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REVIEW

The Impact of Mindfulness-Based Interventions on Brain Functional Connectivity: a Systematic Review

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Abstract

Objectives Despite the growing popularity of mindfulness-based interventions (MBIs), little is known about the neural connectivity changes that underlie the effects of MBI. The aim of this systematic review was to summarize the effects of MBI on functional brain connectivity.

Methods We summarized findings of longitudinal controlled studies investigating the impact of standardized and manualized 6- to 8-week MBIs on functional connectivity in healthy and clinical populations as measured with functional MRI. Web of Science, PubMed, and Scopus were searched to identify articles published up to August 2021. Quality was assessed using the Cochrane risk-of-bias tools. Fourteen studies, investigating 681 participants, were eligible for a qualitative synthesis.

Results Our summary of results shows altered functional connectivity between networks involved in attention, executive function, emotional reactivity, and mind wandering. More specifically, three studies reported increased amygdala-frontoparietal network connectivity after MBI compared to a control group. Two other studies reported altered connectivity between salience- and dorsal attention/frontoparietal network regions. Increased connectivity between a default mode network seed and areas in the prefrontal cortex was reported in two studies.

Conclusions We speculate that increased amygdala-frontoparietal network connectivity might translate as improved emotion regulation after MBI. Furthermore, the capacity to be aware of unfolding experiences may be expressed in enhanced connectivity between attentional control- and salience-related brain areas. An increased focus after MBI might be reflected in enhanced default mode network-prefrontal cortex connectivity. However, studies investigating whole-brain connectivity or similar seed regions are needed to generalize conclusions.

Keywords Mindfulness · MBI · fMRI · Brain connectivity · Attention · Awareness

Research on the effects and mechanisms of mindfulness has considerably grown in recent years. In a mindfulness-based intervention (MBI), people are taught to purposely pay non-judgmental attention to the unfolding experience in the present moment (Kabat-Zinn, 2013). Evidence so far suggests that MBIs can have a moderate to large effect on psychological outcomes such as stress, depression, and anxiety (Khoury et al., 2015; Wang et al., 2018). Furthermore, attentional skills may underpin the ability to maintain an open and non-judgmental attitude to experiences, which

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could lead to positive health outcomes and increased well-being (Malinowski, 2013). More specifically, MBIs may improve neuropsychological outcomes like attention, executive function, memory, and emotion regulation (Verhaeghen, 2020; Wheeler et al., 2017).

However, to unravel the working mechanisms of MBIs, longitudinal controlled research on the psychological and neural mechanisms is needed (Malinowski, 2013). Over the past years, there has been increasing interest to estimate the effect of mindfulness on functional brain connectivity, a good candidate to provide new insights in brain communication (Pawela & Biswal, 2011).

Initially, functional MRI was used to investigate brain activity while performing a task, based on the blood oxygen level–dependent (BOLD) signal. Nowadays, researchers increasingly focus on discovering correlations between BOLD activity time series in the brain, referred to as functional connectivity (FC) (Lv et al., 2018). Unlike structural connectivity, FC does not necessarily reflect physical connections between brain regions, but rather co-activation. More specifically, when regions show highly correlated BOLD activity, we may infer that these brain regions are frequently co-activated and therefore functionally linked.

FC can be investigated during rest (rs-fMRI) or while performing a task (tb-fMRI) (Lv et al., 2018). The three most common methods to assess changes in FC are seed-based, region of interest (ROI)–based, and independent component analysis (ICA). As all studies described in this review used seed-based or ROI-ROI FC analysis, we will only elaborate on these methods below.

In short, seed-based analysis starts from a predefined hypothesis about a brain region that is involved in the process to be studied. The seed region, sometimes also referred to as ROI, may be selected based on a brain atlas or results of prior (whole brain) analysis. Functional coupling between the averaged BOLD time course of the predefined seed and all other voxels in the brain is investigated. While seed-based analysis investigates connectivity between one seed and the rest of the brain, ROI-to-ROI analysis investigates functional coupling between a set of predefined ROIs. ROIs can be selected based on a specific brain network under investigation, or a more explorative whole-brain atlas-based ROI analysis can be performed. Both seed-based and ROI-to-ROI analysis are model-dependent methods. They have the advantage to provide a clear view of the regions that are functionally connected, and results are easily interpretable (van den Heuvel & Hulshoff, 2010). However, the obtained results highly depend on the predefined regions of interest. One study included in this systematic review (Santarnecchi et al., 2021) used a special form of FC, Granger causality, to calculate changes in brain connectivity. This method provides additional information on the direction of FC (Friston et al., 2013).

FC changes after various forms of (long-term) meditation have been reported in different brain networks. The four most frequently reported brain networks are the default mode network, dorsal attention network, frontoparietal control network, and salience network (Brandmeyer & Delorme, 2021; Mooneyham et al., 2016).

Firstly, the *default mode network* (DMN) has been associated with mind wandering and self-referential processing, which can be viewed as processes of internally focused attention. Mind wandering may be provoked by a negative mood and has been associated with poorer cognitive functioning on tasks of sustained attention and working memory (Banks et al., 2019). The posterior cingulate cortex (PCC) is considered a key hub of the DMN and has been linked to episodic memory and self-reflection. Additionally, it has been associated with goal-directed behavior, spatial-topographical and related memory functions (Rolls, 2019). Other brain regions frequently associated with the DMN include the medial prefrontal cortex, superior and inferior frontal gyri, medial and lateral temporal lobes, and the inferior parietal lobule (Spreng et al., 2013).

Secondly, the *dorsal attention network* (DAN) is an attention-related network that is involved in externally oriented attention. Next to this, regions within this network have been associated with the control of motor movements and interaction with the environment (Banker & Tadi, 2021; Passarelli et al., 2021). The DAN consists of the frontal eye fields, inferior precentral sulcus, superior occipital gyrus, middle temporal motion complex, and superior parietal lobule (Spreng et al., 2013). This network is involved in top-down cognitive control.

A third spatially interposed network, the *frontoparietal control network* (FPN), flexibly couples with either the DMN or DAN. It plays a central role in executive control, which is the ability to deliberately guide goal-based actions (Spreng et al., 2010). The prefrontal cortex is a key hub of the FPN and has additionally been linked to cognitive processes like attention, working memory, and salience detection. Furthermore, it has been associated with emotional and social behavior (Chini & Hanganu-Opatz, 2021). Other brain regions that are associated with the FPN are the precuneus, the anterior extent of the inferior parietal lobule, and medial superior prefrontal cortex (Spreng et al., 2013). The network also couples with the salience network, which modulates interactions between other networks involved in internally and externally focused attention (Spreng et al., 2013).

Fourthly, the *salience network* (SN) guides behavior by selecting the most relevant internal and external stimuli (Menon & Uddin, 2010). The insula and anterior cingulate cortex (ACC) are considered key nodes of the salience network. The ACC is linked to emotion and reward-related processing (Rolls, 2019), while the insula is involved in interoception and allows to rapidly capture and process

information for decision-making and motivated behavior (Centanni et al., 2021). By modulating the allocation of attentional resources, this network plays a key role in mindfulness (Mooneyham et al., 2016).

Finally, altered functional connectivity with the amygdala has frequently been reported (Gotink et al., 2016; Marchand, 2014). The amygdala plays an important role in processing emotional responses and emotion-based decision-making (Šimić et al., 2021).

As there is quite some heterogeneity in the reported mindfulness interventions, we aim to summarize the effects of standardized MBIs on the complex interactions between regions in the brain. As various forms of meditation can have differential effects on the brain (Raffone et al., 2019) and MBIs with varying duration (Creswell et al., 2016; King et al., 2016; Seminowicz et al., 2020; Taren et al., 2017) might impact the brain differently (Jha et al., 2017; Verhaeghen, 2020), we summarize the findings of studies investigating the impact of 6- to 8-week MBSR, MBCT, and closely derived interventions on functional brain connectivity in healthy and clinical populations as measured with task-based and resting-state fMRI. Moreover, longitudinal controlled within-subject designs are needed to allow for causal inferences (Young et al., 2018). So, in contrast to reviews that included cross-sectional and cohort studies in novices as well as in long-term meditators (Fox et al., 2014; Gotink et al., 2016; Marchand, 2014; Mooneyham et al., 2016; Shen et al., 2020), we only focus on longitudinal studies investigating brain connectivity changes from pre- to post-MBI compared to a control group.

Methods

A systematic review based on the PRISMA guidelines (Page et al., 2021) was conducted. We assessed the validity of the studies with validated risk-of-bias tools (Sterne et al., 2016, 2019).

Eligibility Criteria

The following inclusion criteria were used: (1) peer-reviewed empirical studies published in English; (2) adult population with mean age of 18 to 65 years old without meditation experience; (3) standardized and manualized MBIs: MBSR, MBCT, or closely derived MBIs, spread over 6–8 weeks with daily home practice. Systematic and sustained training in mindfulness-based practices include formal and informal practices; (4) longitudinal changes in FC from pre- to post-intervention as measured with fMRI; (5) active or waitlist control condition; and (6) randomized (RCT) or non-randomized controlled designs (non-RCT).

Search Strategy

We employed the following search terms on Web of Science, PubMed, and Scopus to identify articles published up to August 20, 2021: (mindfulness or MBI or MBP or MBSR or MBCT) AND (fMRI or resting state or rsFC or MRI or magnetic resonance or BOLD or neuroimaging or DWI or DTI or diffusion or connectom*) AND (attention or network or connectivity or DAN or SN or CEN or frontoparietal network or default mode or DMN or resting state network or task positive network or white matter or tract or executive). On Scopus, we added "ALL[]" before the search string. Duplicates were first removed using EndNote. The titles and abstracts of the records were then screened independently in the web-based tool Rayyan (Ouzzani et al., 2016) to identify eligible studies by two researchers (MM, JP/GS). Disagreements were solved with the assistance of a third reviewer (SD/KVDG). The full-text articles of the selected records were further screened according to the eligibility criteria.

Data Collection

Two reviewers (MM, JP/GS) independently extracted information, using a data sheet based on the PRISMA protocol, about (1) study design, (2) participant characteristics, (3) characteristics of the intervention, (4) measure characteristics, (5) statistical analysis methods, and (6) resting-state and task-based fMRI outcomes. Disagreements were solved with the support of a third reviewer (SD/KVDG), depending on their expertise in MRI or MBI.

Risk of Bias

Following the PRISMA guidelines (Page et al., 2021), the risk of bias of the included studies was assessed to retrieve validity measures. The RoB-2 tool (Sterne et al., 2019) and the ROBINS-I tool (Sterne et al., 2016) were employed to assess the risk of bias of the (quasi-)RCTs and non-RCTs respectively. Two reviewers (MM, JP/GS) independently estimated the risk of bias per domain. The domains include bias due to (1) randomization/participant selection, (2) deviations from the intended interventions, (3) missing outcome data, (4) outcome measurement, and (5) selection of the reported result. The ROBINS-I tool evaluates two extra domains compared with the RoB-2 tool: (1) bias due to confounding and (2) bias due to classification of interventions. The risk of bias was classified as low, some concerns, or high according to the scoring principles of both tools.

Results

Study Selection and Characteristics

The PRISMA flow diagram (Fig. 1) shows the information regarding study selection. In short, 2185 records were identified after duplicates had been removed and 14 studies were eligible for our systematic review (Chumachenko et al., 2021; Hölzel et al., 2013; Kirk et al., 2016; Korponay et al., 2019; Kral et al., 2018, 2019; Pagni et al., 2020; Santarnecchi et al., 2021; Sevinc et al., 2019; Smith et al., 2021; Su et al., 2016; Turpyn et al., 2021; Van der Gucht et al., 2020; Xiao et al., 2019).

A summary of the study characteristics, ordered alphabetically, can be found in Table 1.All studies investigated the impact of MBI on changes in brain FC from pre- to post-intervention. Nine studies reported on healthy populations, while five other studies focused on various clinical populations, such as patients suffering from generalized anxiety disorder, autism spectrum disorder, breast cancer survivors with cognitive complaints or neuropathic pain, and participants with self-reported pain. Of the identified studies, 12 followed the standard MBCT or MBSR format that consists of 8 weekly 2- to 2.5-h group sessions. The other two studies made use of closely derived MBIs. All studies reported daily home practice. Of the 14 included studies, 11 were RCTs, one was a quasi-RCT (using time of enrollment in the study as allocation method), and two were non-RCTs. Three studies used a waitlist control group, eight used an active control group, and two used a combination of both. One study used a healthy population as control for a pain-inflicted sample, but both groups received the same MBI. For more information about measure characteristics and statistical analyses, we refer to Table 2.

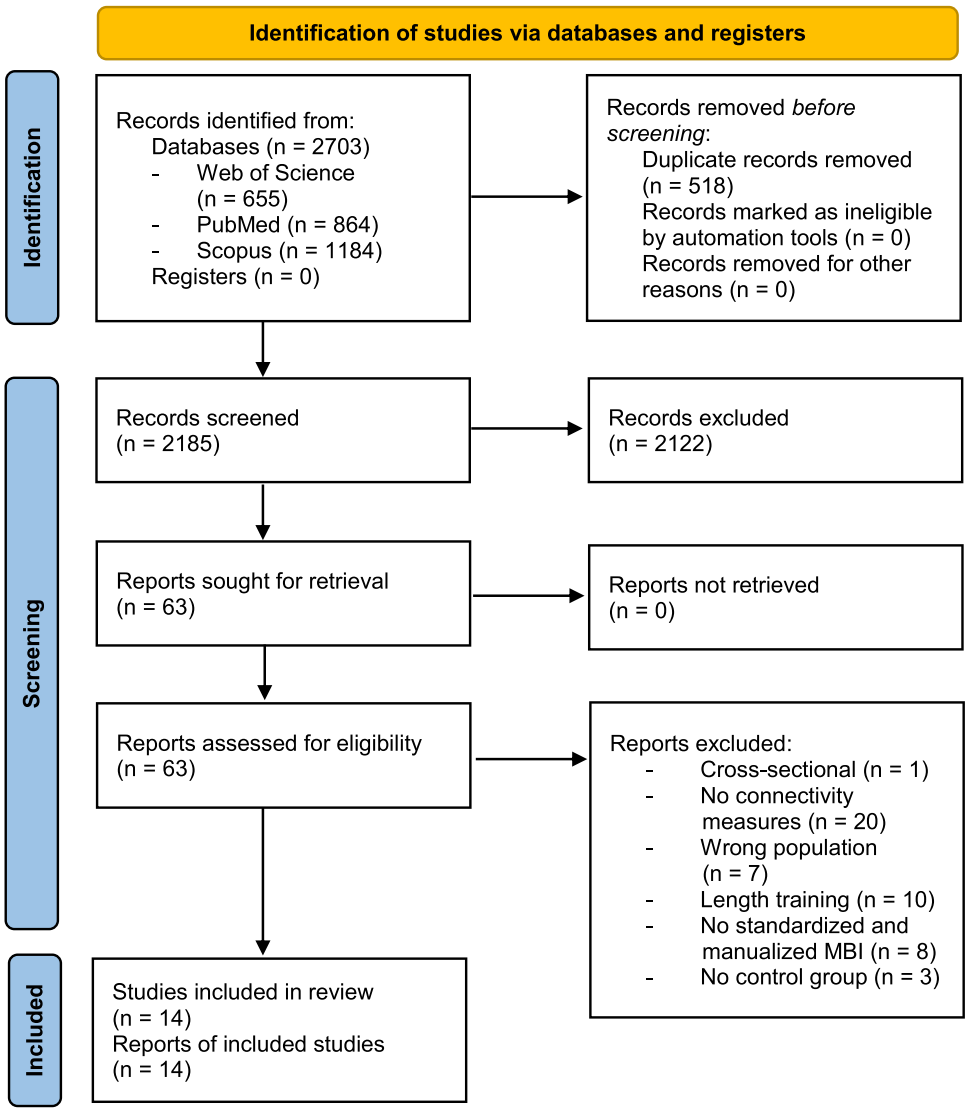

Fig. 1 PRISMA 2009 flow diagram of screened and selected studies

Table 1 Summary of study characteristics

Authors	Study design	Controlgroup	Diagnosis	Experimentalsample	Controlsample	Mindfulnessintervention	Baseline connectivitydifferences	Key findings
Chumachenko et al. (2021)	RCT	Healthy living course	Healthy individuals who lost body weight and intend to maintain weight loss	n=29, mean age=44.5, 76% female	n=23, mean age=44.5, 87% female	MBSR (8 weekly sessions of 1.5h, ? min home practice, full day retreat)	Not significant	↑ **Amygdala-FPN**
Hölzel et al. (2013)	quasi-RCT	Stress management education	Generalized anxiety disorder	n=15, mean age=38.5, 60% female	n=11, mean age=35.6, 45% female	MBSR (8 weekly sessions of 2.5h, 20 min home practice, full day retreat)	Not significant	↑ **Amygdala-FPN**
Kirk et al. (2016)	RCT	Progressive muscle relaxation	Healthy	n=26, mean age=32.2, 62% female	n=24, mean age=31.1, 47% female	MT (8 weekly sessions of 2.5h, 20 min home practice, full day retreat)	?	↑ Septal region-SN
Korponay et al. (2019)	RCT	Health enhancement program & waitlist	Healthy	n=34, mean age=50.3, 65% female	HEP/WL: n=36/35, mean age=47.9/47.8, 56/66% female	MBSR (8 weekly sessions of 2.5h, 45-60 min home practice, full day retreat)	?	**Not significant**
Kral et al. (2018)	RCT	Health enhancement program	Healthy	n=32, mean age=50.8, 69% female	n=35, mean age=48.1, 54% female	MBSR (8 weekly sessions of 2.5h, 45 min home practice, full day retreat)	Yes, but controlled for	↑ **Amygdala-FPN**
Kral et al. (2019)	RCT	Health enhancement program & waitlist	Healthy	n=31, mean age=41.4, 58% female	HEP/WL: n=34/30, mean age=43.6/43.0, 65/63% female	MBSR (8 weekly sessions of 2.5h, 45 min home practice, full day retreat)	Not significant	↑ **DMN-FPN**
Pagni et al. (2020)	RCT	Education support group	Autism spectrum disorder	n=15, mean age=32.3, 47% female*	n=13, mean age=31.2, 15% female*	MBSR (8 weekly sessions of 2h, 45 min home practice, no retreat)	?	↑ SN-pre/postcentral gyrus
Santarnecchi et al. (2021)	RCT	Waitlist	Healthy	n=23, mean age=31.0, 52% female	n=21, mean age=29.0, 50% female	MBSR (8 weekly sessions of 2.5h, 45 min home practice, full day retreat)	?	↓ **SN putamen** ↓ **Cerebellum-putamen and right orbitofrontal cortex** ↑ **Cerebellum-somatosensory cortex**

Table 1 (continued)

Authors	Study design	Controlgroup	Diagnosis	Experimentalsample	Controlsample	Mindfulnessintervention	Baseline connectivitydifferences	Key findings
Sevinc et al. (2019)	RCT	Stress management education	Healthy	n=48, mean age=31.1, 67% female	n=25, mean age=33.1, 60% female	MBSR (8 weekly sessions of 2h, 40 min home practice, half day retreat)	?	↑ Hippocampus-primary sensory cortex and supramarginal gyrus
Smith et al. (2021)	RCT	Waitlist	Breast cancer with chronic neuropathic pain	n=13, mean age=48.4, 100% female	n=10, mean age=56.5, 100% female	MBSR (8 weekly sessions of 2h, ? min home practice, full day retreat)	Not significant	↑ **DMN-FPN** ↓ **DMN-motor and pain pathways**
Su et al. (2016)	non-RCT	No-pain group**	Self-reported pain	n=18, mean age total sample=38.6	n=16, 74% female in total sample	MT (6 weekly sessions of 2.5h, ? min home practice, full day retreat)	?	↑ within SN
Turpyn et al. (2021)	RCT	Parent education	Healthy primary caregivers with elevated stress levels	Total n=20, mean age total sample=48.5, 100% female	Total n=20, mean age total sample=48.5, 100% female	Parenting Mindfully (8 weekly sessions of 2h, 45 min home practice, no retreat)	?	↓↑ **SN-DAN**
Van der Gucht et al. (2020)	RCT	Waitlist	Cancer-related cognitive complaints in breast cancer	n=18, mean age=43.9, 100% female	n=15, mean age=47.4, 100% female	Combination of MBCT and MBSR (4 biweekly sessions of 3h, 20 min home practice, no retreat)	Not significant	↑ **SN-DAN**
Xiao et al. (2019)	non-RCT	General health education course	Healthy	n=16, mean age=27.6, 50% female	n=16, mean age=28.1, 50% female	MBSR (8 weekly sessions of 2h, 30 min home practice, no retreat)	Not significant	↑ Postcentral gyrus-SN and precentral gyrus ↓ Postcentral gyrus-FPN

The key findings in bold represent significant group-by-time interaction effects, while the studies in normal font represent significant withingroupchanges? no information, *DMN* default mode network, *FPN* frontoparietal network, *HEP* Health Enhancement Program, *MBSR* Mindfulness-BasedStress Reduction, *MT* mindfulness training, n number, *RCT* randomized controlled trial, *SN* salience network, *WL* waitlist, *DAN* dorsal attentionnetwork, *MBCT* Mindfulness-Based Cognitive Therapy* Significant difference in gender between both groups at baseline ($p < 0.05$)** The control group received the same mindfulness intervention as the experimental group

Table 2 Brain structural and functional connectivity changes

Authors	MRImodality	Analysis	Outcome	Task	Group-by-time interaction effect	Main effect of time in mindfulness-based intervention group	Main effect of time in control group(s)	Association with self-report questionnaire
Chumachenko et al. (2021)	rs-fMRI	ROI-to-network	FC changes between ROIs in mOFC, dACC, amygdala and anterior insula and network-ROIs: aDMN,pDMN, SN, dDMN, vmPFC and basal ganglia	N/A	↑ Amygdala to vmPFC	Not significant	Not significant	Not significant
Hölzel et al. (2013)	tb-fMRI	Seed-to-whole-brain	FC changes between seed in amygdala and all voxels in the prefrontal cortex	Affect labeling	↑ Right amygdala to left rostral middle frontal cortex (including bilateral dorsolateral and dorsomedial prefrontal regions) and right superior frontal cortex	↑ Right amygdala to left rostral anterior cingulate cortex, bilateral rostral middle frontal cortex and right superior frontal cortex	Not significant	*(Negative correlation between BAI change score and connectivity of the right amygdala seed region and the left rostral middle frontal cortex, the right rostral middle frontal cortex and the right superior frontal cortex)**
Kirk et al. (2016)	tb-fMRI	Seed-to-whole-brain (PPI)	FC changes between left septal seed region and the rest of the brain	Ultimatum game	Not significant	↑ *(Septal seed region to right posterior insula)**	Not significant	N/A
Korponay et al. (2019)	rs-fMRI	Seed-to-whole-brain	FC changes between seeds in the striatum, midbrain and the rest of the brain	N/A	Not significant	Not significant	Not significant	N/A
Kral et al. (2018)	tb-fMRI	ROI-to-ROI (PPI)	FC changes between right amygdala and vmPFC	Automatic emotion regulation	↑ Right amygdala to vmPFC	Not significant	Not significant	N/A
Kral et al. (2019)	rs-fMRI	ROI-to-ROI	FC changes between PCC and DLPFC	N/A	↑ PCC and right DLPFC compared to HEP and waitlist PCC and the left DLPFC compared to HEP	Not significant	Not significant	N/A
			FC changes between PCC and LPFC	N/A	Not significant	Not significant	Not significant	N/A

Table 2 (continued)

Authors	MRImodality	Analysis	Outcome	Task	Group-by-time interaction effect	Main effect of time in mindfulness-based intervention group	Main effect of time in control group(s)	Association with self-report questionnaire
Kral et al. (2019) continued	rs-fMRI	Seed-to-whole-brain	FC changes between PCC seed and the rest of the brain	N/A	↑ PCC to right inferior temporal gyrus compared to HEP	↑ PCC to network of regionsthat included DLPFC	Not significant	Positive correlation between ESQ change score and PCC–left DLPFC connectivity from pre- to post-MBSR
		Small-volume-corrected voxel-wise analysis	FC voxel-wise changes within the DLPFC and PCC ROIs	N/A	Not significant	↑ PCC and right DLPFC	Not significant	N/A
Pagni et al. (2020)	tb-fMRI	Seed-to-whole-brain	FC changes between MCC and vmPFC seeds and the rest of the brain	Self-reflection	Not significant	↑ Right middle cingulate cortex to bilateral pre- and postcentral gyrus	Not significant	N/A
Santarnecchi et al. (2021)	rs-fMRI	Seed-to-whole-brain (Granger causality)	FC changes between seeds in right anterior putamen and right insula and the rest of the brain	N/A	↓ Excitatory activity from ACC towards right anterior putamen	N/A	N/A	N/A
	tb-fMRI	Seed-to-whole-brain (Granger causality)	FC changes between seeds in the right cerebellum and the rest of the brain	Concentrate on physical experience	↓ Inhibitory activity from right cerebellum towards right posterior putamen and right orbitofrontal cortex ↓ Exitatory activity from left posterior putamen towards right cerebellum ↓ Inhibitory activity from left somatosensory cortex towards right cerebellum	N/A	N/A	N/A
Sevinc et al. (2019)	tb-fMRI	Seed-to-whole-brain	FC between seed in the left hippocampus and the rest of the brain (all trials)	2-day classical fear conditioning and extinction paradigm	Not significant	↑ Left hippocampus to right primary sensory cortex	Not significant	N/A

Table 2 (continued)

Authors	MRImodality	Analysis	Outcome	Task	Group-by-time interaction effect	Main effect of time in mindfulness-based intervention group	Main effect of time in control group(s)	Association with self-report questionnaire
			Based on first 4 extinction recall trials		Not significant	↑ Left hippocampus to a cluster in the right supramarginal gyrus	Not significant	N/A
Smith et al. (2021)	rs-fMRI	Seed-to-whole-brain	FC between PCC seed and the rest of the brain	N/A	↑ PCC to ACC/medial prefrontal cortex ↓ PCC to bilateral precentral gyrus, right superior frontal gyrus, and pons	↑ PCC to ACC/medial prefrontal cortex and bilateral angular gyri	↑ PCC to ACC/medial prefrontal cortex and bilateral angular gyri	Negative correlation between BPI change score and PCC-ACC/medial prefrontal cortex FC Positive correlation between BPI change score and PCC-precentral gyrus FC
Su et al. (2016)	rs-fMRI	Seed-to-whole-brain	FC changes between seed in the AIC and the rest of the brain, with daMCC mask	N/A	Not significant	↑ Anterior insular cortex to daMCC (within the pain-afflicted group, but not in the healthy control group without pain)	N/A	Negative correlation between SFMPQ change score and AIC-daMCC connectivity strength
Turpyn et al. (2021)	rs-fMRI	Seed-to-whole-brain	FC changes between seeds in the amygdala, posterior insula, anterior insula, and dACC and the rest of the brain	N/A	↓ Right posterior insula to a cluster encompassing SPL and precuneus ↓ Right anterior insula to left pMTC ↑ dACC to a cluster encompassing precentral gyrus and MFG	N/A	N/A	Negative correlation between IM-P and right posterior insula-SPL/precuneus FC Positive correlation between PAIT-sadness and anterior insula-posterior temporal cortex FC
Van der Gucht et al. (2020)	rs-fMRI	ROI-to-ROI	FC changes between ROIs in the DMN, SN, DAN and FPN	N/A	↑ ACC to bilateral intraparietal sulcus	N/A	N/A	Negative correlation between change in DASS and ACC-left intraparietal sulcus FC

Table 2 (continued)

Authors	MRImodality	Analysis	Outcome	Task	Group-by-time interaction effect	Main effect of time in mindfulness-based intervention group	Main effect of time in control group(s)	Association with self-report questionnaire
Xiao et al. (2019)	rs-fMRI	Seed-to-whole-brain	FC changes between seeds in the right SPL and left PoCG and the rest of the brain	N/A	Not significant	↑ Left postcentral gyrus to the midcingulate gyrus, precentral gyrus and insula in the left side ↓ Left postcentral gyrus tothe right precuneus andsuperior frontal medial gyrus	Not significant	N/A

aDMN anterior default mode network, *BAI* Beck Anxiety Inventory, *dACC* dorsal anterior cingulate cortex, *dDMN* dorsal default mode network, *FC* functional connectivity, *HEP* health enhancement program, *mOFC* medial orbitofrontal cortex, *MRI* magnetic resonance imaging, *N/A* notapplicable, Not significant $p > 0.05$, *PCC* posterior cingulate cortex, *pDMN* posterior default mode network, *PPI* psychophysiological interactionanalysis, *ROI* region of interest, *rs-fMRI* resting-state functional *MRI*, *SN* salience network, *tb-fMRI* task-based functional *MRI*, *vmPFC* ventromedialprefrontal cortex, *ACC* anterior cingulate cortex, *DLPFC* dorsolateral prefrontal cortex, *ESQ* Emotional Style Questionnaire, *MBSR* mindfulness-based stress reduction, *MCC* middle cingulate cortex, *AIC* anterior insular cortex, *BPI* Brief Pain Inventory, *daMCC* dorsal anteriormidcingulate cortex, *DAN* dorsal attention network, *DASS* Depression Anxiety Stress Scale, *DMN* default mode network, *FC* functional connectivity,FPN frontoparietal network, *IM-P* Interpersonal Mindfulness in Parenting scale, *MFG* middle frontal gyrus, *PAIT* Parent-AdolescentInteraction Task, *pMTC* posterior middle temporal cortex, *PoCG* postcentral gyrus, *SFMPQ* Short Form McGill Pain Questionnaire, *SPL* superiorparietal lobule* Not corrected for multiple comparisons

Risk of Bias Assessment

Table 2 shows a summary of the risk of bias of the 12 included RCTs as assessed with the RoB-2 tool and the two included non-RCTs as assessed with the ROBINS-I tool. The studies are sorted from low to higher risk of bias. More details can be found in Supplementary Materials 1.

Functional Connectivity Changes

Table 1 provides a detailed summary of the FC changes observed after MBI and the association with self-report measures. The significant group-by-time interaction effects will be discussed in more detail below. These results provide the most powerful evidence for the existence of an effect of MBI on FC from pre- to post-intervention compared to control groups. For the significant within-group changes, we refer to Table 3. Both within-group and interaction effects of FC changes are visualized in Fig. 2.

Functional Connectivity Based on Task-Based fMRI

Two of the included studies reported FC changes from pre- to post-intervention as a function of group while completing an emotion-focused task in the MRI scanner in healthy participants (Kral et al., 2018) and individuals with generalized anxiety disorder (Hölzel et al., 2013). Both studies calculated amygdala-prefrontal cortex connectivity differences between MBI and an active control intervention. They reported increased connectivity between the amygdala and the ventromedial prefrontal cortex (Kral et al., 2018), and right superior frontal cortex and left rostral middle frontal cortex (Hölzel et al., 2013). These regions have been associated with executive control and can thus be considered part of the FPN (Hölzel et al., 2013; Kral et al., 2018). Both authors interpret the enhanced connectivity as evidence for an improved top-down emotion regulation strategy after MBI.

Santarnecchi et al. (2021) investigated healthy individuals while meditating in the MRI scanner using Granger causality analysis. They reported altered connectivity between the cerebellar seed region and sensorimotor areas. Connectivity decreased from the right cerebellum towards the right posterior putamen and from the left posterior putamen towards the right cerebellum. Connectivity increased from the left somatosensory cortex towards the right cerebellum. The authors interpret these findings as improved sensorimotor regulation. Additionally, connectivity decreased from the right cerebellum towards the right orbitofrontal cortex, a region linked with sensory integration. According to the authors, this might be linked to cognitive and affective functions.

Functional Connectivity Based on Resting-State fMRI

When evaluating resting-state FC changes, various seed regions have been the focus of investigation in the context of MBI, depending on the pathology under investigation. Like the task-based studies discussed above, one study reported increased ROI-to-ROI connectivity between the amygdala and FPN from pre- to post-MBI compared to an active control group (Chumachenko et al., 2021). Similar to Hölzel et al. (2013) and Kral et al. (2018), the authors interpret the enhanced amygdala-prefrontal cortex connectivity as evidence for an improved emotion regulation strategy after MBI.

Increased FC between the anterior cingulate cortex (ACC), a key region of the SN, and regions in the DAN was reported in two studies (Turpyn et al., 2021; Van der Gucht et al., 2020). Connectivity between the ACC and bilateral intraparietal sulcus was higher after MBI compared to a waitlist control condition in breast cancer survivors with cognitive complaints (Van der Gucht et al., 2020). Turpyn et al. (2021) reported strengthened connectivity between the dorsal ACC and a cluster encompassing the precentral and middle frontal gyrus in stressed mothers compared to an active control group. Both authors speculate that MBI might improve emotion regulation strategies. Santarnecchi et al. (2021) reported decreased FC from ACC towards the anterior putamen and interpreted these findings in the context of executive function. Additionally, Turpyn et al., (2021) reported decreased connectivity between the other key hub of the SN, the insula, and a cluster encompassing the superior parietal lobule and precuneus, regions related to the DAN and FPN respectively. The authors proposed that these connectivity changes represented a decrease in self-referential, narrative processing of internal sensations. Furthermore, connectivity decreased between the insula and left posterior temporal cortex. The authors link this to a decrease in emotional reactivity in response to social-emotional interactions.

Two studies investigated connectivity changes starting from the posterior cingulate cortex (PCC), a key region of the DMN. Both studies reported increased PCC-prefrontal cortex connectivity and interpreted this as an enhanced ability to control the focus of attention (Kral et al., 2019; Smith et al., 2021). Additionally, Kral et al., (2019) reported increased PCC-right inferior temporal gyrus connectivity in healthy individuals compared to a control group (Kral et al., 2019). In a sample of breast cancer survivors, decreased connectivity with the bilateral precentral gyrus, right superior frontal gyrus, and pons was reported (Smith et al., 2021).

Two of the reported studies examined the long-term effects of MBI on FC. Three (Van der Gucht et al., 2020) and five and a half (Kral et al., 2019) months after completion of the intervention, FC changes were assessed again to

Table 3 Risk of bias of (quasi-)randomized and non-randomized controlled trials

Authors	Bias due to randomization process (RCT) or selection of participants into the study (non-RCT)	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Bias due to confounding (only non-RCT)	Bias in classification of interventions (only non-RCT)	Overall bias
Chumachenko et al. (2021)	+	+	+	+	+	N/A	N/A	+
Kral et al. (2019)	+	+	+	+	+	N/A	N/A	+
Sevinc et al. (2019)	?	+	+	+	+	N/A	N/A	?
Smith et al. (2021)	+	+	?	+	+	N/A	N/A	?
Van der Gucht et al. (2020)	+	+	?	+	?	N/A	N/A	?
Kral et al. (2018)	+	?	+	+	?	N/A	N/A	?
Santarnecchi et al. (2020)	?	+	+	+	?	N/A	N/A	?
Kirk et al. (2016)	?	+	+	+	?	N/A	N/A	?
Turpyn et al. (2021)	?	+	+	+	?	N/A	N/A	?
Korponany et al. (2019)	?	+	?	+	?	N/A	N/A	?
Hölzel et al. (2013)	−	+	+	+	+	N/A	N/A	−
Xiao et al. (2019)*	+	+	−	+	?	+	+	−
Su et al. (2016)*	+	+	−	+	?	−	+	−
Pagni et al. (2020)	−	+	−	+	?	N/A	N/A	−

ROB-2 tool was used for (quasi-)randomized controlled trials (RCT); ROBINS-I tool was used for non-randomized controlled trials (non-RCT)
+ low risk (green circles), *?* some concern (yellow circles), − high risk (red circles), *N/A* not applicable

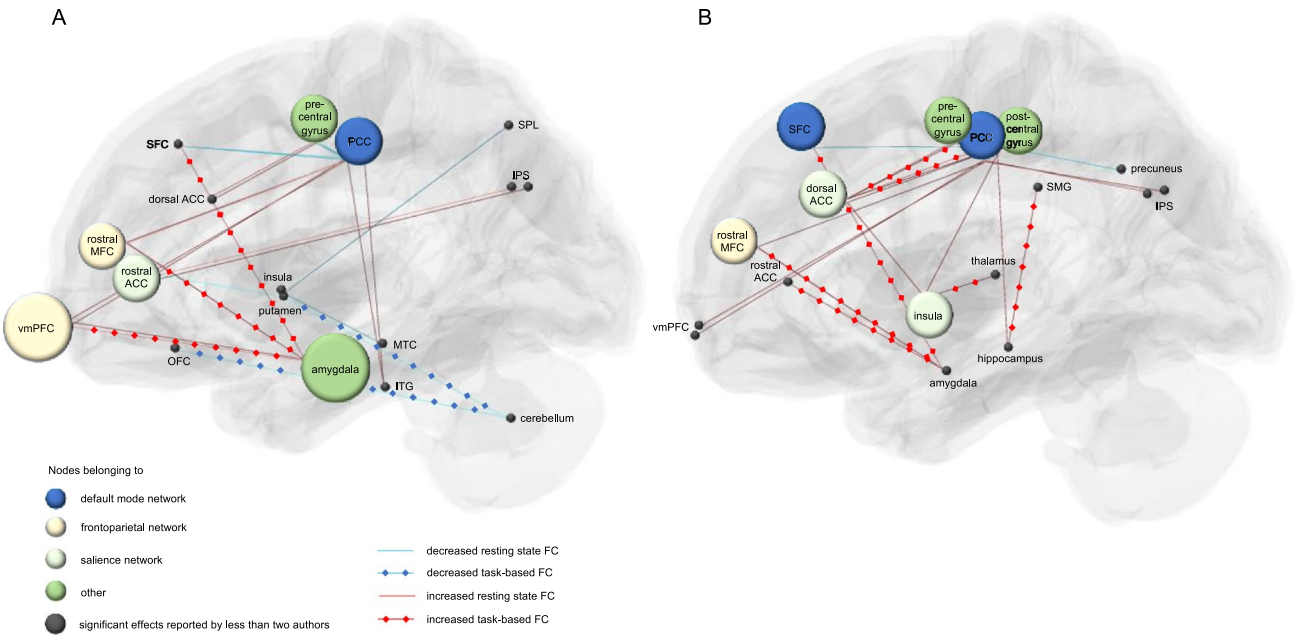

Fig. 2 Functional connectivity (FC) differences from pre- to post-intervention. Regions are color coded in relation to the network categorization of Spreng et al. (2013). The size of the circles increases with the number of studies reporting the given brain region. Regions that only have been reported by one study are represented by black circles. **A** Group-by-time interaction effects. **B** Effects within the mindfulness-intervention group. ACC = anterior cingulate cortex; IPS = intraparietal sulcus; ITG = inferior temporal gyrus; MCC = medial cingulate cortex; MFC = medial frontal cortex; MTC = medial temporal cortex; OFC = orbitofrontal cortex; PCC = posterior cingulate cortex; SFC = superior frontal cortex; SMG = supramarginal gyrus; SPL = superior parietal lobule; vmPFC = ventromedial prefrontal cortex

study long-term effects of MBI, but no significant changes were found.

Association with Self-Report Questionnaires

Associations between FC changes and self-reported attention, pain, mindful parenting skills, emotional distress, sadness, and anxiety were reported. The associations that were corrected for multiple comparisons are visualized in Fig. 3.

Increased DMN-PFC connectivity has been associated with higher self-reported attention from pre- to post-MBI (Kral et al., 2019) and lower pain severity scores (Smith et al., 2021). In addition, decreased DMN-precentral gyrus FC has been associated with lower pain severity scores post-MBI (Smith et al., 2021). Another study reported a link between increased SN-medial cingulate cortex connectivity and reduced self-reported pain, when measured with the Short Form McGill Pain Questionnaire. However, when pain was assessed with the Dallas Pain Questionnaire in the same study, the association with SN connectivity was not significant (Su et al., 2016). Therefore, caution must be taken when interpreting these findings. Furthermore, stronger ACC (SN)-DAN connectivity was linked with a reduction in symptoms of emotional distress (Van der Gucht et al., 2020), while decreased insula (SN)-DAN/FPN connectivity was associated with greater mindful parenting skills. Additionally, decreased insula-posterior temporal cortex FC was linked to lower levels of self-reported sadness (Turpyn et al., 2021). Finally, increased amygdala-FPN connectivity was related to reduced anxiety (Hölzel et al., 2013). Contrary to the other reported studies, the latter findings were not corrected for multiple comparisons, so they must be interpreted with caution.

Discussion

The aim of this systematic review was to summarize the effects of standardized MBIs on brain FC changes from pre- to post-intervention. There is considerable heterogeneity in the selected seed locations, which limits comparability of the included results. In what follows, we will provide a possible explanation for the significant group-by-time interaction effects and classify them under the process of deliberately paying attention and being aware of the unfolding experience with an open attitude of acceptance.

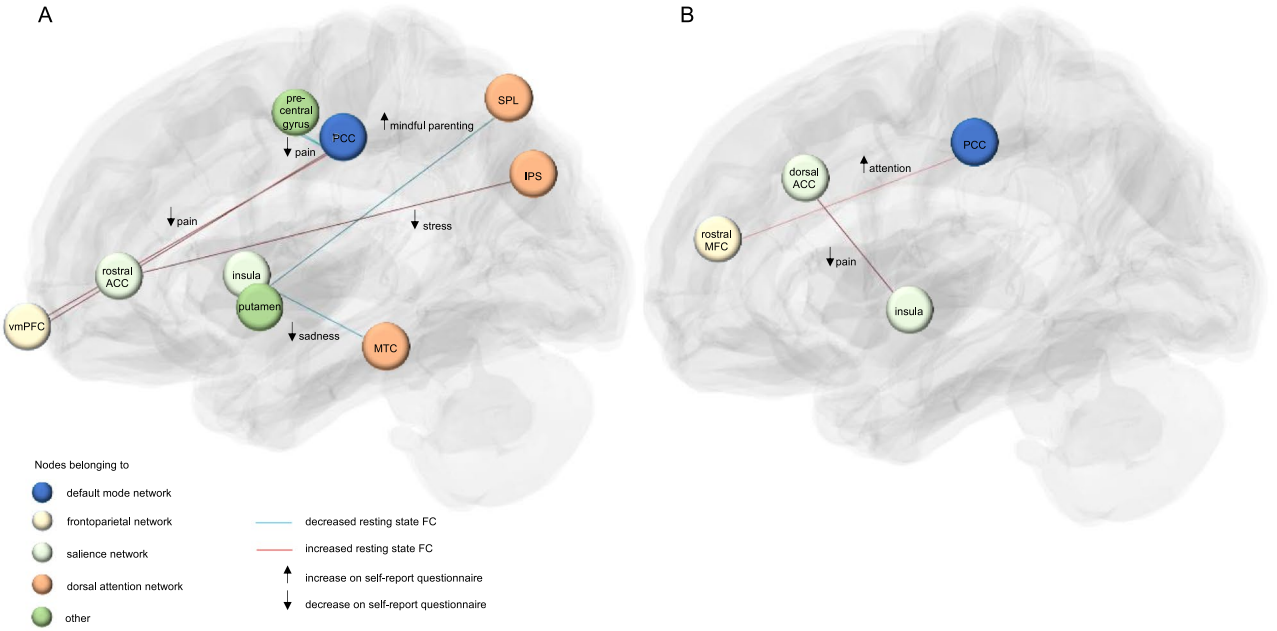

Fig. 3 Functional connectivity (FC) differences from pre- to post-intervention that correlated significantly with self-report questionnaires. Regions are color coded in relation to the network categorization of Spreng et al. (2013). The size of the circles does not reflect the number of times it has been reported in various studies. **A** Group-by-time interaction effects. **B** Effects within the mindfulness-intervention group. ACC = anterior cingulate cortex; IPS = intraparietal sulcus; MFC = medial frontal cortex; MTC = medial temporal cortex; PCC = posterior cingulate cortex; SPL = superior parietal lobule; vmPFC = ventromedial prefrontal cortex

Deliberately Paying Attention

During MBIs, participants are instructed to bring their attention back to their breath or another focus of attention, whenever their mind starts to wander (Kabat-Zinn, 2013). In that way, participants are trained to acknowledge that attention can be regulated and optimized through practice (Crane et al., 2017). In our review, increased resting-state DMN-FPN connectivity after MBI was reported in healthy individuals (Kral et al., 2019) and breast cancer survivors (Smith et al., 2021).

More specifically, increased FC between the PCC, a key hub of the DMN, and the prefrontal cortex was found. The PCC has been linked to spatial-topographical and related memory functions, goal-directed behavior, episodic memory, and self-reflection (Rolls, 2019). On the other hand, the prefrontal cortex has been associated with cognitive control and goal-directed behavior (Miller & Cohen, 2001). In studies investigating various forms of meditation, increased FC between hubs of the DMN and FPN has repeatedly been linked to improvements in attentional skills (King et al., 2016; Patsenko et al., 2019). Similarly, a recent meta-analysis found increased DMN-FPN connectivity in long-term meditators compared to less experienced meditators. The authors interpreted these findings as more control over mind wandering, which could lead to improvements in sustained attention (Shen et al., 2020). Preliminary evidence already indicated that MBI can improve different domains of attention as measured by neuropsychological tests (Verhaeghen, 2020). In accordance with this perspective, increased DMN-FPN connectivity correlated with enhanced self-reported attention (Kral et al., 2019) and performance on an attentional task (Patsenko et al., 2019). These studies also found altered white matter microstructure of the superior longitudinal fasciculus, which is the tract connecting DMN-FPN regions (King et al., 2016; Patsenko et al., 2019). Structural differences in the superior longitudinal fasciculus have been linked to enhanced connectivity between body awareness, attention, and executive function (Fox et al., 2014).

An increased focus might not only benefit healthy individuals to perform better, but it can also positively impact the experience of a disease by moving away from rumination about the condition. Initial evidence showed that lower pain severity scores after MBI were linked with increased DMN-FPN FC (Smith et al., 2021). Moreover, rumination has been associated with various mental disorders like depression, anxiety, and post-traumatic stress disorder (Brandmeyer & Delorme, 2021). By increasing the control over repetitive negative thinking, MBIs might influence psychological outcomes such as stress, depression, and anxiety. Increased DMN-FPN FC has also been linked to reduced amygdala reactivity, and therefore might impact the physiology of emotion regulation (Bauer et al., 2019).

In short, the process of deliberately paying attention might be reflected by enhanced DMN-FPN FC. Downregulation of the DMN by the FPN might indicate more control over mind wandering and less ruminative self-reflection.

Being Aware of the Unfolding Experience

Participants learn to monitor present-moment experiences without elaborating on them (Chiesa, 2013). They are requested to notice all thoughts, feelings, and sensations that come up in their stream of consciousness and welcome them with an open, accepting, and curious attitude. This could result in developing a different relationship with stressful sensations, thoughts, and feelings (Bishop et al., 2006).

Consistent with this view, significantly increased amygdala-prefrontal cortex connectivity has been reported during rest (Chumachenko et al., 2021) or while performing an emotion-focused task (Hölzel et al., 2013; Kral et al., 2018). The amygdala is associated with emotional processing and emotion-based decision-making (Šimić et al., 2021). It has been suggested that a poor connection between the amygdala and FPN–related regions might reflect poor decision-making and maladaptive emotion regulation skills (Bechara et al., 1999). By enhancing the coupling between the amygdala and regions in the FPN, participants might be better able to regulate their emotions and subsequent decisions/behavior by improvements in top-down cognitive control mechanisms following MBI (Dahl et al., 2020). For example, individuals who normally eat lots of food when they are stressed might be inhibited by the increased top-down control of the FPN on the amygdala after MBI, leading ultimately to weight loss (Chumachenko et al., 2021).

Another finding supporting an improvement in emotion regulation was the observation of altered resting-state connectivity between SN- and DAN/FPN-related regions. More specifically, increased connectivity between the ACC, and the intraparietal sulcus (Van der Gucht et al., 2020) and precentral gyrus (Turpyn et al., 2021) has been linked to improved emotion regulation strategies after MBIs.

On the one hand, the ACC had been linked to emotion and reward-related processing (Rolls, 2019). As a key hub of the SN, it has already been suggested to play a key role in the effect of MBIs on depression and anxiety (Brandmeyer & Delorme, 2021). On the other hand, the intraparietal sulcus and precentral gyrus are structures that can control movement and interaction with the environment (Banker & Tadi, 2021; Passarelli et al., 2021). Although the latter two structures can be classified as part of the dorsal attention network (Spreng et al., 2013), they have also been associated with the frontoparietal network because of their role in executive functioning (Duda & Sweet, 2020; Marek & Dosenbach, 2018).

As the increased SN-DAN/FPN FC correlated with a reduction in emotional distress (Van der Gucht et al., 2020), these findings might reflect improved emotion regulation skills. This aligns with the interpretation that participants might have more control over their emotions after MBI (Turpyn et al., 2021). We suggest that instead of reacting to their emotions based on previous experiences, participants might be more aware of the emotional sensations and non-judgmentally attend to these sensations.

Decreased resting-state connectivity between the other key hub of the SN, the insula, and the precuneus and middle temporal cortex, has also been linked to improved emotion regulation (Turpyn et al., 2021). The insula is involved in interoception and allows capturing and processing information rapidly to inform decision-making and guide motivated behavior (Centanni et al., 2021). Although the precuneus has been classified as part of the FPN, and the middle temporal cortex as part of the DAN (Spreng et al., 2013), both structures are involved in episodic and spatial memory (Cavanna & Trimble, 2006; Cutsuridis & Yoshida, 2017). Additionally, the precuneus has been linked to self-referential processing (Cavanna & Trimble, 2006), while the middle temporal cortex has been related to various memory processes (Cutsuridis & Yoshida, 2017).

The decreased SN-DAN/FPN FC has been associated with greater self-reported mindful parenting skills and lower sadness. Therefore, it can be interpreted as the ability to bring non-judgmental awareness to present-moment experiences and interactions with others (Turpyn et al., 2021). More specifically, because of the role of the DAN/FPN–related regions in episodic memory, we interpret the decreased SN-DAN/FPN connectivity as the ability to decenter from emotionally salient memories.

Although both the ACC and insula are considered key hubs of the SN, both increased and decreased FC with DAN/FPN–related regions might be induced by MBIs, depending on the function of the brain areas involved. Therefore, we suggest investigating data on a whole-brain level, in addition to a network level.

Less attention has been given to subcortical compared to cortical structures. Recent work, however, has highlighted the importance of the connection between the basal ganglia and cerebellum in emotion processing and cognition (Pierce & Péron, 2020). Satarnecchi et al., (2021) observed decreased connectivity between the putamen, one part of the basal ganglia, and the cerebellum while meditating in the MRI scanner. In contrast, increased FC between the caudate nucleus, another structure of the basal ganglia, and the cerebellum has been reported during rest after 2 weeks of MBI (Tang et al., 2017). Further studies are needed to offer additional insight in how sensorimotor regulation pathways are influenced by MBIs.

Taken together, the impact of MBIs on emotional functioning has been linked to amygdala-FPN and SN-DAN/FPN FC. Additionally, FC between the cerebellum and basal ganglia also deserves closer investigation in this context.

Limitations and Future Research

We see five major limitations of our review. First, we linked the observed brain activation patterns to specific cognitive processes. However, there are numerous cognitive processes that can explain changes in FC in the brain. This is referred to as "reverse inferences" (Poldrack, 2006). Therefore, we do not rule out alternative interpretations of the findings.

Second, because there is no common tool or gold standard available to assess the validity of RCTs and non-RCTs, we used two different instruments to assess the risk of bias. Guidelines regarding the use of risk-of-bias tools are currently missing (Farrah et al., 2019).

Third, we planned to perform a meta-analysis on the retrieved studies. However, this was not feasible given the considerable heterogeneity in study design, patient characteristics, and choice of ROIs. It would be favorable to report whole-brain effects to make a comparison of different study outcomes feasible. Moreover, the included studies used different network categorizations for classifying the reported brain areas. A consensus on which network categorization to use would be favorable to facilitate comparison between studies.

Fourth, as we included various clinical groups as well as healthy participants in our review, it is possible that disease and concomitant treatment already altered brain connectivity patterns to some extent. However, this enabled us to report more general mechanisms of MBI rather than population-specific processes.

Fifth, as we only focused on standardized and manualized 8-week MBIs in controlled longitudinal studies, we did not summarize all FC changes that have been described in the context of meditation. For example, increased SN-DMN has been reported repeatedly (King et al., 2016; Xiao et al., 2019; Yang et al., 2016).

In future research, several limitations could be addressed. First, the reported studies showed considerable heterogeneity in terms of control groups. Active control groups are recommended in mindfulness research to control for non-specific intervention effects such as group support, attention from the trainer, and expectations for improvement (Bower, 2016). Therefore, we believe that the use of active control groups should become standard practice.

Second, the validity of studies could be improved by addressing several factors that pose the studies at risk of bias. For example, a risk of bias arises when researchers and participants are not adequately blinded. It is desirable not to provide information about which intervention is the focus of the research (Davidson & Kaszniak, 2015). Next to this, there was considerable risk of bias due to selection of the reported results. Neuroimaging data can be analyzed with various methods which can induce false-positive results. Therefore, pre-registration of analysis plans is recommended in MRI research (Poldrack et al., 2017).

Finally, reasons for drop-out could provide valuable insights into individual motivation to complete a mindfulness training. Therefore, we suggest reporting the drop-out reasons to help guide a more personalized therapy approach.

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Author Contribution MM: design of the review, screening and review of articles, data analysis, data interpretation, and manuscript writing; GS and JP: screening and review of articles, data analysis, and manuscript editing; FR, AS, and SS: data interpretation and manuscript editing; SD and KVDG: conceptualization, design of the review, data interpretation, and manuscript editing; SD and KVDG share last authorship. All of the authors approved the final version of the manuscript for submission.

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Declarations

Conflict of Interest KVDG and FR are co-founders and members of the managing committee of the Leuven Mindfulness Centre Fund. They receive payments for workshops and presentations related to mindfulness. The authors declare that they have no other competing interests.

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