Interoception, mindfulness and touch: A meta-review of functional MRI studies

Sergi Casals-Gutiérrez*, Hilary Abbey

The University College of Osteopathy, 275, Borough High Street, London, SE1 1JE, UK

* Corresponding author.
E-mail address: sergi.gutierrez@uco.ac.uk (S. Casals-Gutiérrez).

Keywords:
Interoception
Mindfulness
Touch
Functional neuroimaging
fMRI

A B S T R A C T

Objectives: Deficits in interoception have been identified in wide range of patients with complex, long-term health conditions including chronic pain, anxiety, depression and somatoform disorders. This review analysed findings from functional MRI studies illustrating the neural correlates of interoception, mindfulness and touch and aimed to identify possible areas of convergence between different neural processing pathways.
Design: A meta-review was conducted to appraise existing systematic reviews (SR) and to explore the potential action mechanisms, which underpin manual therapy approaches that combine touch and mindfulness interventions.
Methods: Five electronic databases were systematically searched from September 2017 to March 2018. SRs were evaluated for methodological quality and risk of bias using the AMSTAR 2 instrument.
Results: Two high quality SRs studied neural correlates of mindfulness, two moderate quality SRs studied interoceptive tasks, and one low quality SR studied touch. Mindfulness and touch showed functional convergence in the interoceptive cortices. However, neural activation in different parts of the cortex was influenced by type of task and individual functional biases in processing tactile stimuli.
Conclusions: These findings provide a rationale for further studies into the effects of combined touch and mindfulness-based interventions for treating conditions associated with central sensitization and interoceptive deficits.

1. Introduction

1.1. Interoception

Interoception is defined as the sense of physiological condition of the whole body, including the visceral inputs originally posited by Sherrington [1] and the skin and musculoskeletal inputs demonstrated in recent neuroanatomical studies [2,3]. From a neurophysiological viewpoint, interoceptive signals are considered as the ongoing homeostatic afferent signals of the autonomic nervous system (ANS) [4,44]). An individual's ongoing perception of their internal physiological state supports homeostatic regulation and allostasis, ensuring their survival by motivating adaptive behaviour through the dynamic interplay between bodily sensations, subjective feelings and cognitive appraisals [5,6].

Interoceptive constructs have been proposed to explain how neurophysiological processes combine afferent stimuli from multiple bodily sources with cognitive assessments of salience. Conditions for accurate interoception are theorised to include the ability and willingness to notice internal bodily sensations and the emotional ability to understand and manage these sensations [7]. As interoception is a complex whole body-mind experience, experimental studies are typically designed to measure outcomes from interoceptive tasks. These tasks have been used to test at least two different domains or dimensions within the construct, namely interoceptive accuracy (IAc) and interoceptive metacognitive awareness (IAw) [8–11]. Whereas IAc is commonly defined as the ability to detect internal states, IAw represents the metacognitive assessment of IAc. Tasks measuring these domains include heartbeat perception and discrimination [12–14], attention to breath [15] and breath detection and discrimination [16], spontaneous sensations (SPS) [11,17], gastric distension [18], tension production [19], aversive interoceptive conditions, e.g. air hunger [20,21], thirst [22,23], and pain [24]; or pleasant interoceptive conditions, e.g. pleasant touch [25,131]; affect labelling, e.g. recognition of facial expressions displaying emotional evocative behaviour such as pain or fear [12,13,24,26,27,133], and tasks measuring discriminative and decision-making processes [28–30].

Other tasks involving interoception used in research studies have included measures designed to discriminate between feeling and thinking [31], affect matching and face matching [32], reappraising emotions and reacting to emotional stimuli [33], and observing or suppressing stimuli [34].

Additionally, self-reported assessment measures such as the MAIA (Multidimensional Assessment of Interoceptive Awareness) questionnaire [7] and Emotional Susceptibility Scale [8] have been used to measure interoceptive sensibility (IAs), where aspects of interoceptive awareness are self-assessed [9,10]. The constructs of IAc, IAw and IAs represent an incomplete model and have not been used systematically in neuroscience due to complexity and evolving understanding of interoceptive experiences. The model proposed by Di Lernia et al. [10], and supported by other studies [8,9,11,35] does, however, provide a useful starting point for understanding different aspects of interoceptive experience.

Interoceptive processing has been found to occur primarily in the insular cortex (IC) [3]. The posterior IC is the primary sensory centre for interoceptive afferents and the anterior IC processes the subjective feelings arising from integrating interoceptive sensations with proprioception, exteroception and cognition. The IC and anterior cingulate cortex (aCC) are conjointly activated in bodily feelings and described as an interoceptive cortex. This has complementary limbic sensory and motor cortices, similar to the somatosensory and motor cortices of the exteroceptive system [3,36]. Varying bodily sensations including pain, touch, temperature, muscular work, thirst, taste, dyspnoea, cardiorespiratory activation, vascular flush, and tension/distension of the oesophagus, stomach, bladder and rectum activate the interoceptive cortex [4,37,38].

1.2. *Interoception and health*

The clinical relevance of interoception has been demonstrated through the discovery of interoceptive deficits in a range of physical and psychological health problems including anxiety, depression addiction, eating disorders [35,38–41], with particular relevance in complex long-term body-mind disorders such as somatoform disorders or chronic pain [10,13,42,43].

A systematic review by Di Lernia et al. [10], reported interoceptive deficits in a chronic pain population (n = 696) compared to a control group (n = 614). The studies reviewed used various tasks including awareness of spontaneous sensations (SPS), tension production, and heartbeat perception and discrimination. Data showed significant trends in reduced interoceptive accuracy (IAc) in chronic pain participants but was insufficient to draw firm conclusions about altered interoceptive metacognitive awareness (IAw) or interoceptive sensibility (IAs) associated with chronic pain. Another review by D'Alessandro et al. [43], suggested there is interdependency between the processes of interoception and sensitization. Sensitization was defined as a neurologically-based amplification state arising from repeated stimuli. The authors proposed that altered interoceptive information leads toward neurological sensitization where dysfunction is expressed through inappropriate ANS activity. This then creates hypersensitivity in peripheral tissues and forms the basis for the metabolic and neurological cycles that underpin chronicity.

Close links between chronic pain and interoceptive deficits [10], and co-dependency between sensitization and interoceptive impairment [43] form the rationale for analysing the implications of current neuroscientific evidence for use by manual therapists. The prevailing model for symptom diagnosis and treatment in manual therapy has typically been based on a proprioceptive, exteroceptive lens of reasoning [43,44]. This is a paradoxical approach since evidence indicates that bodily feelings, such as pain, itch, temperature, or gastrointestinal tract tension/distension amongst others, are integrated via neurologically pathways that are distinct from proprioception [2,3]. Emerging evidence also highlights the relevance of a specific kind of touch, known as affective or gentle touch, in eliciting signals that are

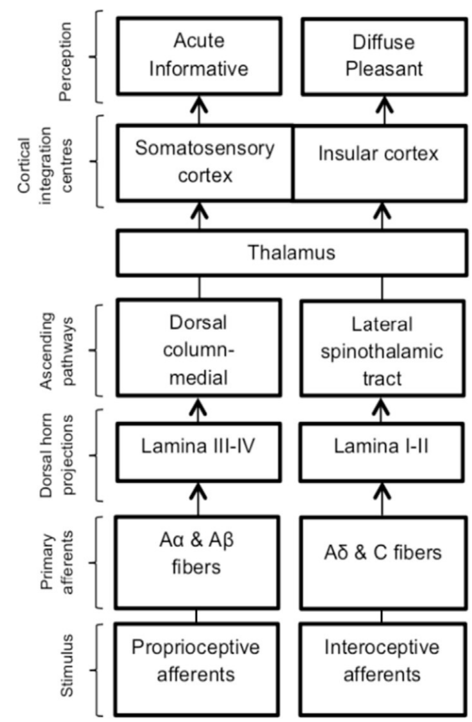

Fig. 1. Schematic model describing discrimininative (proprioceptive/exteroceptive) and affective (interoceptive) touch pathways, adapted from Craig [2,3], BjÖrsdotter et al. [49], & Morrison et al., [50]. This is a limited model which does not take into account contextual factors such as top-down functional biases in individual processing [55], but that may provide a basic framework for further development and expansion in the field of manual therapy.

integrated via interoceptive pathways [45–51,56], discussed in the section below.

1.3. *Interoception, touch and manual therapy*

Touch is now recognized as a cross-modal sensory system transmitting signals through proprioceptive, exteroceptive and interoceptive pathways [46,50,52,53]. Sensations processed via discriminative and affective pathways activate distinct mechanisms in the somatosensory and insular cortex respectively [54]. In contrast to proprioceptive or exteroceptive touch processing, interoceptive networks convey emotionally-valent information through low mechanical threshold unmyelinated C fibres (also named C-tactile; CTs), which project to the insula (Fig. 1) [45–48,56]. CT-targeted touch has been linked with pain inhibition [57], ANS regulation [58,59] and positive hedonia [51].

Increasing interest in the effects of touch in manual therapy on interoception was partially prompted by discoveries relating to the presence of interoceptive skin receptors [43,45,46,48,54,60–62].

In line with this, Bordoni & Marelli [63] have recently proposed that the fascial continuum is the primary supportive network in which interoceptors are embedded. From a therapeutic perspective, touch has been suggested as an input that can potentially modify sensitization states [43,54] and may be an action mechanism for effects in manual therapy [61]. These hypotheses are supported by various experimental studies showing outcomes from craniosacral therapy [64,65], osteopathic manipulative treatment [44,66–69] and deep touch [44,70,71] with ANS regulation, as well as studies showing links between myofascial release [72] and osteopathic HVLA thrust and mobilization techniques [44,73] with increases in interoceptive accuracy (IAc).

The studies described above illustrate positive neurophysiological outcomes with links to domains within the interoceptive construct from specific forms of external touch on patients' internal bodily experiences. They do not, however, explore the mechanisms of interventions that aim to enhance patients' awareness of sensations, discussed below.

1.4. Interoception and mindfulness

Mindfulness was introduced as a healthcare intervention in the 1970s in the form of Mindfulness Based Stress Reduction (MBSR) programmes [74]. More recently Mindfulness Based Cognitive Therapy (MBCT) was developed to help patients manage depression, long-term health conditions and to promote wellbeing [75]. Less structured approaches to mindfulness are also central to some functional contextual Cognitive Behavioural Therapy (CBT) approaches such as Acceptance and Commitment Therapy (ACT) [76].

Mindfulness has been described as a non-judgmental process of directing attention to present moment experience including thoughts, emotions, sensations and perceptions [35]. Kabat-Zinn's [77] commonly used definition considers mindfulness as the practice of directing attention to present moment experience with an attitude of non-judgmental acceptance [78]. It aims to cultivate two processes: present moment awareness of thoughts, emotions, sensations and perceptions; and ability to experience with an open, non-reactive mindset [35]. An implicit element of mindfulness is therefore to develop volitional regulation of attention for somato-visceral sensations, emotions and cognitive appraisals [16].

However, mindfulness has also been defined as a state, a trait, a disposition or a skill [79]. Variations in the concept are also illustrated by differing constructs in outcome measures including: attention and awareness - Mindful Attention Awareness Scale [80]; non-reactivity, observing, acting with awareness, describing, non-judging - Five-Facet Mindfulness Questionnaire [81], and attention self-regulation and curiosity, openness, and acceptance - State Mindfulness Scale [82]. Different concepts of mindfulness underpin the formal and less formal interventions used in healthcare interventions and the research studies conducted to assess their outcomes and underlying mechanisms.

Research into meditation, MBSR/MBCT programmes and mindfulness practices as an integral part of ACT have demonstrated improvements in interoceptive attention and self-regulation [21,31,83], reduced anticipation of pain and unpleasantness [84], coping with pain [85,130], as well as neurophysiological changes including modulation in IC and aCC activity [29,30,86] and ANS homeostatic regulation [87].

1.5. Integrating touch and mindfulness in manual therapy

Research indicates that biopsychosocial models of healthcare are helpful for understanding complex long-term health problems [88] and that multidisciplinary approaches which incorporate physical, psychological and educational interventions are more effective for managing conditions such as chronic pain [89]. Traditionally, manual therapy diagnosis and treatment has been based on assessing the proprioceptive or exteroceptive properties of symptoms relating to movement, musculoskeletal chains and posture [43]. Craig's [2,3] findings, however, suggest that interoceptive awareness of bodily feelings differs neurologically from proprioception and exteroception. This implies that manual therapy approaches that do not include an understanding of the patients' own body awareness and responses to internal physiological changes may be incomplete. It also suggests the need for further research into the interoceptive effects of touch, including new approaches guided by practitioner and patient mindfulness.

A previous systematic review suggested that mindfulness practices could be a viable adjunct for manual therapy when treating somatic manifestations of stress and chronic pain [90]. The rationale for integrating mindfulness into manual therapy is based on the fact that interoceptive processing and central sensitization do not only involve bottom-up afferent peripheral inputs but are also influenced by top-down modulation processes supported by the central nervous system [5,6,91]. Therefore, it is arguable to state that touch-based approaches across manual therapies alone would only influence bottom-up interoceptive modulation, e.g. reducing peripheral nociceptive drive, leaving top-down cognitive aspects of interoceptive processing untouched. Furthermore, the rationale for combining both approaches is also supported by the understanding that interpersonal tactile communication, implicit in manual therapies such as osteopathy, physiotherapy or craniosacral therapy, is a bidirectional process involving cognitive-attentional modulations in both subject and operator [54]. In line with this, some studies have showed that interoceptive processing triggered by touch is not only influenced by the type of touch [50]; Björnsdotter et al., 2012; [51], but also by top-down cognitive influences on affective representations of the individuals being touched [92] and the cognitive-attentional dynamics of the operator [54].

Promising results have been shown in mindfulness-based interventions for patients with persistent pain delivered by physiotherapists and osteopaths. Recent examples include the Physiotherapy informed by Acceptance and Commitment Therapy study (PACT) [93,94]; Mindfulness-Based Functional Therapy [95]; a brief ACT-based intervention [96]; and the Osteopathy, Mindfulness and Acceptance Programme (OsteoMAP) [97,98].

The objective of this review was therefore to examine fMRI evidence about the neural correlates of touch and mindfulness and identify evidence to explain potential action mechanisms of a combined treatment approach on interoceptive processing.

2. Methods

The meta-review protocol was formulated in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Fig. 2) [99,100], and methodological considerations for SRs [101,102]. Choice of method was motivated by the aim to analyse findings from existing outcome studies and functional neuroimaging evidence.

2.1. Literature search

The search strategy followed the Peer Review of Electronic Search Strategies (PRESS) guidelines [103]. Keywords included clinical neuroscience terms (e.g. "neural correlates" or "brain activity") and linked syntax, Boolean operators and widely used descriptors (e.g. 'fMRI' and "functional neuroimaging") to increase specificity [104] (Table 1). "Neural correlates" is a frequently used descriptor referring to the ongoing activity in the brain corresponding with, and necessary to produce, a particular experience. AMED, CINAHL, Cochrane Database of Systematic Reviews, MEDLINE and PubMed databases were systematically searched from September 2017 to March 2018 (see Table 2).

2.2. Study selection and eligibility criteria

2.3. Methodological quality - risk of bias assessment (ROB)

Quality of evidence was appraised using the 16 item AMSTAR 2 (A MeaSurement Tool to Assess Reviews) instrument (Appendix 1). Guidelines suggest AMSTAR 2 outcomes are not based on numerical scores but a 'final confidence rating' relating to critical and non-critical weaknesses [105]. Confidence is: 'high' (zero or one 'non-critical weakness'), 'moderate' (more than one 'non-critical weakness'), 'low' (one 'critical flaw' with/without 'non-critical weakness') or 'critically low' (more than one 'critical flaw' with/without 'non-critical weakness').

2.4. Data extraction

Using standardised methodological criteria, information was collected into customised data extraction tables [106] containing descriptive details (author, year, topic, database, size, design, sample, intervention or task, and fMRI measurements (Table 4). Table 5 summarised fMRI findings by category (i.e. interoception, mindfulness or touch), and activation clusters by region (i.e. insular, cingulate or

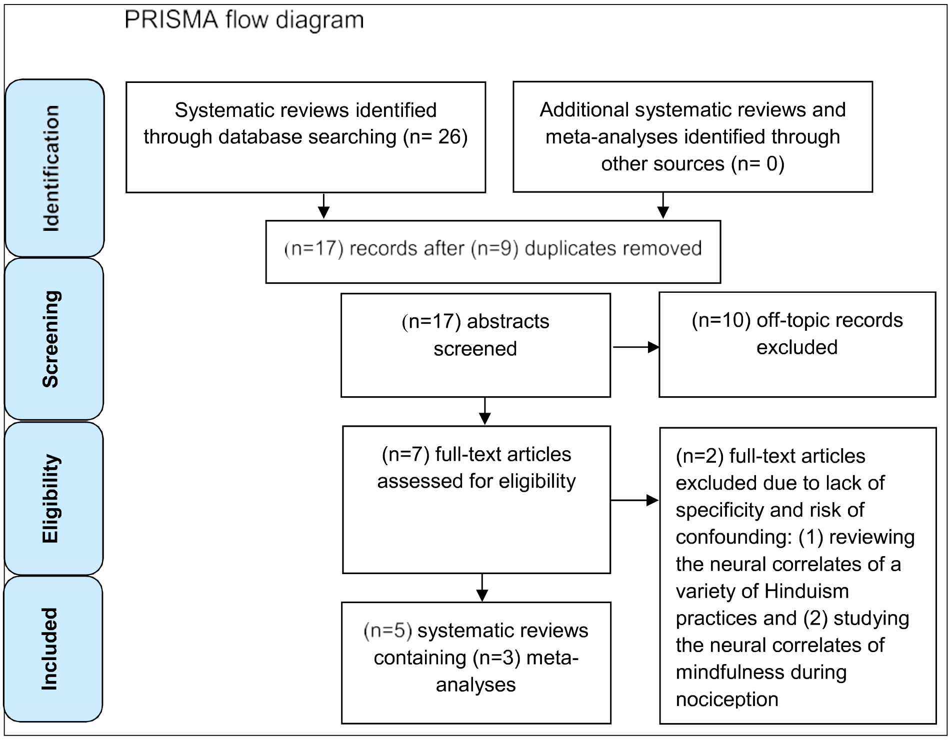

Fig. 2. PRISMA flow diagram.

Table 1
Search strategy.

("Interoception" OR "Interoception" [MeSH] OR "Touch" OR "Touch" [MeSH] OR "Mindfulness" OR "Mindfulness" [MeSH]) AND ("Insula" OR "Neural correlates" OR "Brain activity" OR "fMRI" OR "Functional neuroimaging") AND ("Systematic Review" [Publication Type] OR "Meta-analyses" [Publication Type])

Table 2
Inclusion criteria.

-Peer-reviewed SRs, with or without meta-analyses
-Investigating neural correlates associated with interoception, mindfulness or touch
-fMRI studies
-All population types
-Publication in the previous 5 years to retrieve current research
-Published in English, due to lack of translation services or funding

prefrontal cortices).

3. Results

3.1. Literature search and study selection

A total of 26 SRs were identified from 4 databases, including 9 duplicates. After screening 17 abstracts, 10 records did not meet inclusion criteria, leaving 7 articles for full-text appraisal. Two studies were excluded due to lack of specificity and risk of confounding variables in the neural correlates of mindfulness. Five SRs containing three meta-analyses were included in the final review (Fig. 2).

3.2. Methodological quality - risk of bias assessment

Five SRs were assessed for risk of bias (RoB) using AMSTAR 2 [105]. Item 2, a 'critical domain' of AMSTAR 2, was excluded. No SRs included it as AMSTAR 2 was published at the same time as these studies.

Two SRs evaluating mindfulness neural correlates had no 'critical flaws' and only one 'non-critical weakness', so the 'final confidence rating' for mindfulness was 'high'. Two SRs on interoception had no 'critical flaws' but more than one 'non-critical weaknesses', so the confidence rating for interoception was 'moderate'. The SR on touch had several 'critical flaws' and 'non-critical weaknesses', so confidence was 'critically low' (Table 3).

3.3. Study characteristics

Three SRs contained meta-analyses. Two SRs studied changes in brain activity after 7–8 week mindfulness-based programs compared to controls [107,108]; two studied the neural correlates of interoceptive tasks involving [109,110]; and one reviewed the neural correlates of affective and discriminative touch [55] (Table 4).

4. Discussion

4.1. Summary of key findings

This meta-review evaluated links between the neural correlates of mindfulness, touch and interoception to identify neurophysiological evidence that might clarify the potential action mechanisms of manual therapy interventions that combine touch and mindfulness on patients' interoceptive outcomes. Neural correlates refer to ongoing activity in the brain that corresponds with, and is necessary to produce, a particular experience.

Interoceptive deficits have been linked to central sensitization and chronic pain [10,43], making interoception a relevant concept for manual therapists. Interoceptive deficits and central sensitization do not only involve bottom-up ongoing interoceptive input, but also top-down cognitive-attentional modulation of bodily sensations [5,6,91]. Promising results have been shown in approaches delivered by physiotherapists and osteopaths that combine manual treatments with mindfulness-based interventions for patients with persistent pain, focusing not only on effecting changes on bodily sensations but also on associated cognitive appraisals [93–98].

Table 3
RoB assessment of included SRs based in AMSTAR 2 instrument.

	AMSTAR 2 items	1	2*	3	4*	5	6	7*	8	9*	10	11*	12	13*	14	15*	16	Critical flaws	Non-critical weaknesses	Overall ’ final confidence
Author (year)	Young et al. [107],	Y	E	Y	P	Y	Y	Y	Y	Y	N	N/	N/	Y	Y	N/	Y	0	1	High
	Gotink et al. [108],				Y							A	A			A		0	1	High
	Adolfi et al. [109],	Y	E	Y	P	Y	Y	Y	Y	Y	N	N/	N/	Y	Y	N/	Y	0	2	Moderate
	Schulz [110],				Y							AY	AY			AY		0	3	Moderate
	Morrison [55],	Y	E	Y	P	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	5	4	Critically low

Abbreviations: E = item excluded; N = no; N/A = not applicable as no meta-analysis was performed; PY = partial yes; Y = yes; * = AMSTAR 2 critical domains.

The insular cortex (IC) was shown to be the most consistent brain area activated by all three modalities, indicating that interoception, mindfulness and touch show functional convergence within the interoceptive cortex. Evidence also indicated that the cingulate cortex (CC) and prefrontal cortex (PFC) were activated during interoceptive and mindfulness-based tasks but not by discriminative and affective touch tasks (Fig. 3).

This was aligned with Craig's [2,3] functional neuroanatomy findings and with previous fMRI studies showing increased insular activation in various neural processes including interoception (e.g. of nociceptive, chemical or mechanical afferents); exteroception (e.g. tactile stimulation and visual information); and emotional and cognitive processing [16,21,29,30,49,60,86,111,112]. It suggests the IC has an integrative role in body-mind interactions, being strategically located at the nexus of the neural systems underlying sensation, emotion and cognition. The IC may therefore constitute a central hub for integrating somato-visceral sensations, subjective feelings, cognitive appraisals and individuals' awareness of their internal and external physiological environment or milieu [6,35].

4.2. Neural correlates of interoception

In functional MRI meta-analyses measuring brain activity during interoceptive tasks, insular activity significantly increased. Adolfi et al. [109], reported an activation cluster in the right anterior (aIC), where Schulz [110] concluded it was in the right posterior insula (PI), although five studies in this meta-analysis reported increased aIC activity. Further analysis of methods suggested discrepancies could have arisen from using different brain atlases (e.g. canonical brain avg152T1. img versus PALS) to contrast the MNI coordinates in fMRI data. Brain atlases are important coordinate systems that provide spatial and structural frameworks for visualizing the brain, and templates for normalizing functional MRI data into the same stereotactic space [113]. They have different advantages and limitations, so conflicting conclusions could relate to labelling brain areas differently, rather than actual discrepancies in activation. Both studies reported that right-sided asymmetry was associated with the nature of the afferents, suggesting that stimuli activating sympathetic afferents were projected to the right aIC and stimuli inducing parasympathetic arousal provided input to the left aIC. This was consistent with previous studies highlighting lateralization trends in processing ANS activity and emotions [5,37].

In contrast to Schulz [110], the anterior cingulate cortex (aCC) was reported to be a key structure in Adolfi et al.,‘s [109] meta-analysis. Schulz [110] explored neural processing in heartbeat detection and discriminations tasks but Adolfi et al. [109], reported that they evaluated a wider range of tasks, including pain and food anticipation, gastric distension, air hunger, thirst, pain, heartbeat and breath detection and discrimination, empathy, affect labelling and decision-making. Discrepancies could therefore be due to different interoceptive processing. Adolfi et al.'s, [109], findings are supported by lesion-based studies which demonstrate that damage in both the aCC and IC results in impairments in different interoceptive domains [114,115]. Schulz [110] reported significant clusters of PFC activity. PFC activation during heart-focused interoception was ascribed to top-down attention and processing of feed-forward cardioceptive information. Schulz's work is supported by studies highlighting the PFC as a higher order cognitive area, which controls executive functions like attentional focus [116,117].

Overall, the studies demonstrate typical activation of the aIC and aCC, which form an interoceptive cortex [2,3,35]. Neuroanatomical tract-tracing, EEG and fMRI studies indicate these structures are coactivated to process most bodily sensations and the affective and motivational aspects of emotions [2,3,12,36]. However, although the insula is a core region for integrating general interoceptive signals, aCC activity is likely to vary by task, so further research is required to assess how different tasks influence aCC recruitment. Importantly, even in

Table 4
Descriptive details of included SRs.

Author (Year)	Meta-analysis methodology	Topic of interest	Database search	No. of studies included & type of design	Total no. of participants & population type	Type of intervention/tasks	Outcome measures
Young et al. [107],	Not possible due to heterogeneity in population and tasks	Neural correlates of mindfulness	PubMed, Scopus	N = 7 - WS (4) - RCT (2) - CT (1)	N = 185 - Healthy subjects (100) - Anxiety disorders (62) - Bipolar disorders (23)	7 to 8-week MBCT/MBSR programs	fMRI measurements pre/post intervention, during mindfulness-based tasks, including labelling of facial expressions, aversive interceptive conditions, and mindful meditation Self-reported outcome measurements pre/post intervention, including BAI, FFMQ, KIMS, RSES, TAS
Gotink et al. [108],	Not possible due to heterogeneity in population and tasks	Neural correlates of mindfulness	PubMed, Medline, Embase, PsychINFO, Web of Science	N = 30 - RCT (13) - Cohort (9) - CS (8)	N = 1207 - Healthy subjects (988) - Anxiety disorders (49) - Depression (37) - Parkinson (27) - Stressed (26) - Back pain (23) - PTSD (23) - Alzheimer (21) - Tinnitus (13)	8-week MBSR programs	fMRI measurements pre/post intervention, during mindfulness-based tasks, feeling vs. thinking, affect labelling vs. gender labelling, affect matching vs. face matching, reappraising emotions vs. reacting to emotional stimuli, and observing vs. suppressing Self-reported outcome measurements pre/post intervention, including MAAS and FFMQ
Adolfi et al. [109],	MKDA	Neural correlates of interoception	PubMed, Medline, BrainMap Database	N = 34 - WS (28) - CT (6)	N = 681 - Healthy subjects (617) - Addiction (35) - Phobia (29)	Variety of interoceptive tasks, including pain and food anticipation, gastric distension, air hunger, thirst, pain, heartbeat and breath detection and discrimination, empathy, affect labelling and decision-making	fMRI measurements at baseline condition and during a variety of interoceptive tasks
Schulz [110],	MKDA	Neural correlates of interoception	PubMed, PsycNet, pubPsych, Psyndex, WorldCat, Web of Science	N = 9 - WS (9)	N = 262 - Healthy subjects (175) - Major depressive disorder (53) - Phobia (34)	Heartbeat detection and discrimination tasks	fMRI measurements at baseline condition and during tasks involving heart-focused interoception
Morrison [55],	ALE	Neural correlates of touch	PubMed	N = 22 - WS (22)	N = 291 - Healthy subjects (291)	Tactile stimulation - (19) Soft brush - (5) Hand - (2) Latex glove - (2) Velvet-covered dowel - (1) Brush - (1) Lotioned glove	fMRI measurements at baseline condition and during a series of different types of skin stroking and other touch conditions

Abbreviations: ALE = Activation Likelihood Estimation; BAI= Beck's Anxiety Inventory; CS= Cross-Sectional study; CT= Controlled Trial; FFMQ= Five-Factor Mindfulness Questionnaire; fMRI = functional Magnetic Resonance Imaging; KIMS= Kentucky Inventory of Mindfulness Skills; MBCT = Mindfulness-Based Cognitive Therapy; MAAS = Mindful Attention Awareness Scale; MBSR = Mindfulness-Based Stress Reduction; MKDA = Multi Kernel Density Analysis; PTSD= Post-Traumatic Stress Disorder; RCT = Randomized Controlled Trial; RSES = Response to Stressful Experience Scale; TAS = Toronto Alexithymia Scale; WS= Within-Subjects study.

Table 5
Summary of fMRI results of included SRs classified in categories and regions of interest.

		Mindfulness		Interoception		Touch
		Young et al. [107],	Gotink et al. [108],	Adolfi et al. [109],	Schulz [110],	Morrison [55],
Regions of interest	Insular cortex	Evidence of increased IC reactivity after 7/8-week MBSR interventions involving labelling of facial expressions and aversive interoceptive stimuli. No sub-regions were specified	Ambiguous results from MSBR studies. One study showed decreased activity during mindfulness tasks. Another showed increased activity during labelling of facial expressions. 7 studies showed increased IC reactivity during mindfulness-based tasks after 8-week MBSR interventions. No sub-regions were specified	Meta-analyses showed robust evidence of increased right aIC activity during varied tasks involving interoception	Meta-analyses showed increased right PI activity with heart-focused interoception. 4 studies showed neural activation with cardioceptive attentiveness in the right aIC	Meta-analyses showed increased PI activity, relative to SI, during affective tactile stimulation when compared to discriminative touch. A degree of shared activation between PI and SI suggested that differences reflected functional biases in tactile processing networks, rather than functionally or anatomically distinct pathways
	Cingulate cortex	Increased aCC reactivity during processing of aversive interoceptive stimuli after 7/8-week mindfulness based-interventions	Disparate results from MBSR interventions. 2 studies reported less activity, 3 showed increased functional connectivity with other cortices, and 8 showed increased reactivity during mindfulness-based tasks, labelling facial expressions and aversive interoceptive stimuli. No subregions were specified	Meta-analysis revealed significant evidence of increased right aCC activity during a variety tasks involving interoceptive focus		
	Prefrontal cortex	Consistent findings showed increased PFC activity associated with amount of practice and dispositional mindfulness. Subregions were specified but had no statistical significance	Results revealed increased PFC activity during mindfulness-based tasks post MBSR interventions; and increased connectivity to the IC and aCC		Meta-analytic evidence showed increased activity in the frontal lobe during heart-focused interoception No subregions were specified	
		High		Moderate		Critically low
		Quality of evidence based in AMSTAR 2 'final confidence rating'				

Abbreviations: aCC = anterior cingulate cortex; aIC = anterior insular cortex; CC = cingulate cortex; IC = insular cortex; MBSR = mindfulness-based stress reduction; PI = posterior insula; PFC = prefrontal cortex; SI: somatosensory cortices.

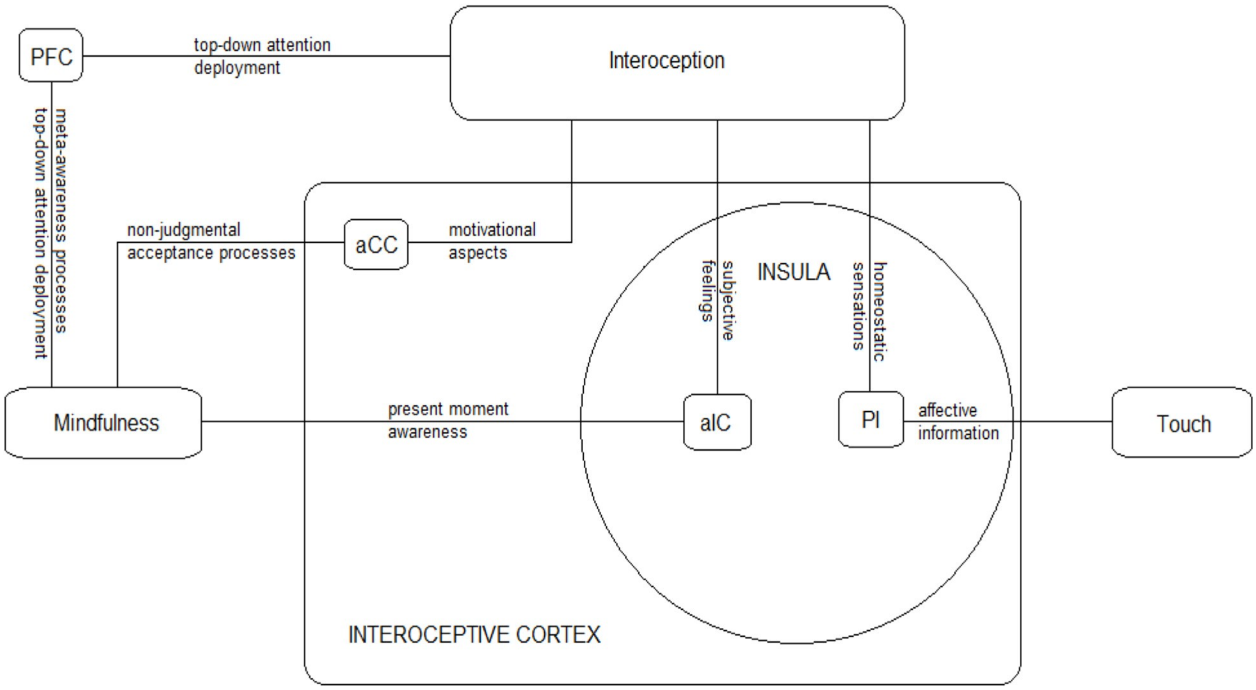

Fig. 3. Schematic model designed by review author showing neurophysiological relationships between interoception, mindfulness and touch, and suggested underlying mechanisms; based on included fMRI studies and Craig's [2,3] neuroanatomical discoveries. Abbreviations: aCC = anterior cingulate cortex; aIC = anterior insular cortex; PFC = prefrontal cortex; PI = posterior insula.

homogenous heartbeat detection tasks, not all participants are likely to respond the same way. For some participants, these tasks can evoke subjective feelings while others may process heartbeat sensations without emotional responses, so individual discrepancies are likely to relate to different activation clusters. If interoceptive tasks are linked to goal-oriented instructions (e.g. counting heartbeats, pressing a button every heartbeat, or decision-making), different motivational aspects of interoception may also be involved.

4.3. *Neural correlates of mindfulness*

A consistent finding was task-relevant activity in the insula following mindfulness-based interventions (MBI), but changes were not observed in all studies and results also showed evidence of increased aCC and PFC activity.

Mindfulness practices aim to increase non-judgmental awareness and acceptance of present moment experience [78] by increasing attentional skills to notice present moment thoughts, emotions, sensations and perceptions; and psychological flexibility involving awareness, openness and willingness to be active [118]. Mindfulness therefore helps to develop volitional regulation of attention for somato-visceral sensations, emotions and cognitive appraisals [35]. The insula supports interoceptive bodily awareness and internal physiological experiences [2,3]. Mindfulness training may create greater insular activation, although some studies report decreased IC activity. Young et al. [107], suggested that differences were due to type of mindfulness intervention and functional task. The authors argued that resilience training to cultivate attentional control and tolerance for aversive interoceptive experiences would increase acceptance, rather than interoception, and be reflected in reduced insular activation.

Gotink et al. [108], did not draw conclusions about sub-region activity, although many of the studies reviewed reported increased aCC activity. This region is assumed to play a role in regulating emotions, detecting conflicting information and motivational aspects of attention. In mindfulness, altered aCC activity might be interpreted in terms of non-judgmental acceptance processes, involving recognition of emotional responses and the attentional cognitive process of distancing [107]. This hypothesis is congruent with functional neuroanatomy studies that demonstrate aCC involvement in motivational aspects of interoceptive processing [2,3].

PFC activation was demonstrated in meditation and dispositional mindfulness but there was lack of consistency in identifying specific sub-regions or networks. The PFC has well-established roles in higher order functions including meta-awareness and meta-cognition, self-awareness of consciousness and thinking about thinking [119]. A recent review about meta-cognitive abilities concluded that the PFC received input from the interoceptive cortex to monitor bodily sensations [120] and generate meta-cognitive representations of a system's state that could be used beyond the immediate task. It is plausible that results showing increased PFC activity after MBI reflect meta-cognitive activities for training flexibility in a meditator's focus of attention; alternatively, increased PFC activity may also illustrate top-down deployment of attention, but not necessarily meta-awareness [110].

However, observations of neural activation are likely to vary depending on the construct of mindfulness being investigated, the type of mindfulness activity used in an intervention, and the experience or disposition of research participants. For example, Alsubiae et al.,'s [121] systematic review reported promising outcomes from MBSR and MBCT programmes but cautioned that lack of methodological rigour in testing different potential mechanisms of action limited the conclusion that could be drawn. This indicates the need for further research exploring different mindfulness-based activities and outcome measures, with and without the addition of body movement and touch.

4.4. *Neural correlates of touch*

Morrison's [55] lower quality meta-analytic review compared fMRI data about the processing of affective (interoceptive) and discriminative (proprioceptive or exteroceptive) tactile stimulation. Results indicated that the posterior insula (PI) was selectively activated for touch associated with positive hedonic ratings but the somatosensory cortex (SI) activity was active in tactile conditions requiring discriminative processing. However, overlaps between the PI and SI suggested that differences reflected individual functional biases within processing networks, rather than functionally or anatomically distinct pathways. Supporting this, results from Wei & Bao [112] and Davidovic et al. [122], showed PI activation during both affective touch and emotionally neutral tactile stimulation.

Further research is needed to explore interplay between pathways but these variable results support the idea that activating different touch processing networks depends on the type of tactile stimulation and an individual's functional biases. The presence of individual functional biases influencing touch processing pathways emphasises how individual past experiences, expectations and predictions shape the physiological integration of touch. From a clinical perspective, this evidence is likely to indicate that potential therapeutic effects of touch (i.e. ANS homeostatic regulation) arise from an interactive regulation (i.e. monitoring and adjusting) amid tactile stimulation, between the operator's intention and the patient's integration of touch.

The 'critically low' score for Morrison's [55] study reflected methodological pitfalls in search strategy and study selection but not in the meta-analytic methods. Although not generalizable, the results were consistent with functional neuroimaging studies highlighting the PI as the primary interoceptive cortex for processing tactile information [45–49,51,56,60,112,122]. Neuroanatomical tract-tracing studies also show the PI receives nociceptive, thermal, visceral and tactile afferent projections that convey interoceptive information about bodily states [2,3] and suggests PI and SI activation in various tactile conditions is worth further investigation.

5. Implications for clinical practice

Recent neurophysiological studies have indicated new directions for research into the aetiological mechanisms that may underpin touch-based treatment outcomes, and it has been proposed that manual therapies like osteopathy may generate positive patient outcomes through their ability to influence central sensitization via interoceptive pathways [43]. Research on interoception has been motivated by clinical questions, as it is relevant to understanding and evaluating brain pathophysiology and bodily disorders [6], although uncertainty about differences between adequate and maladaptive interoceptive processes remains [132]. Interoceptive deficits have been identified in varied psychological and physical healthcare conditions such as anxiety, addiction, depression, chronic pain, and eating and somatoform disorders [10,13,35,38–43].

Results from this review indicated consistent processing of interoception, mindfulness and touch in the insular cortex, which is anatomically positioned as a primary interface between afferent bodily signals and cognitively-oriented processes. Neurophysiological effects of touch-based therapies on interoception have just been recently tested [44,72,73] but mindfulness and touch are thought to influence aIC and PI activity through top-down cognitive modulation and bottom-up physical stimulation. There may therefore be a neurophysiologically evidence-informed role for interventions that combine manual therapy and mindfulness-informed psychological approaches. Combined approaches could help patients with symptoms that are not adequately explained by exteroceptive or proprioceptive theories, such as medically unexplained symptoms or alexithymia [62], or patients who demonstrate limited responses to practitioner-led physical treatment, where mindfulness-based interventions could enhance self-awareness of, and ability to respond effectively to, bodily experiences [97].

6. Suggestions for further research

In fMRI literature, attention on perceptual modalities has been shown to amplify activity in relevant brain regions (e.g. tasks involving sight activate the visual cortex; [111]. Current understanding about neural mechanisms for interoception, mindfulness and touch is based on the type of tasks used in research studies. Although this meta-review's results for IC activation were robust, there were discrepancies regarding the insular subregions, CC and PFC. These were ascribed to sample heterogeneity [108], type of MBI [107], type of touch [55], or task [107,109,110]. To investigate mechanisms more clearly, future fMRI studies need homogenous, standardised task-based methods to assess if task differences explain these variations.

Neuroimaging studies in neuropathic patients indicated two separate networks for processing touch [53]. Other authors [54,55,92,112] have suggested these networks overlap in touch processing and are at least influenced by type of stimulation, top-down individual functional biases stemming from cognitive modulation of touch processing, and top-down operator's cognitive-attentional influences. Further fMRI research studying the influence of these factors on interoceptive stimulation evoked by touch is therefore needed to clarify underlying action mechanisms in manual therapies. These studies may benefit from testing scenarios that are more representative of clinical settings with tasks for the participants giving and receiving touch. These could include focusing on hands, heart, breathing or whole-body sensations, or using mindful awareness to focus participants' attention on ongoing experiences relating to touch. Including physiological measurements such as heart rate variability or skin conductance [87] could provide valuable information by showing the effects of type of task, corresponding neural correlates and ANS activity and could be more representative of patient-practitioner dynamics in touch-based therapies.

Current literature is based on fMRI studies analysing proprioceptive/exteroceptive (discriminative) and interoceptive (affective) aspects of touch. Many interoceptive studies have used soft brush stroking techniques to test affective processing [45,50,51,60]. This is targeted at specific stroking velocities to stimulate CT afferents, which has been linked to PI activation and positive hedonic values [47,49–52]. Brush stroking techniques are not representative of clinical settings, especially in manual therapies where touch and movement are used in evaluation and treatment [43]. Future research should include methodological procedures in line with real clinical contexts, especially in settings where touch represents a therapeutic tool such as osteopathy in perinatal care [61], craniosacral therapy [64,65], palliative care [123,124] and post-traumatic stress disorder [125].

This review also highlighted potential bias stemming from the use of different brain atlases to plot the MNI coordinates of fMRI data, so future research could compare inter-reliability across commonly used atlases.

7. Limitations

Study selection was discussed with two independent reviewers but the first author conducted the review and acknowledges potential selection and publication bias. Due to the integrative aims of the review, there is a risk of oversimplification in translating complex evidence into a synthesised summary. For example, Gotink et al. [108], reported amygdala and hippocampal modulation across MBI studies, but these structures were not included. The regions of interest highlighted in this review are part of broad functional connectivity networks (i.e. salience, default mode, and central executive networks), which support efficient cognition. Functional connectivity between networks is being studied to understand pathophysiology in disorders including chronic pain [126], depression [127], anxiety [128] and Parkinson's disease [129], but was beyond the scope and conclusions possible from this review.

8. Conclusions

This meta-review evaluated neurophysiological findings from fMRI studies and indicated that neural mechanisms for mindfulness and touch show functional convergence at the interoceptive cortex. Variations in activation clusters were considered, however to relate to the types of interoceptive task used in different studies and to functional biases in individual participants. The findings are of relevance to practitioners who are interested in patients' responses to different types of tactile stimulation and interoceptive sensations, and in the influences of central sensitization and previous experiences or expectations of touch. Previous research has demonstrated that both manual therapy and mindfulness-based interventions can separately influence interoceptive deficits associated with a range of physical and psychological health conditions. The evidence from this review demonstrates functional convergence in the interoceptive cortex and provides a clear rationale for further studies into the effects of combining touch and mindfulness in manual therapy for patients with conditions that are associated with central sensitization and interoceptive deficits.

Funding sources

None.

Ethical approval details

UCOREC.

Declaration of competing interest

None.

Acknowledgments

The first author would like to thank family and friends for their unconditional support and engagement throughout the review process.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijosm.2019.10.006.

References

[1] Sherrington CS. The interactive action of the nervous system. sixth ed. New Haven: Yale University Press; 1920.
[2] Craig AD. How do you feel? Interoception: the sense of the physiological condition of the body. Nat Rev Neurosci 2002;3(8):655–66. Aug.
[3] Craig AD. Interoception: the sense of the physiological condition of the body. Curr Opin Neurobiol 2003;13(4):500–5. Aug.
[4] Craig AD. Cooling, pain, and other feelings from the body in relation to the autonomic nervous system. Handb Clin Neurol 2013;117:103–9.
[5] Strigo IA, Craig AD. Interoception, homeostatic emotions and sympathovagal balance. Philos Trans R Soc Lond B Biol Sci 2016;371:1708. Nov.
[6] Tsakiris M, Critchley H. Interoception beyond homeostasis: affect, cognition and mental health. Philos Trans R Soc Lond B Biol Sci 2016;371:1708. Nov.
[7] Mehling WE, Price C, Daubenmier JJ, Acree M, Bartmess E, Stewart A. The multidimensional assessment of interoceptive awareness (MAIA). PLoS One 2012;7(11):e48230.
[8] Cali G, Ambrosini E, Picconi L, Mehling WE, Committeri G. Investigating the relationship between interoceptive accuracy, interoceptive awareness, and emotional susceptibility. Front Psychol 2015(6):1202. Aug 24.
[9] Garfinkel SN, Seth AK, Barrett AB, Suzuki K, Critchley HD. Knowing your own heart: distinguishing interoceptive accuracy from interoceptive awareness. Biol Psychol 2015;104:65–74. Jan.
[10] Di Lernia D, Serino S, Riva G. Pain in the body. Altered interoception in chronic pain conditions: a systematic review. Neurosci Biobehav Rev 2016;71:328–41. Dec.
[11] Borg C, Chouchou F, Dayot-Gorlero J, Zimmerman P, Maudoux D, Laurent B, Michael GA. Pain and emotion as predictive factors of interoception in Fibromyalgia. J Pain Res 2018;11:823–35. Apr 19.
[12] Pollatos O, Gramann K, Schandry R. Neural systems connecting interoceptive awareness and feelings. Hum Brain Mapp 2007;28(1):9–18. Jan.
[13] Pollatos O, Herbert BM, Wankner S, Dietel A, Wachsmuth C, Henningsen P, Sack M. Autonomic imbalance is associated with reduced facial recognition in somatoform disorders. J Psychosom Res 2011;71(4):232–9. Oct.
[14] Tracy J, Goyal N, Flanders A, Weening R, Laskas J, Natale P, Waldron B. Functional magnetic resonance imaging analysis of attention to one's heartbeat. Psychosom Med 2007;69(9):952–60. Dec.
[15] Doll A, Hölzel BK, Boucard CC, Wohlschläger AM, Sorg C. Mindfulness is associated with intrinsic functional connectivity between default mode and salience networks. Front Hum Neurosci 2015(9):461. Aug 25.
[16] Farb N, Segal ZV, Anderson AK. Mindfulness meditation training alters cortical representations of interoceptive attention. Soc Cogn Affect Neurosci 2013;8(1):15–26. Jan.
[17] Bauer CC, Díaz JL, Concha L, Barrios FA. Sustained attention to spontaneous thumb sensations activates brain somatosensory and other proprioceptive areas. Brain Cogn 2014;87:86–96. Jun.
[18] Wang GJ, Tomasi D, Backus W, Wang R, Telang F, Geliebter A, Korner J, Bauman A, Fowler JS, Thanos PK, Volkow ND. Gastric distention activates satiety circuitry in the human brain. Neuroimage 2008;39(4):1824–31. Feb 15.
[19] Flor H, Fürst M, Birbaumer N. Deficient discrimination of EMG levels and overestimation of perceived tension in chronic pain patients. Appl Psychophysiol Biofeedback 1999;24(1):55–66. Mar.
[20] Parsons Lawrence M, Egan Gary, Liotti Mario, Brannan Stephen, Denton Derek, Shade Robert, Robillard Rachael, Madden Lisa, Abplanalp Bart, Fox Peter T. Neuroimaging evidence implicating cerebellum in the experience of hypercapnia and hunger for air. Proc Natl Acad Sci U S A 2001;98(4):2041–6. Feb 13.
[21] Haase L, Thom NJ, Shukla A, Davenport PW, Simmons AN, Stanley EA, Paulus MP, Johnson DC. Mindfulness-based training attenuates insula response to an aversive interoceptive challenge. Soc Cogn Affect Neurosci 2016;11(1):182–90. Jan.
[22] Egan G, Silk T, Zamarripa F, Williams J, Federico P, Cunnington R, Carabott L, Blair-West J, Shade R, McKinley M, Farrell M, Lancaster J, Jackson G, Fox P, Denton D. Neural correlates of the emergence of consciousness of thirst. Proc Natl Acad Sci U S A 2003;100(25):15241–6. Dec 9.
[23] Farrell MJ, Egan GF, Zamarripa F, Shade R, Blair-West J, Fox P, Denton DA. Unique, common, and interacting cortical correlates of thirst and pain. Proc Natl Acad Sci U S A 2006;103(7):2416–21. Feb 14.
[24] Corradi-Dell'Acqua C, Hofstetter C, Vuilleumier P. Felt and seen pain evoke the same local patterns of cortical activity in insular and cingulate cortex. J Neurosci 2011;31(49):17996–8006. Dec 7.
[25] Migliorini R, Stewart J, May A, Tapert S, Paulus P. What do you feel? Adolescent drug and alcohol users show altered brain response to pleasant interoceptive stimuli. Drug Alcohol Depend 2013;133(2):661–8. Dec 1.
[26] Creswell JD, Way BM, Eisenberger NI, Lieberman MD. Neural correlates of dispositional mindfulness during affect labeling. Psychosom Med 2007;69(6):560–5. Jul-Aug.
[27] Hölzel BK, Hoge EA, Greve DN, Gard T, Creswell JD, Brown KW, Barrett LF, Schwartz C, Vaitl D, Lazar SW. Neural mechanisms of symptom improvements in generalized anxiety disorder following mindfulness training. Neuroimage Clin 2013;25(2):448–58. Mar.
[28] Stewart J, May A, Poppa T, Davenport P, Tapert S, Paulus P. You are the danger: attenuated insula response in methamphetamine users during aversive interoceptive decision-making. Drug Alcohol Depend 2014(0):110–9. Sep. 1.
[29] Kirk U, Gu X, Harvey AH, Fonagy P, Montague PR. Mindfulness training modulates value signals in ventromedial prefrontal cortex through input from insular cortex. Neuroimage 2014;100:254–62. Oct.
[30] Kirk U, Gu X, Sharp C, Hula A, Fonagy P, Montague PR. Mindfulness training increases cooperative decision making in economic exchanges: evidence from fMRI. Neuroimage 2016;138:274–83. Sep.
[31] Herwig U, Kaffenberger T, Jäncke L, Brühl AB. Self-related awareness and emotion regulation. Neuroimage 2010;50(2):734–41. Apr 1.
[32] Way BM, Creswell JD, Eisenberger NI, Lieberman MD. Dispositional mindfulness and depressive symptomatology: correlations with limbic and self-referential neural activity during rest. Emotion 2010;10(1):12–24. Feb.
[33] Modinos G, Ormel J, Aleman A. Individual differences in dispositional mindfulness and brain activity involved in reappraisal of emotion. Soc Cogn Affect Neurosci 2010;5(4):369–77. Dec.
[34] Murakami H, Katsunuma R, Oba K, Terasawa Y, Motomura Y, Mishima K, Moriguchi Y. Neural networks for mindfulness and emotion suppression. PLoS One 2015;10(6):e0128005. Jun17.
[35] Farb N, Daubenmier J, Price CJ, Gard T, Kerr C, Dunn BD, Klein AC, Paulus MP, Mehling WE. Interoception, contemplative practice, and health. Front Psychol 2015;6:763. Jun.
[36] Medford N, Critchley HD. Conjoint activity of anterior insular and anterior cingulate cortex: awareness and response. Brain Struct Funct 2010;214(5–6):535–49. Jun.
[37] Craig AD. Forebrain emotional asymmetry: a neuroanatomical basis? Trends Cogn Sci 2005;9(12):566–71.
[38] Craig AD. How do you feel - now? The anterior insula and human awareness. Nat Rev Neurosci 2009;10(1):59–70. Jan.
[39] Naqvi NH, Bechara A. The insula and drug addiction: an interoceptive view of pleasure, urges, and decision-making. Brain Struct Funct 2010;214(5–6):435–50. Jun.
[40] Paulus MP, Stein MB. Interoception in anxiety and depression. Brain Struct Funct 2010;214(5–6):451–63. Jun.
[41] Herbert BM, Pollatos O. Attenuated interoceptive sensitivity in overweight and obese individuals. Eat Behav 2014;15(3):445–8. Aug.
[42] Mirams L, Poliakoff E, Brown RJ, Lloyd DM. Interoceptive and exteroceptive attention have opposite effects on subsequent somatosensory perceptual decision making. *Q J Exp Psychol* (Hove). 2012;65(5):926–38.
[43] D'Alessandro G, Cerritelli F, Cortelli P. Sensitization and interoception as key neurological concepts in osteopathy and other manual medicines. Front Neurosci 2016;10:100. Mar 10.
[44]] Edwards DJ, Young H, Johnston R. The immediate effect of therapeutic touch and deep touch pressure on range of motion, interoceptive accuracy and heart rate

variability: a randomized controlled trial with moderation analysis. Front Integr Neurosci 2018;12:41. Sep. 21.
[45] Olausson H, Lamarre Y, Backlund H, Morin C, Wallin BG, Starck G, Ekholm S, Strigo I, Worsley K, Vallbo AB, Bushnell MC. Unmyelinated tactile afferents signal touch and project to insular cortex. Nat Neurosci 2002;5(9):900–4. Sep.
[46] Olausson H, Cole J, Vallbo A, McGlone F, Elam M, Krämer HH, Rylander K, Wessberg J, Bushnell MC. Unmyelinated tactile afferents have opposite effects on insular and somatosensory cortical processing. Neurosci Lett 2008;436(2):128–32. May.
[47] McGlone F, Vallbo AB, Olausson H, Loken L, Wessberg J. Discriminative touch and emotional touch. Can J Exp Psychol 2007;61(3):173–83. Sep.
[48] McGlone F, Olausson H, Boyle JA, Jones-Gotman M, Dancer C, Guest S, Essick G. Touching and feeling: differences in pleasant touch processing between glabrous and hairy skin in humans. Eur J Neurosci 2012;35(11):1782–8. Jun.
[49] Björnsdotter M, Morrison I, Olausson H. Feeling good: on the role of C fiber mediated touch in interoception. Exp Brain Res 2010;207(3–4):149–55. Dec.
[50] Morrison I, Löken LS, Olausson H. The skin as a social organ. Exp Brain Res 2010;204(3):305–14. Jul.
[51] Perini I, Olausson H, Morrison I. Seeking pleasant touch: neural correlates of behavioral preferences for skin stroking. Front Behav Neurosci 2015;9:8. Feb 5.
[52] Olausson H, Wessberg J, Morrison I, McGlone F, Vallbo A. The neurophysiology of unmyelinated tactile afferents. Neurosci Biobehav Rev 2010;34(2):185–91. Feb.
[53] McGlone F, Wessberg J, Olausson H. Discriminative and affective touch: sensing and feeling. Neuron 2014;82(4):737–55. May 21.
[54] Cerritelli F, Chiacchiaretta P, Gambi F, Ferretti A. Effect of continuous touch on brain functional connectivity is modified by the operator's tactile attention. Front Hum Neurosci 2017;11:368. Jul 20.
[55] Morrison I. ALE meta-analysis reveals dissociable networks for affective and discriminative aspects of touch. Hum Brain Mapp 2016;37(4):1308–20. Apr.
[56] Zimmerman A, Bai L, Ginty DD. The gentle touch receptors of mammalian skin. Science 2014;346(6212):950–4. Nov.
[57] Habig K, Schänzer A, Schirner W, Lautenschläger G, Dassinger B, Olausson H, Birklein F, Gizewski ER, Krämer HH. Low threshold unmyelinated mechanoafferents can modulate pain. BMC Neurol 2017;17(1):184. Sep.
[58] Pawling R, Trotter PD, McGlone FP, Walker SC. A positive touch: C-tactile afferent targeted skin stimulation carries an appetitive motivational value. Biol Psychol 2017;129:186–94. Oct.
[59] Triscoli C, Croy I, Steudte-Schmiedgen S, Olausson H, Sailer U. Heart rate variability is enhanced by long-lasting pleasant touch at CT-optimized velocity. Biol Psychol 2017;128:71–81. Sep.
[60] Björnsdotter M, Löken L, Olausson H, Vallbo A, Wessberg J. Somatotopic organization of gentle touch processing in the posterior insular cortex. J Neurosci 2009;29(29):9314–20. Jul 22.
[61] McGlone F, Cerritelli F, Walker S, Esteves J. The role of gentle touch in perinatal osteopathic manual therapy. Neurosci Biobehav Rev 2017;72:1–9. Jan.
[62] Calsius J, De Bie J, Hertogen R, Meesen R. Touching the lived body in patients with medically unexplained symptoms. How an integration of hands-on bodywork and body awareness in psychotherapy may help people with alexithymia. Front Psychol 2016;29(7):253. Feb.
[63] Bordoni B, Marelli F. Emotions in motion: myofascial interoception. Compl Med Res 2017;24(2):110–3.
[64] Castro-Sánchez AM, Matarán-Peñarrocha GA, Sánchez-Labraca N, Quesada-Rubio JM, Granero-Molina J, Moreno-Lorenzo C. A randomized controlled trial investigating the effects of craniosacral therapy on pain and heart rate variability in fibromyalgia patients. Clin Rehabil 2011;25(1):25–35. Jan.
[65] Girsberger W, Bänziger U, Lingg G, Lothaller H, Endler PC. Heart rate variability and the influence of craniosacral therapy on autonomous nervous system regulation in persons with subjective discomforts: a pilot study. J Integr Med 2014;12(3):156–61. May.
[66] Arroyo-Morales M, Olea N, Martínez MM, Hidalgo-Lozano A, Ruiz-Rodríguez C, Díaz-Rodríguez L. Psychophysiological effects of massage-myofascial release after exercise: a randomized sham-control study. J Altern Complement Med 2008;14(10):1223–9. Dec.
[67] Henley CE, Ivins D, Mills M, Wen FK, Benjamin BA. Osteopathic manipulative treatment and its relationship to autonomic nervous system activity as demonstrated by heart rate variability: a repeated measures study. Osteopath Med Prim Care 2008(2):7. Jun 5.
[68] Toro-Velasco C, Arroyo-Morales M, Fernández-de-Las-Peñas C, Cleland JA, Barrero-Hernández FJ. Short-term effects of manual therapy on heart rate variability, mood state, and pressure pain sensitivity in patients with chronic tension-type headache: a pilot study. J Manip Physiol Ther 2009;32(7):527–35. Sep.
[69] Giles PD, Hensel KL, Pacchia CF, Smith ML. Suboccipital decompression enhances heart rate variability indices of cardiac control in healthy subjects. J Altern Complement Med 2013;19(2):92–6. Feb.
[70] Lindgren L, Rundgren S, Winsö O, Lehtipalo S, Wiklund U, Karlsson M, Stenlund H, Jacobsson C, Brulin C. Physiological responses to touch massage in healthy volunteers. Auton Neurosci 2010;158(1–2):105–10. Dec 8.
[71] Chen HY, Yang H, Chi HJ, Chen HM. Physiological effects of deep touch pressure on anxiety alleviation: the weighted blanket approach. J Med Biol Eng 2013;33(5):463–70.
[72] Cathcart E, McSweeney T, Johnston R, Young H, Edwards DJ. Immediate biomechanical, systemic, and interoceptive effects of myofascial release on the thoracic spine: a randomised controlled trial. J Bodyw Mov Ther 2019;23(1):74–81. Jan.
[73] Griffiths FS, McSweeney T, Edwards DJ. Immediate effects and associations between interoceptive accuracy and range of motion after a HVLA thrust on the thoracolumbar junction: a randomised controlled trial. J Bodyw Mov Ther 2019. https://doi.org/10.1016/j.jbmt.2019.06.007. Article in press.
[74] Kabat-Zinn J. Full Catastrophe Living. How to cope with stress, pain and illness using mindfulness meditation. Piatkus Ltd; 2013.
[75] Day MA. Mindfulness-based cognitive therapy for chronic pain: a clinical manual and guide. Wiley-Blackwell; 2017.
[76] Hayes SC, Strosahl KD, Wilson KG. Acceptance and commitment therapy: the process and practice of mindful change. second ed. New York: Guildford Press; 2012.
[77] Kabat-Zinn J. Wherever you go there you are: mindfulness meditation in everyday life. New York: Hyperion; 1994.
[78] Keng SL, Smoski MJ, Robins CJ. Effects of mindfulness on psychological health: a review of empirical studies. Clin Psychol Rev 2011;31(6):1041–56.
[79] Park T, Reilly-Spong M, Gross CR. Mindfulness: a systematic review of instruments to measure an emergent patient-reported outcome (PRO). Qual Life Res 2013;22(10):2639–59. Dec.
[80] Brown KW, Ryan RM. The benefits of being present: mindfulness and its role in psychological well-being. J Personal Soc Psychol 2003;84(4):822–48. Apr.
[81] Baer RA, Smith GT, Hopkins J, Krietemeyer J, Toney L. Using self-report assessment methods to explore facets of mindfulness. Assessment 2006;13(1):27–45. Mar.
[82] Tanay G, Bernstein A. State Mindfulness Scale (SMS): development and initial validation. Psychol Assess 2013;25(4):1286–99. Dec.
[83] Bornemann B, Herbert BM, Mehling WE, Singer T. Differential changes in self-reported aspects of interoceptive awareness through 3 months of contemplative training. Front Psychol 2015;6(5):1504. Jan.
[84] Bilevicius E, Kolesar TA, Kornelsen J. Altered neural activity associated with mindfulness during nociception: a systematic review of functional MRI. Brain Sci 2016(2):6. Apr 19.
[85] Veehof MM, Trompetter HR, Bohlmeijer ET, Schreurs KM. Acceptance- and mindfulness-based interventions for the treatment of chronic pain: a meta-analytic review. Cogn Behav Ther 2016;45(1):5–31.
[86] Braden BB, Pipe TB, Smith R, Glaspy TK, Deatherage BR, Baxter LC. Brain and behavior changes associated with an abbreviated 4-week mindfulness-based stress reduction course in back pain patients. Brain Behav 2016;6(3):e00443. Feb 16.
[87] Pascoe MC, Thompson DR, Jenkins ZM, Ski CF. Mindfulness mediates the physiological markers of stress: systematic review and meta-analysis. J Psychiatr Res 2017;95:156–78. 2017 Dec.
[88] Penney JN. The biopsychosocial model of pain and contemporary osteopathic practice. Int J Osteopath Med 2010;13(2):42–7.
[89] Kamper SJ, Apeldoorn AT, Chiarotto A, Smeets RJ, Ostelo RW, Guzman J, van Tulder MW. Multidisciplinary biopsychosocial rehabilitation for chronic low back pain: Cochrane systematic review and meta-analysis. BMJ 2015. Feb 18; 350:h444.
[90] Mars T, Abbey H. Mindfulness meditation practice as a healthcare intervention: a systematic review. Int J Osteopath Med 2010;13(2):56–66.
[91] Harte SE, Harris RE, Clauw DJ. The neurobiology of central sensitization. J Appl Biobehav Res 2018;23(2):e12137. Jun.
[92] McCabe C, Rolls ET, Bilderbeck A, McGlone F. Cognitive influences on the affective representation of touch and the sight of touch in the human brain. Soc Cogn Affect Neurosci 2008;3(2):97–108. Jun.
[93] Critchley DJ, McCracken L, Talewar R, Nicholas W, Sanders D, Godfrey EL. Physiotherapy informed by acceptance and commitment therapy for persistent low back pain: the pact study. Physiotherapy 2015;101:e277.
[94] Godfrey E, Galea Holmes M, Wileman V, McCracken L, Norton S, Moss-Morris R, Pallet J, Sanders D, Barcellona M, Critchley D. Physiotherapy informed by Acceptance and Commitment Therapy (PACT): protocol for a randomised controlled trial of PACT versus usual physiotherapy care for adults with chronic low back pain. BMJ Open 2016;6(6):e011548. Jun 7.
[95] Schütze R, Slater H, O'Sullivan P, Thornton J, Finlay-Jones A, Rees CS. Mindfulness-Based Functional Therapy: a preliminary open trial of an integrated model of care for people with persistent low back pain. Front Psychol 2014(5):839. Aug 4.
[96] Saracutu M, Edwards DJ, Davies H, Rance J. Protocol for a feasibility and acceptability study using a brief ACT-based intervention for people from Southwest Wales who live with persistent pain. BMJ Open 2018;8(11):e021866. Nov 1.
[97] Carnes D, Mars T, Plunkett A, Nanke L, Abbey H. A mixed methods evaluation of a third wave cognitive behavioural therapy and osteopathic treatment programme for chronic pain in primary care (OsteoMAP). Int J Osteopath Med 2017;24:12–7. Jun.
[98] Nanke L, Abbey H. Developing a new approach to persistent pain management in osteopathic practice. Stage 1: a feasibility study for a group course. Int J Osteopath Med 2017;26:10–7. Dec.
[99] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;339:b2700. Jul.
[100] Moher D, Liberati A, Tetzlaff J, Altman DG. PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535. Jul.
[101] Whitlock EP, Lin JS, Chou R, Shekelle P, Robinson KA. Using existing systematic reviews in complex systematic reviews. Ann Intern Med 2008;148(10):776–82. May.
[102] Mallett R, Hagen-Zanker R, Slater R, Duvendack M. The benefits and challenges of using systematic reviews in international development research. J Develop Effect 2012;4(3):445–55. Sept.
[103] McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS

peer review of electronic search Strategies: 2015 guideline statement. J Clin Epidemiol 2016;75:40–6. Jul.
[104] Glover GH. Overview of functional magnetic resonance imaging. Neurosurg Clin N Am 2011;22(2):133–9. Apr.
[105] Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. Amstar 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ 2017;358:j4008. Sep.
[106] Furlan AD, Malmivaara A, Chou R, Maher CG, Deyo RA, Schoene M, Bronfort G, van Tulder MW. Editorial Board of the Cochrane Back, Neck Group. Updated method guideline for systematic reviews in the Cochrane back and neck group. Spine 2015;40(21):1660–73. (Phila Pa 1976). Nov.
[107] Young KS, van der Velden AM, Craske MG, Pallesen KJ, Fjorback L, Roepstorff A, Parsons CE. The impact of mindfulness-based interventions on brain activity: a systematic review of functional magnetic resonance imaging studies. Neurosci Biobehav Rev 2018;84:424–33. Jan.
[108] Gotink RA, Meijboom R, Vernooij MW, Smits M, Hunink MG. 8-week Mindfulness Based Stress Reduction induces brain changes similar to traditional long-term meditation practice - a systematic review. Brain Cogn 2016;108:32–41. Oct.
[109] Adolfi F, Couto B, Richter F, Decety J, Lopez J, Sigman M, Manes F, Ibáñez A. Convergence of interoception, emotion, and social cognition: a twofold fMRI meta-analysis and lesion approach. Cortex 2017;88:124–42. Mar.
[110] Schulz SM. Neural correlates of heart-focused interoception: a functional magnetic resonance imaging meta-analysis. Philos Trans R Soc Lond B Biol Sci 2016(1708):371. Nov.
[111] Simmons WK, Avery JA, Barcalow JC, Bodurka J, Drevets WC, Bellgowan P. Keeping the body in mind: insula functional organization and functional connectivity integrate interoceptive, exteroceptive, and emotional awareness. Hum Brain Mapp 2013;34(11):2944–58. Nov.
[112] Wei P, Bao R. The role of insula-associated brain network in touch. BioMed Res Int 2013:734326. Jul; 2013.
[113] Van Essen DC. A Population-Average, Landmark- and Surface-based (PALS) atlas of human cerebral cortex. Neuroimage 2005;28(3):635–62. Nov.
[114] Couto B, Adolfi F, Sedeño L, Salles A, Canales-Johnson A, Alvarez-Abut P, Garcia-Cordero I, Pietto M, Bekinschtein T, Sigman M, Manes F, Ibanez A. Disentangling interoception: insights from focal strokes affecting the perception of external and internal milieus. Front Psychol 2015;6:503. May.
[115] García-Cordero I, Sedeño L, Fraiman D, Craiem D, de la Fuente LA, Salamone P, Serrano C, Sposato L, Manes F, Ibañez A. Stroke and neurodegeneration induce different connectivity aberrations in the insula. Stroke 2015;46(9):2673–7. Sep.
[116] Solbakk AK, Løvstad M. Effects of focal prefrontal cortex lesions on electrophysiological indices of executive attention and action control. Scand J Psychol 2014;55(3):233–43. Jun.
[117] Paneri S, Gregoriou GG. Top-down control of visual attention by the prefrontal cortex. Functional specialization and long-range interactions. Front Neurosci 2017;29(11):545. Sep.
[118] McCracken LM, Vowles KE. Acceptance and commitment therapy and mindfulness for chronic pain: model, process, and progress. Am Psychol 2014;69(2):178–87. Feb-Mar.
[119] Molenberghs P, Trautwein FM, Böckler A, Singer T, Kanske P. Neural correlates of metacognitive ability and of feeling confident: a large-scale fMRI study. Soc Cogn Affect Neurosci 2016;11(12):1942–51. Dec.
[120] Fleming SM, Dolan RJ. The neural basis of metacognitive ability. Philos Trans R Soc Lond B Biol Sci 2012;367(1594):1338–49. May.
[121] Alsubaie M, Abbott R, Dunn B, Dickens C, Keil TF, Henley W, Kuyken W. Mechanisms of action in mindfulness-based cognitive therapy (MBCT) and mindfulness-based stress reduction (MBSR) in people with physical and/or psychological conditions: a systematic review. Clin Psychol Rev 2017;55:74–91. Jul.
[122] Davidovic M, Starck G, Olausson H. Processing of affective and emotionally neutral tactile stimuli in the insular cortex. Dev Cogn Neurosci 2017. Dec; S1878-9293(17)30048-8.
[123] Henneghan AM, Schnyer RN. Biofield therapies for symptom management in palliative and end-of-life care. Am J Hosp Palliat Care 2015;32(1):90–100. Feb.
[124] Tabatabaee A, Tafreshi MZ, Rassouli M, Aledavood SA, AlaviMajd H, Farahmand SK. Effect of therapeutic touch on pain related parameters in patients with cancer: a randomized clinical trial. Mater Sociomed 2016;28(3):220–3. Jun.
[125] Jain S, McMahon GF, Hasen P, Kozub MP, Porter V, King R, Guarneri EM. Healing Touch with Guided Imagery for PTSD in returning active duty military: a randomized controlled trial. Mil Med 2012;177(9):1015–21. Sep.
[126] Baliki MN, Mansour AR, Baria AT, Apkarian AV. Functional reorganization of the default mode network across chronic pain conditions. PLoS One 2014;9(9):e106133. Sep.
[127] Hamilton JP, Farmer M, Fogelman P, Gotlib IH. Depressive rumination, the default-mode network, and the dark matter of clinical neuroscience. Biol Psychiatry 2015;78(4):224–30. Aug.
[128] Coutinho JF, Fernandes SV, Soares JM, Maia L, Gonçalves ÓF, Sampaio A. Default mode network dissociation in depressive and anxiety states. Brain Imaging Behav 2016;10(1):147–57. Mar.
[129] Putcha D, Ross RS, Cronin-Golomb A, Janes AC, Stern CE. Salience and default mode network coupling predicts cognition in aging and Parkinson's disease. J Int Neuropsychol Soc 2016;22(2):205–15. Feb.
[130] Hilton L, Hempel S, Ewing BA, Apaydin E, Xenakis L, Newberry S, Colaiaco B, Maher AR, Shanman RM, Sorbero ME, Maglione MA. Mindfulness meditation for chronic pain: systematic review and meta-analysis. Ann Behav Med 2017;51(2):199–213. Apr.
[131] May A, Stewart J, Tapert S, Paulus P. The effect of age on neural processing of pleasant soft touch stimuli. Front Behav Neurosci 2014;8:52.
[132] Murphy J, Brewer R, Catmur C, Bird G. Interoception and psychopathology: a developmental neuroscience perspective. Dev Cogn Neurosci 2016;23:45–56. Dec.
[133] Wetherill RR, Childress AR, Jagannathan K, Bender J, Young KA, Suh JJ, O'Brien CP, Franklin TR. Neural responses to subliminally presented cannabis and other emotionally evocative cues in cannabis-dependent individuals. Psychopharmacology (Berlin) 2014;231(7):1397–407. Apr.

Appendix 1 Amstar 2 checklist

1. Did the research questions and inclusion criteria for the review include the components of PICO?

For Yes:
- ☐ Population
- ☐ Intervention
- ☐ Comparator group
- ☐ Outcome

Optional (recommended)
- ☐ Timeframe for follow-up

- ☐ Yes
- ☐ No

2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

For Partial Yes:
The authors state that they had a written protocol or guide that included ALL the following:
- ☐ review question(s)
- ☐ a search strategy
- ☐ inclusion/exclusion criteria
- ☐ a risk of bias assessment

For Yes:
As for partial yes, plus the protocol should be registered and should also have specified:
- ☐ a meta-analysis/synthesis plan, if appropriate, *and*
- ☐ a plan for investigating causes of heterogeneity
- ☐ justification for any deviations from the protocol

- ☐ Yes
- ☐ Partial Yes
- ☐ No

3. Did the review authors explain their selection of the study designs for inclusion in the review?

For Yes, the review should satisfy ONE of the following:
- ☐ *Explanation for* including only RCTs
- ☐ OR *Explanation for* including only NRSI
- ☐ OR *Explanation for* including both RCTs and NRSI

- ☐ Yes
- ☐ No

4. Did the review authors use a comprehensive literature search strategy?

For Partial Yes (all the following):
- ☐ searched at least 2 databases (relevant to research question)
- ☐ provided key word and/or search strategy
- ☐ justified publication restrictions (e.g. language)

For Yes, should also have (all the following):
- ☐ searched the reference lists / bibliographies of included studies
- ☐ searched trial/study registries
- ☐ included/consulted content experts in the field
- ☐ where relevant, searched for grey literature
- ☐ conducted search within 24 months of completion of the review

- ☐ Yes
- ☐ Partial Yes
- ☐ No

5. Did the review authors perform study selection in duplicate?

For Yes, either ONE of the following:
- ☐ at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include
- ☐ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.

- ☐ Yes
- ☐ No

6. Did the review authors perform data extraction in duplicate?

For Yes	
For Yes, either ONE of the following: ☐ at least two reviewers achieved consensus on which data to extract from included studies ☐ OR two reviewers extracted data from a sample of eligible studies <u>and</u> achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.	☐ Yes ☐ No

7. Did the review authors provide a list of excluded studies and justify the exclusions?

For Partial Yes	For Yes	
For Partial Yes: ☐ provided a list of all potentially relevant studies that were read in full-text form but excluded from the review	For Yes, must also have: ☐ Justified the exclusion from the review of each potentially relevant study	☐ Yes ☐ Partial Yes ☐ No

8. Did the review authors describe the included studies in adequate detail?

For Partial Yes	For Yes	
For Partial Yes (ALL the following): ☐ described populations ☐ described interventions ☐ described comparators ☐ described outcomes ☐ described research designs	For Yes, should also have ALL the following: ☐ described population in detail ☐ described intervention in detail (including doses where relevant) ☐ described comparator in detail (including doses where relevant) ☐ described study's setting ☐ timeframe for follow-up	☐ Yes ☐ Partial Yes ☐ No

9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?

For Partial Yes	For Yes	
RCTs For Partial Yes, must have assessed RoB from ☐ unconcealed allocation, *and* ☐ lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)	For Yes, must also have assessed RoB from: ☐ allocation sequence that was not truly random, *and* ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome	☐ Yes ☐ Partial Yes ☐ No ☐ Includes only NRSI
NRSI For Partial Yes, must have assessed RoB: ☐ from confounding, *and* ☐ from selection bias	For Yes, must also have assessed RoB: ☐ methods used to ascertain exposures and outcomes, *and* ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome	☐ Yes ☐ Partial Yes ☐ No ☐ Includes only RCTs

10. Did the review authors report o n the sources of funding for the studies included in the review?

For Yes	
For Yes ☐ Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies	☐ Yes ☐ No

11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?

RCTs
For Yes:

- ☐ The authors justified combining the data in a meta-analysis
  - ☐ AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present.
  - ☐ AND investigated the causes of any heterogeneity

☐ Yes
☐ No
☐ No meta-analysis conducted

For NRSI
For Yes:

- ☐ The authors justified combining the data in a meta-analysis
  - ☐ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present
  - ☐ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available
  - ☐ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review

☐ Yes
☐ No
☐ No meta-analysis conducted

12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?

For Yes:

- ☐ included only low risk of bias RCTs
- ☐ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.

☐ Yes
☐ No
☐ No meta-analysis conducted

13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?

For Yes:

- ☐ included only low risk of bias RCTs
- ☐ OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results

☐ Yes
☐ No

14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?

For Yes:

- ☐ There was no significant heterogeneity in the results
- ☐ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review

☐ Yes
☐ No

15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?

For Yes:

- ☐ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias

☐ Yes
☐ No
☐ No meta-analysis conducted

16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	
For Yes: ☐ The authors reported no competing interests OR ☐ The authors described their funding sources and how they managed potential conflicts of interest	☐ Yes ☐ No