Cortex 19 (1), 72–78. https://doi.org/10.1093/cercor/bhn059.

Hampshire, A., Chamberlain, S.R., Monti, M.M., Owen, A.M., 2010. The role of the right inferior frontal gyrus: inhibition and attentional control. NeuroImage 50 (3), 1313–1319. https://doi.org/10.1016/j.neuroimage.2009.12.109.

Heyes, C., 2018. Empathy is not in our genes. Neurosci. Biobehav. Rev. 95, 499–507. https://doi.org/10.1016/j.neubiorev.2018.11.001.

Immordino-Yang, M.H., McColl, A., Damasio, H., Damasio, A., 2009. Neural correlates of admiration and compassion. PNAS 106 (19), 8021–8026. https://doi.org/10.1073/pnas.0810363106.

Jankowiak-Siuda, K., Rymarczyk, K., Zurawski, L., Jednorog, K., Marchewka, A., 2015. Physical attractiveness and sex as modulatory factors of empathic brain responses to pain. Front. Behav. Neurosci. 9 (236), 1–11. https://doi.org/10.3389/fnbeh.2015.00236.

Japee, S., Holiday, K., Satyshur, M.D., Mukai, I., Ungerleider, L.G., 2015. A role of right middle frontal gyrus in reorienting of attention: a case study. Front. Syst. Neurosci. 9, 1–16. https://doi.org/10.3389/fnsys.2015.00023.

Katzev, M., Tu, O., 2013. Revisiting the functional specialization of left inferior frontal gyrus in phonological and semantic fluency: the crucial role of task demands and individual ability. J. Neurosci. 33 (18), 7837–7845. https://doi.org/10.1523/JNEUROSCI.3147-12.2013.

Kim, J., Kim, S., Kim, J., Jeong, B., Park, C., Son, A.R., Song, J.E., Ki, S.W., 2009. Compassionate attitude towards others’ suffering activates the mesolimbic neural system. Neuropsychologica 47, 2073–2081. https://doi.org/10.1016/j.neuropsychologia.2009.03.017.

Kirby, J.N., 2017. Compassion interventions: the programmes, the evidence, and implications for research and practice. Psychol. Psychother. Theory Res. Pract. 90 (3), 432–455. https://doi.org/10.1111/papt.12104.

Kirby, J.N., Gilbert, P., 2017. The emergence of the compassion focused therapies. In: Gilbert, Paul (Ed.), Compassion: Concepts, Research and Applications. Routledge – Taylor and Francis, Abingdon, Oxon United Kingdom, pp. 258–285. https://doi.org/10.4324/9781315564296.

Kirby, J.N., Doty, J.R., Petrocchi, N., Gilbert, P., 2017a. The current and Future role of Heart rate variability for assessing and training compassion. Front. Public Health 5, 1–6. https://doi.org/10.3389/fpubh.2017.00040.

Kirby, J.N., Tellegen, C.L., Steindl, S.R., 2017b. A meta-analysis of compassion-based interventions: current state of knowledge and future directions. Behav. Ther. 48 (6), 778–792. https://doi.org/10.1016/j.beth.2017.06.003.

Kirby, J.N., Day, J., Sagar, V., 2019. The 'Flow' of compassion: a meta-analysis of the fears of compassion scales and psychological functioning. Clin. Psychol. Rev. 70, 26–39. https://doi.org/10.1016/j.cpr.2019.03.001.

Klimecki, O.M., Leiberg, S., Ricard, M., Singer, T., 2014. Differential pattern of functional brain plasticity after compassion and empathy training. Soc. Cogn. Affect. Neurosci. 9 (6), 873–879. https://doi.org/10.1093/scan/nst060.

Klimecki, O.M., Singer, T., 2017. The compassionate brain. In: Seppälä, E.M., Simon-Thomas, E., Brown, S.L., Worline, M.C. (Eds.), The Oxford Handbook of Compassion Science. Oxford University Press, New York, pp. 109–120.

Kragel, P.A., Bianciardi, M., Hartley, L., Matthewson, G., Choi, J., Quigley, K.S., Wald, L.L., Wager, T.D., Barrett, L.F., Satpute, A.B., 2019. Functional involvement of human Periaqueductal Gray and other midbrain nuclei in cognitive control. J. Neurosci. 39 (31), 6180–6189. https://doi.org/10.1523/jneurosci.2043-18.2019.

Laird, A.R., Fox, P.M., Price, C.J., Glahn, D.C., Uecker, A.M., Lancaster, J.L., Turkeltaub, P.E., Kochunov, P., Fox, P.T., 2005. ALE meta-analysis: controlling the false discovery rate and performing statistical contrasts. Hum. Brain Mapp. 25 (1), 155–164. https://doi.org/10.1002/hbm.20136.

Lamm, C., Batson, C.D., Decety, J., 2007. The neural substrate of human empathy: effects of perspective-taking and cognitive appraisal. J. Cogn. Neurosci. 19 (1), 42–58. https://doi.org/10.1162/jocn.2007.19.1.42.

Lamm, C., Decety, J., Singer, T., 2011. Meta-analytic evidence for common and distinct neural networks associated with directly experienced pain and empathy for pain. NeuroImage 54 (3), 2492–2502. https://doi.org/10.1016/j.neuroimage.2010.10.014.

Lancaster, J.L., Tordesillas-Gutiérrez, D., Martinez, M., Salinas, F., Evans, A., Zilles, K., Mazziotta, J.C., Fox, P.T., 2007. Bias between MNI and talairach coordinates analyzed using the ICBM-152 brain template. Hum. Brain Mapp. 28, 1194–1205. https://doi.org/10.1002/hbm.20345.

Laneri, D., Krach, S., Paulus, F.M., Kanske, P., Schuster, V., Sommer, J., Müller-Pinzler, L., 2017. Mindfulness meditation regulates anterior insula activity during empathy for social pain. Hum. Brain Mapp. 38 (8), 4034–4046. https://doi.org/10.1002/hbm.23646.

Lang, P.J., Bradley, M.M., Cuthbert, B.N., 1997. International Affective Picture System (IAPS). NIMH Center for the Study of Emotion and Attention. Accessed from https://csea.phhp.ufl.edu/media/iapsmessage.html.

Leung, M., Lau, W.K.W., Chan, C.C.H., Wong, S.S.Y., Fung, L.C., Lee, T.M.C., 2017. Meditation-induced neuroplastic changes in amygdala activity during negative affective processing. Soc. Neurosci. 13 (3), 277–288. https://doi.org/10.1080/17470919.2017.1311939.

Levy, R., Dubois, B., 2006. Apathy and the functional anatomy of the prefrontal cortex-basal ganglia circuits. Cereb. Cortex 16 (7), 916–928. https://doi.org/10.1093/cercor/bhj043.

Linnman, C., Moulton, E.A., Becerra, L., Borsook, D., 2013. Neuroimaging of the periaqueductal gray: state of the field. NeuroImage 60 (1), 505–522. https://doi.org/10.1016/j.neuroimage.2011.11.095.Neuroimaging.

Longe, O., Maratos, F.A., Gilbert, P., Evans, G., Volker, F., Rockcliff, H., Rippon, G., 2010. Having a word with yourself: neural correlates of self-criticism and self-reassurance. NeuroImage 49, 1849–1856. https://doi.org/10.1016/j.neuroimage.2009.09.019.

Lutz, A., Brefczynski-Lewis, J., Johnstone, T., Davidson, R.J., 2008. Regulation of the neural circuitry of emotion by compassion meditation: effects of meditative expertise. PLoS One 3 (3), e1897. https://doi.org/10.1371/journal.pone.0001897.

Marsh, A.A., 2019. The caring continuum: evolved hormonal and proximal mechanisms explain prosocial and antisocial extremes. Annu. Rev. Psychol. 70 (1), 347–371. https://doi.org/10.1146/annurev-psych-010418-103010.

Mascaro, J.S., Rilling, J.K., Negi, L.T., Raison, C.L., 2013a. Pre-existing brain function predicts subsequent practice of mindfulness and compassion meditation. NeuroImage 69, 35–42. https://doi.org/10.1016/j.neuroimage.2012.12.021.

Mascaro, J.S., Rilling, J.K., Tenzin, N.L., Raison, C.L., 2013b. Compassion meditation enhances empathic accuracy and related neural activity. Soc. Cogn. Affect. Neurosci. 8 (1), 48–55. https://doi.org/10.1093/scan/nss095.

Matos, M., Duarte, C., Duarte, J., Pinto-gouveia, J., Petrocchi, N., Basran, J., Gilbert, P., 2017. Psychological and physiological effects of compassionate mind training: a Pilot randomised controlled study. Mindfulness 8, 1699–1712. https://doi.org/10.1007/s12671-017-0745-7.

Mayseless, O., 2016. The Caring Motivation: An Integrated Theory, 1st ed. Oxford University Press, New York.

Menon, V., 2015. Salience network. In: In: Toga, A.W. (Ed.), Brain Mapping: An Encyclopedic Reference Vol. 2. Academic Press: Elsevier, pp. 597–611. https://doi.org/10.1016/B978-0-12-397025-1.00052-X.

Mercadillo, R.E., Diaz, J.L., Pasaye, E.H., Barrios, F.A., 2011. Perception of suffering and compassion experience: brain gender disparities. Brain Cogn. 76, 5–14. https://doi.org/10.1016/j.bandc.2011.03.019.

Mercadillo, R.E., Alcauter, S., Fernández-Ruiz, J., Barrios, F.A., 2015. Police culture influences the brain function underlying compassion: a gender study. Soc. Neurosci. 10 (2), 135–152. https://doi.org/10.1080/17470919.2014.977402.

Molenberghs, P., Johnson, H., Henry, J.D., Mattingley, J.B., 2016. Understanding the minds of others: a neuroimaging meta-analysis. Neurosci. Biobehav. Rev. 65, 276–291. https://doi.org/10.1016/j.neubiorev.2016.03.020.

Nephew, B.C., Bridges, R.S., Lovelock, D.F., Byrnes, E.M., 2010. Enhanced maternal aggression and associated changes in neuropeptide gene expression in multiparous rats. Behav. Neurosci. 123 (5), 949–957. https://doi.org/10.1037/a0016734.

Onoda, K., Kuroda, Y., Yamamoto, Y., Abe, S., Oguro, H., Nagai, A., Bokura, H., Yamaguchi, S., 2010. Post-stroke apathy and hypoperfusion in Basal ganglia: SPECT study. Cerebrovasc. Dis. 31 (1), 6–11. https://doi.org/10.1159/000319771.

Oveis, C., Horberg, E.J., Keltner, D., 2010. Compassion, pride, and social intuitions of self-other similarity. J. Pers. Soc. Psychol. 98 (4), 618–630. https://doi.org/10.1037/a0017628.

Panksepp, J., 2011. The basic emotional circuits of mammalian brains: Do animals have affective lives? Neurosci. Biobehav. Rev. 35 (9), 1791–1804. https://doi.org/10.1016/j.neubiorev.2011.08.003.

Patil, I., Zanon, M., Novembre, G., Zangrando, N., Chittaro, L., Silani, G., 2018. Neuroanatomical basis of concern-based altruism in virtual environment. Neuropsychologica 116, 34–43. https://doi.org/10.1016/j.neuropsychologia.2017.02.015.

Paradiso, S., Ostedgaard, K., Vaidya, J., Ponto, L.B., Robinson, R., 2013. Emotional blunting following left basal ganglia stroke: the role of depression and fronto-limbic functional alterations. Psychiatry Res. Neuroimaging 211 (2), 148–159. https://doi.org/10.1016/j.pscychresns.2012.05.008.

Paulmann, S., Bleichner, M., Kotz, S.A., 2013. Valence, arousal, and task effects in emotional prosody processing. Front. Psychol. 4 (June), 1–10. https://doi.org/10.3389/fpsyg.2013.00345.

Pereira, E.A.C., Lu, G., Wang, S., Schweder, P.M., Hyam, J.A., Stein, J.F., Paterson, D.J., Aziz, T.Z., Green, A.L., 2010. Ventral periaqueductal grey stimulation alters heart rate variability in humans with chronic pain. Exp. Neurol. 223 (2), 574–581. https://doi.org/10.1016/j.expneurol.2010.02.004.

Petrocchi, N., Cheli, S., 2019. The social brain and heart rate variability: implications for psychotherapy. Psychol. Psychother. Theory Res. Pract. 92 (2), 1–16. https://doi.org/10.1111/papt.12224.

Poldrack, R.A., Wagner, A.D., Prull, M.W., Desmond, J.E., Glover, G.H., Gabrieli, J.D.E., 1999. Functional specialization for semantic and phonological processing in the left inferior prefrontal cortex. NeuroImage 10 (1), 15–35 35.

Porges, S.W., 2007. The polyvagal perspective. Biol. Psychol. 74 (2), 116–143. https://doi.org/10.1016/j.biopsycho.2006.06.009.

Seppälä, E.M., Simon-Thomas, E., Brown, S.L., Worline, M.C., Cameron, C.D., Doty, J.R. (Eds.), 2017. The Oxford Handbook of Compassion Science, 1st ed. Oxford University Press, New York.

Simon-Thomas, E.R., Godzik, J., Castle, E., Antonenko, O., Ponz, A., Kogan, A., Keltner, D.J., 2012. An fMRI study of caring vs self-focus during induced compassion and pride. Soc. Cogn. Affect. Neurosci. 7, 635–648. https://doi.org/10.1093/scan/nsr045.

Shdo, S.M., Ranasinghe, K.G., Gola, K.A., Mielke, C.J., Paul, V., Miller, B.L., Rankin, K.P., 2018. Deconstructing empathy: neuroanatomical dissociations between affect sharing and prosocial motivation using a patient lesion model. Neuropsychologica 116, 126–135. https://doi.org/10.1016/j.neuropsychologia.2017.02.010.Shdo.

Stephan, K.E., Penny, W.D., Moran, R.J., den Ouden, H.E.M., Daunizeau, J., Friston, K.J., 2010. Ten simple rules for dynamic causal modeling. NeuroImage 49 (4), 3099–3109. https://doi.org/10.1016/j.neuroimage.2009.11.015.

Stevens, L., Woodruff, C.C., 2018. What Is This Feeling That I Have for Myself and for Others? Contemporary Perspectives on Empathy, Compassion, and Self- Compassion, and Their Absence. The Neuroscience of Empathy, Compassion, and Self-Compassion. Elsevier Inc.https://doi.org/10.1016/B978-0-12-809837-0/00001-5.

Strauss, C., Lever, B., Gu, J., Kuyken, W., Baer, R., Jones, F., Cavanagh, K., 2016. What is compassion and how can we measure it? A review of definitions and measures. Clin. Psychol. Rev. 47, 15–27. https://doi.org/10.1016/j.cpr.2016.05.004.

Suddendorf, T., 2018. Inside our heads: two key features created the human mind. Sci. Am. 319 (3), 42–47. https://doi.org/10.1038/scientificamerican0918-42.

Swick, D., Ashley, V., Turken, U., 2008. Left inferior frontal gyrus is critical for response inhibition. BMC Neurosci. 11, 1–11. https://doi.org/10.1186/1471-2202-9-102.

Talati, A., Hirsch, J., 2005. Functional specialization within the medial frontal gyrus for perceptual go/no-go decisions based on "what," "when," and "where" related information: an fMRI Study. J. Cogn. Neurosci. 17 (7), 981–993.

Turkeltaub, P.E., Eickhoff, S.B., Laird, A.R., Fox, M., Wiener, M., Fox, P., 2012. Minimizing within-experiment and within-group effects in activation likelihood estimation meta-analyses. Hum. Brain Mapp. 20 (1), 48–55. https://doi.org/10.1007/s10995-015-1800-4.

Uddin, L.Q., Nomi, J.S., Herbert-Seropian, B., Ghaziri, J., Boucher, O., 2017. Structure and function of the human insula. J. Clin. Neurophysiol. 34 (4), 300–306. https://doi.org/10.1097/WNP.0000000000000377.Structure.

van Noordt, S.J.R., Segalowitz, S.J., 2012v. Performance monitoring and the medial prefrontal cortex: a review of individual differences and context effects as a window on self-regulation. Front. Hum. Neurosci. 6 (July), 1–16. https://doi.org/10.3389/fnhum.2012.00197.

Vogt, B.A., 2005. Pain and emotion interactions in subregions of the cingulate gyrus. Nat. Rev. Neurosci. 6, 533–544.

Wallace, B.A., 1999. The four immeasurables. Cultivating the Boundless Heart. Snow Lion Publications, New York.

Weng, H.Y., Fox, A.S., Shackman, A.J., Stodola, D.E., Caldwell, J.Z.K., Olson, M.C., Rogers, G.M., Davidson, R.J., 2013. Compassion training alters altruism and neural responses to suffering. Psychol. Sci. 24 (7), 1171–1180. https://doi.org/10.1177/0956797612469537.

Weng, H.Y., Lapate, R.C., Stodola, D.E., Rogers, G.M., Davidson, R.J., 2018. Visual attention to suffering after compassion training is associated with decreased amygdala responses. Front. Psychol. 9, 1–13. https://doi.org/10.3389/fpsyg.2018.00771.