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Review article

The impact of mindfulness-based interventions on brain activity: A systematic review of functional magnetic resonance imaging studies

Katherine S. Young[a], Anne Maj van der Velden[b,c], Michelle G. Craske[a], Karen Johanne Pallesen[c], Lone Fjorback[c], Andreas Roepstorff[b], Christine E. Parsons[b,*]

[a] Anxiety and Depression Research Center, Department of Psychology, University of California, Los Angeles, CA, USA
[b] Interacting Minds Centre, Dept. of Clinical Medicine, Aarhus University, Aarhus, Denmark
[c] Danish Center for Mindfulness, Department of Clinical Medicine, Aarhus University, Aarhus, Denmark

A R T I C L E I N F O

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A B S T R A C T

Mindfulness-based interventions are increasingly used in the treatment and prevention of mental health conditions. Despite this, the mechanisms of change for such interventions are only beginning to be understood, with a number of recent studies assessing changes in brain activity. The aim of this systematic review was to assess changes in brain functioning associated with manualised 8-session mindfulness interventions. Searches of PubMed and Scopus databases resulted in 39 papers, 7 of which were eligible for inclusion. The most consistent longitudinal effect observed was increased insular cortex activity following mindfulness-based interventions. In contrast to previous reviews, we did not find robust evidence for increased activity in specific prefrontal cortex sub-regions. These findings suggest that mindfulness interventions are associated with changes in functioning of the insula, plausibly impacting awareness of internal reactions 'in-the-moment'. The studies reviewed here demonstrated a variety of effects across populations and tasks, pointing to the need for greater consistency in future study design.

1. Introduction

The popularity of mindfulness interventions has exploded over the past decade. Used both to prevent and treat, mindfulness programmes can be found in various healthcare settings, the workplace as well as in schools and community organisations. Despite this surge in uptake, scientific understanding of the mechanisms of mindfulness interventions is in the early stages. There have been numerous calls for the use of neuroscience to better understand the mechanisms underlying effective psychological treatment (Craske, 2014; Holmes et al., 2014) and investigation of the neural mechanisms associated with effective mindfulness interventions is on the rise. Neuroimaging offers a tool for: i) expanding our understanding of why and how treatments work, ii) providing insight into adaptations of existing treatments to better target underlying mechanisms and iii) to assess factors associated with an individual's likelihood of responding to a particular treatment (Wise et al., 2014).

1.1. Standard mindfulness-based interventions

Mindfulness involves practicing the awareness of 'in-the-moment' experiences, as well as an attitude of non-judgemental acceptance of current experiences (Kabat-Zinn, 2013). The overarching aim of mindfulness practice is to "maintain awareness of moment-to moment experiences, disengaging oneself from strong attachment to beliefs, thoughts or emotions thereby developing a greater sense of emotional balance and well-being" (Ludwig and Kabat-Zinn, 2008, p.1350). Two standardised forms of mindfulness training, mindfulness-based stress reduction (MBSR) and mindfulness-based cognitive therapy (MBCT) have garnered most support for their efficacy. MBSR and MBCT are manualised, group-based 8-week training programs that teach mindfulness skills through a range of formal and informal practices.

MBSR was originally developed in 1979 as a mental health training intervention for chronic health conditions (Kabat-Zinn, 2013). It has been shown to be effective for a range of conditions with meta-analyses

Abbreviations: (d/v)ACC, (dorsal/ventral) anterior cingulate cortex; BAI, Beck's Anxiety Inventory; BOLD, blood oxygen level dependent; CBT, cognitive behavioural therapy; FFMQ, five factor mindfulness questionnaire; fMRI, functional magnetic resonance imaging; GAD, generalised anxiety disorder; KIMS, Kentucky Inventory of Mindfulness Skills; MBCT, mindfulness-based cognitive therapy; MBI, mindfulness-based intervention; MBSR, mindfulness-based stress reduction; MFG, middle frontal gyrus; MMFT, mindfulness-based mind fitness training; MOM, mindfulness oriented meditation; OFC, orbitofrontal cortex; (vl/dl/dm/m)PFC, (ventrolateral/dorsolateral/dorsomedial/medial) prefrontal cortex; RCT, randomised controlled trial; ROI, region of interest; SAD, social anxiety disorder

* Corresponding author at: Jens Chr Skous Vej 4, Building 1483, 8000 Aarhus C, Denmark.
E-mail address: christine.parsons@clin.au.dk (C.E. Parsons).

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demonstrating efficacy in the treatment of anxiety (effect size, Cohen's d = 0.47), depression (0.26), pain (0.33) and stress (0.55; Bohlmeijer et al., 2010; Khoury et al., 2015). MBCT is an adaptation of MBSR, developed as a preventative treatment for recurrent depression (Segal et al., 2002). It combines psychological educational components of cognitive behavioural therapy (CBT) for depression with meditation elements of MBSR (Chiesa and Malinowski, 2011; Williams et al., 2014). MBCT has been shown to halve the risk of relapse (Kuyken et al., 2016) and is currently a recommended treatment for relapse prevention of recurrent depression in a number of national clinical guidelines, such as the UK National Institute for Health and Clinical Excellence (NICE).

1.2. *Mechanisms of change*

While evidence for the efficacy of MBSR/MBCT is accumulating, the mechanisms through which these treatments act are yet to be fully elucidated. Mindfulness practice can be considered to cultivate two broad aspects of mental processing: awareness of cognitive, emotional and somatic processes ('present-moment awareness') and the ability to experience these processes with a non-judgemental and non-reactive attitude ('non-judgemental acceptance'). It has been proposed that these abilities help to enhance psychological flexibility and reduce engagement in maladaptive habits and reactions (Kabat-Zinn, 2013; Segal et al., 2013). Additionally, MBCT is specifically theorized to decrease depressive recurrence by i) developing the ability to recognize, decentre and disengage from self-devaluing ruminative thought-patterns, ii) developing meta-awareness i.e. becoming able to observe thoughts and feelings as temporary and automatic events in the mind instead of as facts or true descriptions, and by iii) fostering self-compassion (Segal et al., 2013).

Recent systematic reviews of the psychological mechanisms of change point to self-reported mindfulness as the most consistent mediator of improved outcomes (Alsubaie et al., 2017; Gu et al., 2015; van der Velden et al., 2015). Other mechanisms may play a role, including: cognitive and emotional reactivity (Gu et al., 2015), compassion, meta-awareness and rumination (MBCT; van der Velden et al., 2015). Each of these reviews, however, have highlighted methodological shortcomings in existing work. In particular, reliance on self-report measures may limit the capacity to dissociate effects of training with participants' beliefs and expectations after learning about the theoretical rationale of the treatment (discussed during the psychoeducation portion of the intervention). One method to address this issue is by incorporating objective methods in addition to self-report, such as neuroimaging, into rigorous trial designs supporting investigations of causal pathways (van der Velden et al., 2015).

1.3. *Neural mechanisms of change: emphasis on higher order brain regions*

There has been a number of important reviews of the neural correlates of meditation and mindfulness to date. Existing work includes narrative reviews (Creswell, 2017; Rubia, 2009; Tang et al., 2015), a meta analytic review of four common meditation techniques (focused attention, mantra recitation, open monitoring, and compassion/loving-kindness; Fox et al., 2016) and a systematic review of structural and functional changes associated with MBSR and closely related mindfulness-based interventions (MBIs; Gotink et al., 2016). The overarching finding has been that practicing meditation is associated with increased neural activation in the insula, prefrontal and anterior cingulate cortices (Fox et al., 2016; Gotink et al., 2016; Tang et al., 2015). The insula has been ascribed a number of roles in higher order cognitive functioning, including awareness of interoceptive experiences. Regions of prefrontal cortex (PFC) and dorsal anterior cingulate cortex (dACC) have been associated more broadly with a range of 'higher-order' cognitive processes, including attentional control and emotion regulation, both of which are implicated in the balance of awareness of in-the-moment experiences with non-judgemental acceptance.

1.4. *Limitations of current understanding of neural mechanisms*

Neuroscientific reviews to date have commented on limitations in previous work and made recommendations for improved methodologies. These include calling for well-controlled prospective studies and use of more advanced analytical tools. In addition, much of the literature on neural mechanisms of meditation has been based on i) cross-sectional studies comparing expert with novice meditators, ii) diverse and heterogenous meditation techniques, iii) limited discussion of subregions of the prefrontal cortex. We discuss these limitations in turn below.

Much of the existing knowledge on neural mechanisms of meditation comes from cross-sectional studies comparing expert with novice meditators. Those who engage in long-term meditation, like other types of long-term training such as musicianship, often differ from the general population in key ways. These include socio-economic status, personality and educational levels (Luders et al., 2013), and could plausibly extend to any number of internal mental processes. Cross-sectional studies comparing expert with novice meditators might therefore be influenced by any of these confounding variables. To enable causal inferences, there is a need for studies using a within-subjects design, affording greater experimental control and greater confidence that observed differences are associated with the intervention.

The scope of meditative approaches included in recent neuroscientific reviews has been typically broad (e.g. loving kindness and compassion meditation, open monitoring, mantra recitation, focussed attention, integrative mind-body training, zen and insight meditations). This approach is useful for assessing effects common across different types of meditation, but is less useful for assessing the specific effects associated with manualised interventions that include meditation exercises. Comparing interventions with core similarities (particularly in terms of duration, course content and home practice) reduces the impact of extraneous variables on outcome measures, with the potential to demonstrate more specific effects. As MBSR and MBCT are complex psychotherapeutic interventions that include components of meditation exercises, but also involve psycho-education, dialogue, and exercises from other treatments (e.g. CBT), there is a need to specifically investigate the neural correlates and putative mechanisms of MBSR, MBCT and closely-related MBIs, and how these relate to the prediction of clinical and well-being outcomes.

Finally, previous reviews have tended to group findings from different subregions of the PFC together. The PFC is a large and multi-faceted area of the frontal lobe of the brain that has well-established links to 'higher-order' cognitive processing including: attention direction, stimulus appraisal, reasoning and decision-making. Advances in cognitive and affective neuroscience have clearly demonstrated evidence for localisation of specific processes to subregions or networks of regions within the PFC (Badre and Wagner, 2002; Etkin et al., 2011; Ridderinkhof et al., 2004). Further specificity on which particular subregions are implicated would be informative with regards to an understanding of neural mechanisms implicated.

1.5. *Aims*

In this review, we investigate changes in task-relevant neural functioning associated with manualised mindfulness-based interventions. We target our search to focus specifically on longitudinal within-subjects designs where participants undergo fMRI both before and after treatment. This is an important study design because participants serve as their own internal control, thereby addressing some of the concerns with previous work synthesising cross-sectional studies. We include studies of manualised mindfulness-based interventions to specifically assess changes in neural activity associated with a 'standard dose' of MBCT/MBSR or closely derived interventions. In contrast to previous work, we examine individual subregions of PFC to provide more specificity on which areas of PFC might be implicated.

2. Methods

2.1. Search strategy

We performed searches using Scopus and PubMed for studies published through to the end of April 2016 (registered at PROSPERO, CRD42016036986 http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016036986). Search terms were: 'mindfulness', 'meditation', 'mindfulness-based stress reduction', 'MBSR', 'mindfulness-based intervention', 'MBI', 'mindfulness based cognitive therapy', 'MBCT', OR 'mindfulness-based' AND 'fMRI', 'MRI', 'functional', 'neuroimaging' OR 'BOLD'. We initially screened (independently by two authors: KSY, KJP) based on the title and abstract to identify relevant articles, removing studies that did not use a mindfulness-based intervention, or did not use fMRI. Upon full-text review, papers were excluded if they failed to meet two *a priori* criteria: use of a manualised 7 or 8-session mindfulness intervention and use of task-based fMRI at two time points. Additionally, where there were multiple papers reporting on data from the same participant group, only the study more relevant to treatment goals was included. We resolved disagreements in screening through discussion or referral to a third reviewer (CEP). We conducted screening using the web-based platform Covidence (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia; www.covidence.org).

2.2. Data extraction and synthesis

Two independent reviewers performed data extraction to assess: i) intervention quality (CEP, AMV), ii) fMRI study design/reporting quality (CEP, AMV) and iii) fMRI data (KSY, AMV). Key aspects of intervention quality were: study design, control group, randomisation procedure, concealment of treatment allocation, differential responding between groups at baseline, reporting of dropouts, withdrawal and power calculations, frequency of practice, method of recording practice, reporting of teacher training, use of scale to check intervention adherence, reporting of class attendance, number of classes and presence of a retreat. fMRI quality measures were reporting of: experimental design, handedness and gender of participants, explanation for rejected data, details of imaging parameters, software analysis package method, method of motion correction during pre-processing, multiple comparison correction and detailed description of first and second level analyses.

We extracted regions of significant activity for comparisons of: i) group (mindfulness intervention or control) by time (pre-/post-intervention) interactions, ii) within-subjects effects (pre-/post-intervention) and iii) associations with self-report scales. The principal outcome measures were reported regions of significant differences of levels of blood-oxygen level dependent (BOLD) signal. Due to the small number of studies, the heterogeneity of tasks and contrasts and the majority of findings reported as region of interest analyses, voxel-wise whole brain meta-analyses were not conducted.

3. Results

3.1. Study characteristics

Fig. 1 presents the PRISMA flow chart for the included studies. A total of seven studies were identified that reported on within-subjects comparisons of task-based fMRI data at two time points, pre- and post-mindfulness-based interventions (N = 124, mean per study n = 17.71, SD = 7.11) or pre- and post-control conditions (n = 62, mean per study n = 15.5, SD = 5.94). Three were RCTs, two were controlled trials and two were 'before and after' studies with no control group.

Of the seven included studies, four examined clinical populations (n = 4; 3 anxiety disorders samples and 1 bipolar disorder), two were resilience training groups (one in active duty marines and one in elite athletes) and one was conducted with healthy adults (see Table 1 for details of interventions and detailed results of quality assessment). Six of the studies had a duration of eight weeks, one had a seven-week duration, and four studies reported including an additional one-day retreat. Participants were asked to practice on average for 10–30 min per day (M = 25.71; SD = 7.87), less than the 45 min of homework assigned in standard format MBCT and MBSR (Kabat-Zinn, 1990; Segal et al., 2002).

3.2. fMRI quality

Key criteria for fMRI quality reporting were selected from a set of guidelines for the standardised reporting of fMRI studies (Poldrack et al., 2008). All studies reported the overall fMRI design, software package used for analysis and methods for multiple comparison correction (see Table 2 for further details).One study met all reporting guidelines, while others were lacking in at least one reporting guideline, most commonly in clear descriptions of first and second level contrasts.

3.3. Group-by-time interaction effects

Fig. 2 displays regions found to demonstrate differences in task-based activation following mindfulness based interventions and details of each study are provided in Table 3. Three studies reported group-by-time interaction effects, describing regions of functional activity that differed from pre- to post-intervention as a function of group (Goldin et al., 2012; Hölzel et al., 2011; Johnson et al., 2014). Greater anterior insula reactivity to face stimuli was observed in a resilience study with marines and in an intervention for generalised anxiety disorder (GAD; Hölzel et al., 2011; Johnson et al., 2014). The military group additionally demonstrated greater ACC responsiveness, while the GAD group showed greater ventrolateral PFC (vlPFC) and middle frontal cortex responsiveness following mindfulness intervention (Johnson et al., 2014). A mindfulness intervention for social anxiety disorder (SAD) was associated with greater posterior cingulate cortex (PCC) activity during a self-referential task, compared to an aerobic exercise control group (Goldin et al., 2012).

3.4. Within-subjects effects (pre- to post-intervention)

Three 'before and after' studies (Goldin and Gross, 2010; Haase et al., 2015; Tomasino and Fabbro, 2016) and one RCT (Hölzel et al., 2011) reported within-subjects effects on neural activity (pre-/post-intervention). The anterior cingulate cortex (ACC) was significantly more reactive to the anticipation of an aversive interoceptive stimulus (breathing load) post-mindfulness intervention, compared to pre-intervention, while recovery from this stimulus was associated with greater activity in right dorsolateral PFC (dlPFC) and greater activity in the insula was observed for both periods in a group of elite athletes (Haase et al., 2015). Observation of emotional facial expressions was associated with greater right middle frontal and lateral orbitofrontal cortex (OFC) in patients with GAD following either MBSR or stress-management education interventions (Hölzel et al., 2011). Comparing neural activity during breath and body-scan focussed attention (compared to rest) post-intervention, compared to pre-intervention in a group of healthy individuals was associated with greater activity in right middle frontal gyrus (MFG) and dlPFC, left caudate and insula and decreased activation in PFC and parietal areas (Tomasino and Fabbro, 2016). MBSR for SAD, however, was associated only with altered activity in parietal, occipital (including cuneus and precuneus) and parahippocampal regions, but not frontal regions, during breath-focussed attention compared to reacting to negative self-beliefs (Freitas-Ferrari et al., 2010).

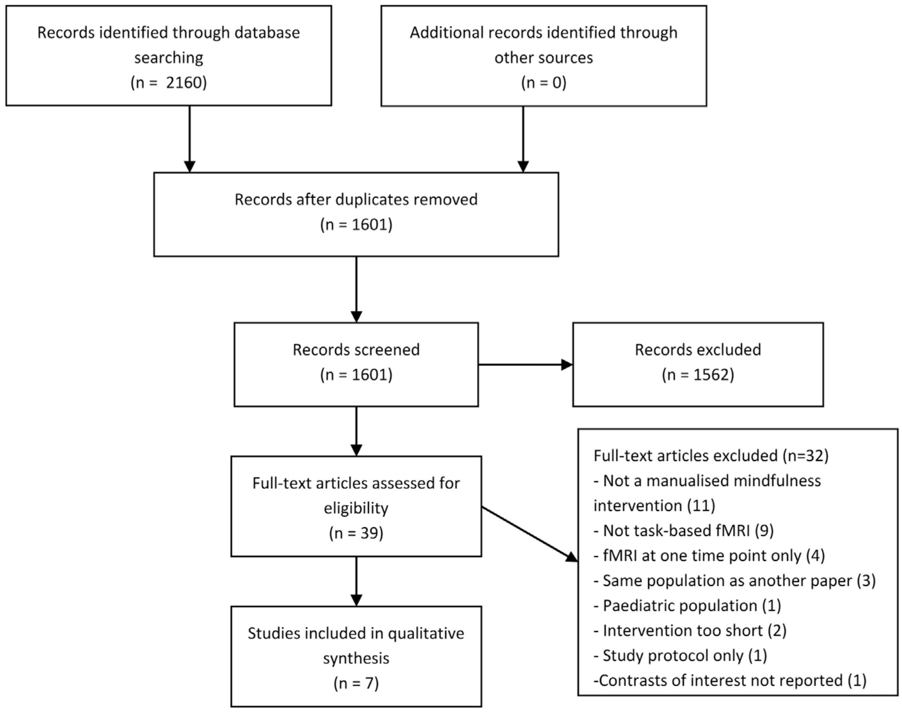

Fig. 1. PRISMA flow diagram depicting numbers of studies identified and included in the review.

3.5. Associations between change in neural activity and change in symptom measures

Six of the included studies additionally compared changes in neural activity from pre- to post-intervention with changes in scores on self-report questionnaires (see Table 3 for details). Among MBSR intervention studies with individuals with SAD, symptom reduction was associated with increased activity across visual attention regions (cuneus and middle occipital gyrus) in one study (Goldin and Gross, 2010) and decreased social anxiety related disability was associated with increased dmPFC activity in another (Goldin et al., 2012). In a study of MBSR for GAD, decrease in Beck's Anxiety Inventory (BAI) scores (i.e. symptom reduction) was correlated with increased activity in the vlPFC during affect labelling (Hölzel et al., 2011). Changes in self-reported mindfulness ability was associated with altered activity in midline prefrontal regions: the dorsomedial PFC (dmPFC) in a group of individuals with SAD (Goldin et al., 2012), medial PFC (mPFC) in a group of individuals with bipolar disorder (Ives-Deliperi et al., 2013) and ACC in a group of elite athletes (Haase et al., 2015). Two studies described associations between self-report scales and reactivity of the insula. In one, reduced insula reactivity to emotional faces was associated with greater improvement in resilience (measured by the response to stressful experiences scale; Johnson et al., 2014) and in the other greater insula activity (post respiratory breathing load) was associated with an improved ability to identify one's emotions (Toronto Alexithymia Scale – feelings subscale; Haase et al., 2015).

4. Discussion

Here, we systematically review studies investigating longitudinal changes in functional brain activity following manualised mindfulness-based interventions (MBSR, MBCT or close adaptations). Across the seven included studies, the most consistent finding was that task-relevant activity in the insula was *increased* following mindfulness-based interventions compared to control. There was also some evidence of increased reactivity of the anterior cingulate cortex during processing of emotional stimuli. Previous reviews of non-standardised interventions (Fox et al., 2016; Tang et al., 2015), or including both within- and between-subjects effects (Gotink et al., 2016) argued for changes in activity in PFC. Here, we investigated evidence for well-established subregions of the PFC (e.g., vlPFC or dmPFC, regions demonstrated to have different 'higher-order' functions) and did not find robust evidence across studies for an effect of mindfulness-based interventions.

Even among the small number of studies reviewed here, there was remarkable heterogeneity in the mechanisms investigated and populations of individuals studied. This is a key consideration in interpretation of these findings. While interventions are largely standardised across studies, the benefit obtained for groups of individuals could plausibly depend on the condition treated (e.g., depression or anxiety) or the particular context of training (in the case of the elite athlete and Marines studies reviewed). An additional variable to consider is the functional task individuals performed during scanning and how these relate to the mechanisms of interventions. In discussing the findings below, we suggest possible interpretations that consider the context of treatment and task condition in relation to the two theoretical constructs of mindfulness interventions described earlier: present-moment awareness and non-judgemental acceptance.

4.1. Insula activity: enhanced present-moment awareness

The most consistent finding observed was increased insula reactivity after completion of a mindfulness intervention. Increased reactivity was observed in: i) healthy individuals while instructed to meditate in the scanner (Tomasino and Fabbro, 2016), ii) individuals with GAD observing emotional facial expressions (Hölzel et al., 2011) and iii) elite athletes experiencing aversive inspiratory loads (Haase et al., 2015). The insula is considered to support interoceptive awareness, the awareness of one's own body and internal physiological experiences (Paulus and Stein, 2006). It is plausible, therefore, that enhanced present-moment awareness through mindfulness training is supported by greater activation of the insula. However, altered insula reactivity was not observed across all studies. No changes in insula activity were observed in individuals with SAD responding to emotional statements (in two studies; Goldin and Gross, 2010; Goldin et al., 2012) or in individuals with bipolar disorder while meditating (Ives-Deliperi et al., 2013). Furthermore, *decreased* insula activity was observed following

Table 1
Summary of features of intervention design and quality. [1 Goldin and Gross, 2010; 2 Goldin et al., 2012; 3 Haase et al., 2015; 4 Hölzel et al., 2013; 5 Ives-Deliperi et al., 2013; 6 Johnson et al., 2014; 7 Tomasino and Fabbro, 2016]. Three studies used MBSR, one used MBCT and three studies used adaptations of standard MBSR/MBCT treatments, adapted for specific populations, but matched on core intervention features [Mindfulness based mind fitness training, MMFT with active duty marines (Johnson et al., 2014; Haase et al., 2015; Tomasino and Fabbro, 2016); mindful performance enhancement awareness and knowledge, mPEAK with elite athletes (Haase et al., 2015); and mindfulness oriented meditation, MOM, with healthy adults (Tomasino and Fabbro, 2016)]. RCT = randomised controlled trial, CT = controlled trial, WS = within-subjects, TAU = treatment as usual, * denotes details not reported in papers, but obtained through contacting authors.

Study	Study Design	Control group	Was the trial randomised?	Randomisation described?	Treatment allocation concealed?	Groups similar at baseline?	Number of dropouts mentioned	Withdrawal reasons stated for dropouts	Practice mins per week	How was practice recorded?	Teacher training reported	Scale used to check intervention adherence	Class attendance reported?	no classes	retreat
1	WS	N/A	N/A	N/A	N/A	N/A	N	N	180 (30 min, 6 days)*	daily self-report form	Y	N	Y	8	Y
2	RCT	active	Y	Y	N	Y	Y	Y	180 (30 min, 6 days)*	daily self-report form	Y	N	N	8	Y
3	WS	N/A	N/A	N/A	N/A	N/A	N	N	210 (30 min, 7 days)	not specified	N	N	N	7	N
4	RCT	active	Y	Y	N	Y	Y	Y	140 (20 min, 7 days)*	not specified	N	N	Y	8	Y
5	WS	N/A	N/A	N/A	N/A	N/A	N	N	70 (10 mins/day)	not specified	N	N	N	8	N
6	CT	TAU	N	N	N	Y	Y	Y	210 (30 min, 7 days)	not specified	N	N	Y	8	Y
7	WS	N/A	N/A	N/A	N/A	N/A	Y	N	120 (30mins, 4 days)	self-report, retrospective	N	N	Y	8	unspecified

Table 2
Summary of fMRI quality [1 Goldin and Gross, 2010; 2 Goldin et al., 2012; 3 Haase et al., 2015; 4 Hölzel et al., 2013; 5 Ives-Deliperi et al., 2013; 6 Johnson et al., 2014; 7 Tomasino and Fabbro, 2016].

Study	fMRI design	Sample handedness reported	Sample gender reported	Scan rejection mentioned	Scan rejection reason	Volumes acquired per session	Software package specified	Method for motion correction described?	Method for multiple comparison correction described?	Type of correction applied	First level contrasts described	Second level contrasts described
1	Block	Y	Y	Y	N/A	Y	Y	Y	Y	voxel wise	Y	Y
2	Block	N	Y	Y	N/A	Y	Y	Y	Y	voxel wise	unclear	unclear
3	Event-related	N	unclear	Y	N/A	N	Y	Y	Y	voxel wise	Y	Y
4	Block	Y	Y	N	N/A	N	Y	Y	Y	cluster	Y	Y
5	Block	Y	Y	Y	Y	Y	Y	Y	Y	voxel wise	unclear	Y
6	Block	N	unclear	Y	Y	N	Y	N	Y	unclear	unclear	unclear
7	Block	Y	Y	Y	N	Y	Y	Y	Y	cluster	Y	Y

mindful 'resilience training' in a group of Marines responding to emotional facial expressions (Johnson et al., 2014). We now turn to offer an explanation for these apparently discrepant findings in terms of the features of the disorders and stated aims of the study interventions.

Here, we consider an increase in insula activation to be the 'typical' response to mindfulness interventions, as it was observed in a group of healthy individuals. Both the GAD group and the elite athletes showed increased insula activity and might be considered to benefit from an increased focus of attention on present moment experiences, albeit for different reasons. A core feature of GAD is rumination on past experiences. An increased interoceptive focus on the present-moment might therefore be an adaptive change for this group. The authors of the study on elite athletes suggest that increased interoceptive awareness would be adaptive for performing optimally in competitive sport (Haase et al., 2015). In contrast, in SAD there is a maladaptive focus on internal cues and physiological responses in anxiety-provoking social contexts (Clark and Wells, 1995). In this case, enhancing interoceptive awareness is unlikely to be a key goal of interventions, which is one possible explanation for a lack of change in insula activation. In the Marines study, where decreased insula activity was observed, the intervention

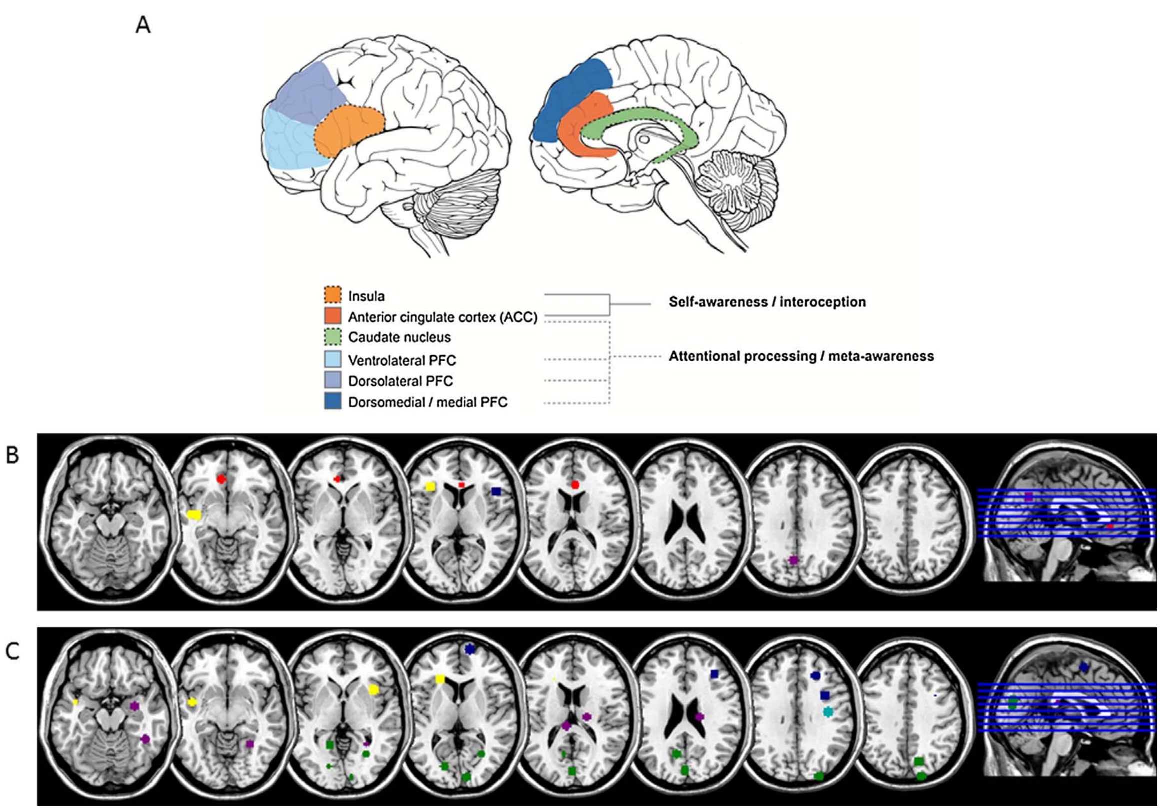

Fig. 2. An overview of regions demonstrating altered task-based activity following manualised 8-week mindfulness-based interventions. A) Regions are listed in order of most replicable finding across studies and colour-coded in relation to function. The insula (yellow; Haase et al., 2015; Hölzel et al., 2011; Johnson et al., 2014; Tomasino and Fabbro, 2016) and ACC (orange; Haase et al., 2015; Johnson et al., 2014) are implicated in attentional processes – namely interoception and conflict detection respectively as well as in emotional processing and regulation. The caudate nucleus (green; Haase et al., 2015; Tomasino and Fabbro, 2016) forms part of the reward circuitry. The regions highlighted in blue are prefrontal cortical areas in which we did not find robust evidence for changes in activity following manualised 8-week mindfulness interventions, but were associated with changes in mindfulness in single studies (ventrolateral PFC (Hölzel et al., 2011), dorsomedial PFC (Goldin et al., 2012), medial PFC (Ives-Deliperi et al., 2013), dorsolateral PFC (Haase et al., 2015)). B & C) Slice montages representing areas of significant changes in activation following mindfulness interventions showing results of: (B) group-by-time interactions and (C) within-subjects effects. ROIs are plotted as 6 mm spheres from peak coordinates reported in papers reviewed in MNI space (Talairach coordinates were converted to MNI where required using MNI to Talairach mapping; Lacadie et al., 2008). Peaks are categorized by colour as follows: insula (yellow), ACC (red), frontal regions (dark blue), parietal regions (light blue), occipital regions (green) and subcortical areas (purple). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 3
Changes in neural activity associated with mindfulness interventions as assessed by group (mindfulness intervention vs. control) by time (pre-/post-intervention) interactions, main effects of time (pre- to post-intervention) or associated with specific self-report scales. Potential interpretations of findings are also proposed, which are described in detail in the discussion section. (Acronyms: Response to Stressful Experience Scale, RSES; Beck's Anxiety Inventory, BAI; Five-factor mindfulness questionnaire, FFMQ; Kentucky Inventory of Mindfulness Skills, KIMS; ROI: region of interest analysis) [1]specific to MBSR group, not present in AE group, [2]a decreased score corresponds to an improved ability to describe emotions [Unless otherwise noted, regions listed demonstrated increased activity post-intervention, compared to pre-intervention], [a] gender not reported, [b] mean age not reported.

	Sample population	Task	Group * time	Main effect of time:	Association with scale	*Possible interpretation*
Tomasino and Fabbro (2016)	Healthy individuals (n = 13, 3 male, mean age = 30.2)	Meditation in scanner	n/a	Increased: right middle frontal gyrus, left caudate/anterior insula, decreased: rostral PFC, right parietal area 3a	None	Increased awareness of self and interoceptive cues
Holzel et al. (2013)	Generalised anxiety disorder (n = 15, 6 male, mean age = 28.5), healthy individuals (n = 11, 6 male, mean age = 35.6)	Affect labelling (viewing faces – different expressions)	*ROI*: vlPFC (right opercularis), right rostal middle frontal cortex/ insula	Decrease in amygdala reactivity Increase in right caudal middle frontal, right lateral OFC (ROI analysis)	Increased vlPFC activity correlated with decrease in BAI	Increased awareness of internal emotional experience
Haase et al. (2015)	Elite athletes (n = 7, mean age = 21.86)[a]	Inspiratory breathing load for uncertain anticipation of interoceptive challenge	n/a	Anticipation: right cuneus, rACC, left insula, lSTG; breathing-load: left lingual, right culmen, right caudate, lSFG, l supramarginal gyrus; post-breathing load: left precuneus, left cuneus, rdlPFC, r insula	Increased ACC correlated with increased FFMQ (during anticipation), increased right insula correlated with decreased TAS[2] (during post-breathing phase)	Increased awareness of internal physical and physiological cues (interoceptive cues)
Goldin et al. (2012)	Social anxiety disorder (n = 31, 12 male, mean age = 32.87) and healthy individuals (n = 24, 15 male, mean age = 32.88)	Self-referential encoding task	*ROI*: Posterior cingulate cortex	none	Negative self-endorsement: increased DMPFC correlated with decreased social anxiety and increased KIMS[1] Positive self-endorsement: decreases in DMPFC correlated with increased KIMS[1]	Changes in non-judgemental acceptance of self-related statements
Goldin and Gross (2010)	Social anxiety disorder (n = 16, 7 male, mean age = 35.2)	React and 'regulate' negative self-belief	n/a	Inferior and superior parietal lobule, cuneus, precuneus, middle occipital gyrus, parahippocampal gyrus	Increased medial cuneus, left cuneus, right middle occipital gyrus correlated with social anxiety symptom reduction	Changes in non-judgemental acceptance of self-related statements
Johnson et al. (2014)	Marines (n = 19), comparison individuals (n = 16)[ab]	Face processing (emotion processing/"interoception")	*ROI*: Reduced right anterior insula, dACC, vACC	not reported	Reduced right anterior insula correlated with decreased RSES (i.e. better resilience)	Changes in attentional control and 'tolerance'/ acceptance
Ives-Deliperi et al. (2013)	Bipolar disorder (n = 23, mean age = 37.6) and healthy individuals (n = 10, mean age = 30.2)[a]	Mindfulness meditation in scanner vs. generate random number	not reported	not reported	Increased mPFC correlated with increased FFMQ	Changes in meta-awareness

described enhancing acceptance, or 'tolerance' through interoceptive awareness. "The program emphasizes interoceptive awareness by cultivating attentional control and tolerance for challenging experiences, both external (i.e., harsh environmental conditions) and internal (e.g., physical pain, intense emotions, distressing thoughts)." We suggest that changes associated with this training may be more apparent in increasing processes supporting 'acceptance', rather than processes supporting 'awareness'. Together, these findings suggest it is important to consider the context of each group and how attentional processes might be disrupted prior to intervention.

While the insula is strongly implicated in interoceptive awareness, it has also been ascribed roles in a broader range of functions, including processing of emotional cues, environmental monitoring and response selection (Taylor et al., 2009). Meta-analytic work suggests at least three functional subdivisions of the insula, involved in cognitive (dorsoanterior), affective and chemosensory (ventroanterior) and sensorimotor (including interoception; posterior) functions (Chang et al., 2012). Future studies may investigate these specific subdivisions in relation to mindfulness training changes.

4.2. ACC activity: non-judgemental acceptance

Two studies demonstrated increases in ACC activity during the processing of emotional stimuli following mindfulness interventions (Haase et al., 2015; Johnson et al., 2014). In conjunction with dl/vlPFC, the ACC is generally assumed to play a role in regulation of emotional reactions related to the detection of conflicting information and subsequent direction of attention (Van Veen and Carter, 2002). In mindfulness interventions, altered ACC activity might be interpreted in terms of non-judgemental acceptance processes. This involves recognition of emotional responses and an attentional or cognitive 'distancing' process. Further investigation of this role for the ACC is clearly warranted. These effects were observed in groups of elite athletes and Marines, and it may be that increased ACC activity is a particular effect of mindfulness-based interventions in high-performance situations.

4.3. Prefrontal cortical regions: a role in meta-awareness?

Activity in subregions of PFC was associated with both practice of mindfulness and dispositional mindfulness (as measured by self-report questionnaire), although the specific subregion identified differed across studies. One study assessing post-intervention changes in neural activity during mindfulness meditation found greater activity in dlPFC and decreased activity in rostral PFC (Tomasino and Fabbro, 2016). Two studies found increased activity in midline prefrontal cortical regions following intervention to be associated with changes in self-reported dispositional mindfulness, but the specific subregions listed were not consistent across studies (dmPFC (Goldin et al., 2012), mPFC (Ives-Deliperi et al., 2013)). In combination, these studies point to a role for specific prefrontal cortical regions during mindfulness meditation or in dispositional mindfulness, yet to date there is a lack of consistent evidence for particular areas or networks involved. Prefrontal cortical regions have well-established roles in higher-order functions including meta-awareness, the ability to be aware of one's own consciousness, or 'thinking about thinking'. Meta-awareness may be key in training flexibility in the focus of one's attention, whether on the awareness of current experiences, or through a more distant 'acceptance-based' lens. Existing methodologies for assessing meta-cognitive processes might usefully be employed to assess this further (for review of tasks, see Insabato et al., 2016).

4.4. Preliminary evidence of altered reward processing

The studies here primarily assessed negatively valenced emotional stimuli, yet mindful awareness (and 'savouring') of positive and pleasant experiences is also addressed in treatment. Two studies demonstrated increases in activity in the caudate nucleus, a key reward region, following mindfulness interventions (Haase et al., 2015; Tomasino and Fabbro, 2016). It is plausible that this increased focus of attention on stimuli facilitates more detailed appraisal of their reward value and associated reactivity in the caudate nucleus. Behavioural studies have started to investigate enhanced responsiveness to positive emotions after MBCT (e.g., Geschwind et al., 2011) and this may also be of interest for neuroimaging designs.

4.5. Dissociation between clinical and neural science

Clinical scientific investigations of mindfulness-based interventions are beginning to identify mechanisms by which mindfulness may effect change. There is a distinct dissociation between the mechanisms identified in this work and the majority of the functional tasks employed in neuroimaging studies reviewed here. While investigation in clinical work is primarily guided by the content of the intervention, neuroscientific research is built upon pre-existing knowledge of emotional processing within the brain. As such, neuroimaging studies discussed here have primarily focused on measures of emotional reactivity or meditation in the scanner, while clinical findings point to key roles for self-reported mindfulness, cognitive reactivity, rumination, compassion, acceptance and meta-awareness (Segal et al., 2002). Greater concordance between these fields, perhaps including the development of novel behavioural tasks may help to bridge this gap, identifying more specific constructs of functioning and disruption that can be understood at different levels of analysis. As highlighted in the Research Domain Criteria (Cuthbert and Insel, 2013), a common framework may help to foster more translational science.

4.6. Strengths and limitations

To ensure a reliable estimate of within-subjects changes, only longitudinal studies assessing functional activity using fMRI at two time points (before and after intervention) were included in this review. This approach provides confidence that observed changes were associated with the intervention itself, and not extraneous variables. This is an important distinction between the current systematic review and previous reviews including studies using both within-subjects and between-subject designs (e.g., Gotink et al., 2016) which have the limitation of introducing variance related to individual, or group differences. A second strength of the current work was the organisation of findings with respect to the core features of mindfulness interventions (present-moment awareness and non-judgemental acceptance). We hope that summarizing neuroscientific findings within a clinical science framework will help to clarify important avenues for future mechanistic research.

As the goal of this review was to assess generalisable effects of mindfulness interventions (as far as currently possible), study selection was agnostic to the study population. We included patient groups undergoing treatment for specific symptomatology and healthy individuals receiving 'resilience' training. Findings presented, therefore, speak to general mechanisms, rather than more specific features of individual study populations. It should be noted that the summary of findings presented above is necessarily preliminary, with only seven studies (N = 238) meeting criteria for inclusion. Related to this, while there was an absence of evidence for intervention-related changes in specific prefrontal cortical regions, this may not be interpreted as evidence of the absence of such an effect (Borenstein et al., 2009). A formal meta-analysis was not conducted as part of this review due to a lack of detailed reporting of treatment effects at the whole brain level (with analyses instead focussing on specific 'regions of interest').

Finally, it is worth noting that by using group-based analyses, we implicitly assume that all participants benefit in an approximately similar way. However, in interventions such as MBCT/MBSR, there is a substantial home practice component. There is evidence to suggest that participants practice to varying extents (Parsons et al., 2017) and the degree to which they benefit is impacted by the level of treatment engagement. It is also possible that different individuals benefit in different ways. For example, some individuals may gain the most from a change in present-moment awareness, while others may gain more from a change in non-judgemental acceptance. Neuroscientific investigation of practice effects and changes associated with individual treatment components may be beneficial in identifying mechanisms with greater therapeutic benefit.

4.7. Future directions

While undertaking longitudinal neuroimaging studies of any psychological intervention is challenging, these types of investigations are clinically valuable. There is preliminary but encouraging evidence that functional neuroimaging data may predict differential response to treatment (for review, see Craske, 2014), such as response to cognitive behavioural therapy versus selective serotonin reuptake inhibitors in patients with major depression (McGrath et al., 2013). Recent work suggests that prediction models based on neural biomarkers, rather than demographic and clinical data, have the potential to considerably improve accuracy in predetermining treatment response (Ball et al., 2014). Combining treatment and imaging measures, has enormous potential in helping us to better identify the links between brain functions and psychological processes. This is of particular interest in the study of mindfulness-based interventions, given their demonstrated efficacy in improving mental health outcomes. There is also much to be learned from studying cases in which mindfulness-based interventions are less effective. For example, recent work suggests that while MBSR may be more effective than 'treatment as usual' in the short-term, these effects were not significant at a two year follow up (Cherkin et al., 2017). A better understanding of neurobiological correlates of long-term treatment efficacy (both for mindfulness-based interventions and other intervention strategies) holds the potential for informing personalised medicine decisions and might ultimately aid selection of the optimal treatment strategy for an individual.

4.8. Six key considerations for neuroimaging studies of mindfulness-based interventions

The recent surge in studies examining the neural mechanisms of mindfulness interventions is both impressive and inspiring. However, as an emerging field, current interpretations are limited to some extent by differing methodological approaches, both in study design and analyses. To enhance the inferences that can be drawn from future work, we suggest six considerations for the design of future studies, described in turn below. These are: i) use of manualised interventions; ii) including control conditions and larger sample sizes; iii) assessing clinically-informed mechanisms; iv) combined use of self-report, behavioural and neural measures, v) including longer-term follow up assessments and vi) reporting and anonymised sharing of whole brain data.

First, as discussed earlier, use of manualised treatments ensures greater consistency of interventions across studies reducing extraneous variance associated with, for example, intervention duration or content. Secondly, inclusion of larger sample sizes and a control condition allows assessment of changes specific to the intervention. This is particularly relevant in fMRI studies where factors such as familiarity with stimuli, novelty/anxiety in the scanner environment (which may reduce with time, Poldrack, 2000) and other scanner-related variables (such as scanner 'drift', Takao et al., 2011) can impact results. Third, there is a theoretical gap between mechanisms assessed in clinical science and mechanisms investigated in neuroimaging studies. Developing novel paradigms and designing fMRI studies based on a priori hypotheses related to clinical theoretical frameworks of treatment mechanisms will increase the extent to which neuroscience can be used to understand the processes involved in treatment.

Fourth, studies reported here represent good examples of relating scores on validated self-report measures to differences in neural activity. This should continue in future studies, and inclusion of behavioural and peripheral psychophysiological indices should be considered to allow further investigation of treatment effects at multiple levels of analysis. Fifth, as the goal of psychological interventions is to effect change in symptoms and functioning beyond the end of treatment, inclusion of follow-up assessments should be a priority in future work. Sixth, detailed reporting of whole-brain effects for all comparisons assessed, as well as key methodological information is a priority for improving neuroimaging reporting quality. There are clear guidelines available for the reporting of fMRI data and analyses which should include reporting of group-based coordinates of whole brain effects (Poldrack et al., 2008) and online repositories where data can be uploaded and freely shared with the research community (e.g., https://openfmri.org/).

5. Conclusion

The incorporation of neuroscientific technologies into the psychologist's toolkit for investigating mechanisms of effective psychological treatments affords the opportunity to understand biological correlates of mental health and well-being. Combining findings across the various levels of analysis at our disposal holds much promise in fostering novel targets and strategies to optimise treatment interventions. Here we review literature regarding the neural mechanisms of manualised mindfulness-based interventions across longitudinal fMRI studies. Our synthesis of results points to a central role for the insula, a region of the frontal lobe associated with self-awareness and interoception. This is consistent with the notion that a primary mechanism of mindfulness interventions is to enhance engagement in 'present-moment' awareness. There was also preliminary evidence for a role for the ACC and midline prefrontal cortical regions for acceptance and meta-awareness respectively. Even in the small number of studies reviewed here with manualised interventions, there was a substantial degree of heterogeneity in findings. Part of this variance may be linked to the different populations sampled, differences in power (i.e. sample size), differences in treatment adherence, imaging tasks involved and analysis strategies employed. Overall, these findings underscore the need for greater consistency and quality in neuroscientific investigation of mindfulness-based interventions to better assess treatment mechanisms.

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