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8-week Mindfulness Based Stress Reduction induces brain changes similar to traditional long-term meditation practice – A systematic review

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ABSTRACT

The objective of the current study was to systematically review the evidence of the effect of secular mindfulness techniques on function and structure of the brain. Based on areas known from traditional meditation neuroimaging results, we aimed to explore a neuronal explanation of the stress-reducing effects of the 8-week Mindfulness Based Stress Reduction (MBSR) and Mindfulness Based Cognitive Therapy (MBCT) program.

Methods: We assessed the effect of MBSR and MBCT (N = 11, all MBSR), components of the programs (N = 15), and dispositional mindfulness (N = 4) on brain function and/or structure as assessed by (functional) magnetic resonance imaging. 21 fMRI studies and seven MRI studies were included (two studies performed both).

Results: The prefrontal cortex, the cingulate cortex, the insula and the hippocampus showed increased activity, connectivity and volume in stressed, anxious and healthy participants. Additionally, the amygdala showed decreased functional activity, improved functional connectivity with the prefrontal cortex, and earlier deactivation after exposure to emotional stimuli.

Conclusion: Demonstrable functional and structural changes in the prefrontal cortex, cingulate cortex, insula and hippocampus are similar to changes described in studies on traditional meditation practice. In addition, MBSR led to changes in the amygdala consistent with improved emotion regulation. These findings indicate that MBSR-induced emotional and behavioral changes are related to functional and structural changes in the brain.

1. Introduction

Mindfulness has a millennia old history and is usually referred to as a mental state characterized by 'full attention to internal and external experiences as they occur in the present moment', and 'an attitude characterized by non-judgment of, and openness to, this current experience' (Bishop et al., 2004; Brown & Ryan, 2003; Kabat-Zinn, Lipworth, & Burney, 1985). Stripped of all religious aspects, application of Mindfulness Based Stress Reduction (MBSR) (Kabat-Zinn et al., 1985) as a stress reduction method, and Mindfulness Based Cognitive Therapy to prevent relapse in depression (Teasdale et al., 2000), has increased over the past 35 years. In 8 weeks, MBSR and MBCT participants learn to cope with stress by means of cognitive exercises, concentration training and mental exposure, using a standardized evidence based protocol (Substance Abuse & Mental Health Services Administration, 2014). The MBSR- and MBCT protocol comprises both focused attention, open monitoring, and breathing meditation but without the transcending atmosphere of traditional meditative practice. The goal is not to reach Nirvana or Enlightenment. Instead, by learning to recognize automatic reactions, and letting go of dysfunctional ones in a non-judgmental manner, participants gain a new coping mechanism that studies have shown to improve perceived stress, anxiety, depression, and quality of life in all types of patients (Gotink et al., 2015; Vibe de, 2012).

Previous research on traditional meditation styles (i.e. Zen, Vipassana, Tibetan etc.) found that individuals who have regularly practiced meditation for several years exhibit significant altered

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brain structure, when compared to demographically matched controls (Holzel et al., 2008; Lazar et al., 2005; Luders, Toga, Lepore, & Gaser, 2009; Pagnoni & Cekic, 2007; Tang, Hölzel, & Posner, 2015; Vestergaard-Poulsen et al., 2009). Recent meta-analyses report eight regions to consistently show structural and functional differences in long-term meditators: the prefrontal cortex (related to enhanced meta-awareness and reappraisal), the sensory cortices and insula (related to body awareness), the hippocampus (related to memory processes), and the cingulate cortex (related to self and emotion regulation) (Boccia, Piccardi, & Guariglia, 2015; Fox et al., 2014; Holzel et al., 2007; Manna et al., 2010; Tomasino, Fregona, Skrap, & Fabbro, 2012).

Former neuroimaging literature focused on traditional meditation styles, or a combination of traditional and secular mindfulness. MBSR and MBCT are in some core aspects different from traditional meditation (i.e. duration and goal), and may therefore have different neuronal effects. In this article, we want to explore *how* the distilled mindfulness techniques in MBSR and MBCT, rather than spirituality of the traditional styles, are related to changes in brain structures and activity. We focus on regions described in studies on long-term meditators, but have not restricted ourselves to these areas. The current systematic review focusses on functional and structural magnetic resonance imaging (MRI) in order to understand the neuronal base of the psychological effects of MBSR and MBCT.

2. Methods

2.1. Inclusion and exclusion criteria

In this systematic review we give an overview of the published effects of the secular mindfulness program MBSR and MBCT, as designed by Kabat-Zinn et al. (1985) and Teasdale et al. (2000), on the function and structure of the brain. Studies reporting specific aspects of the program such as nonjudgmental awareness or focus on the breath, were also included to see whether these components have an impact on the brain and thus could explain more about the working mechanism of the 8-week program. To be included, the studies had to have the following characteristics: MBSR/MBCT or aspects of the program as intervention, and functional and/or structural MRI as imaging technique. When the intervention concerned a specific aspect of the 8-week protocols or it was a very similar secular derivative, like Mindfulness Based Exposure Therapy, studies were captioned under 'supportive studies'. Dispositional mindfulness was also included in order to take its effect into account in discussing found neuronal differences. There were no inclusion restrictions regarding age range, health status or ethnicity. Our primary outcome was activation, deactivation or functional connectivity, or structural changes (density, concentration or volume). As spatial resolution of Electroencephalography (EEG) is less, we restricted imaging method to (f)MRI. Other types of meditation such as Transcendental Meditation, Vipassana or Zen meditation were excluded, as heterogeneity of method and focus would make comparison to the standardized 8-week program difficult. Unpublished dissertations and conference papers were not taken into consideration.

2.2. Search strategy

Five electronic databases were used: *PubMed*, *Embase*, *PsycInfo*, *Medline OvidSP and Web-of-Science.* June 2016, the databases were searched for English language studies using the following terms: "mindfulness" or "meditation" or "mindfulness-based stress reduction" or "MBSR", in combination with "MRI" or "magnetic resonance imaging" or "neuroimaging" and "brain".

2.3. Study selection process

Two reviewers (RG and RM) independently read the abstracts of the studies to exclude those that were irrelevant. Any citation considered potentially relevant by at least one reviewer was retrieved in full text form. Inclusion was based on inclusion criteria mentioned earlier, studies of all date and design were considered. Discrepancies were evaluated together with a third reviewer (MH) and decisions were made by consensus.

2.4. Data extraction and quality assessment

Studies were analyzed independently on both content and on quality by the two reviewers. The data extracted were study design, population characteristics, type of intervention, type of measurement and neuronal changes. If information was missing or data were incomplete, the authors of the study were contacted to provide missing data. To assess the quality of the included RCTs we used the Cochrane Collaboration tool for assessing Risk of Bias (Higgins et al., 2011) and for non-RCTs we used the Newcastle-Ottowa criteria (Wells et al., 2000). We searched for explicit mentioning of each criterium, for example 'blinding'; when mentioned as present or not present explicitly, that article would receive a + or a − respectively, when nothing regarding this criterium was mentioned, the article would get a '?', To assess the degree of consensus we calculated the proportional agreement between the quality scores.

2.5. Outcome measures

The outcome measures were changes in (de)activation, functional connectivity and gray matter density/volume. As meta-analyses on the traditional styles identified the prefrontal cortex, the insula, cingulate cortex, and the hippocampus as main areas of change, we reported these as main areas of interest.

2.6. Analysis approach

Due to the heterogeneity in population (healthy participants, anxiety disorder and patients with neurodegenerative disease), task-based versus resting state, and outcome measures (structural voxels, connectivity and activity), the number of comparable studies within the included sample was too small to conduct formal quantitative meta-analysis of the results. An activation Likelihood Estimation meta-analysis was therefore not performed, and conclusions were drawn using a qualitative approach.

3. Results

3.1. Literature search

A total number of 1156 potentially relevant articles were identified, retrieved, and screened for potential inclusion (Fig. 1). 597 studies were excluded as being duplicates and 425 studies were discarded based on their titles. From the remaining 134 articles, 74 were excluded based on the abstract: 67 did not have MBSR, MBCT, or components as intervention, 26 did not use MRI or fMRI as imaging technique, and five were conference abstracts. Overall, 36 articles met our inclusion criteria and were reviewed by the two reviewers independently. In six cases, authors published multiple articles of one actually performed study; these were therefore presented together as one study (see Table 1), resulting in 30 actual studies. 11 neuroimaging studies reported on MBSR effects, 15 studies on aspects of the MBSR program and four on dispositional mindfulness. There were 13 RCTs, nine cohort studies and eight

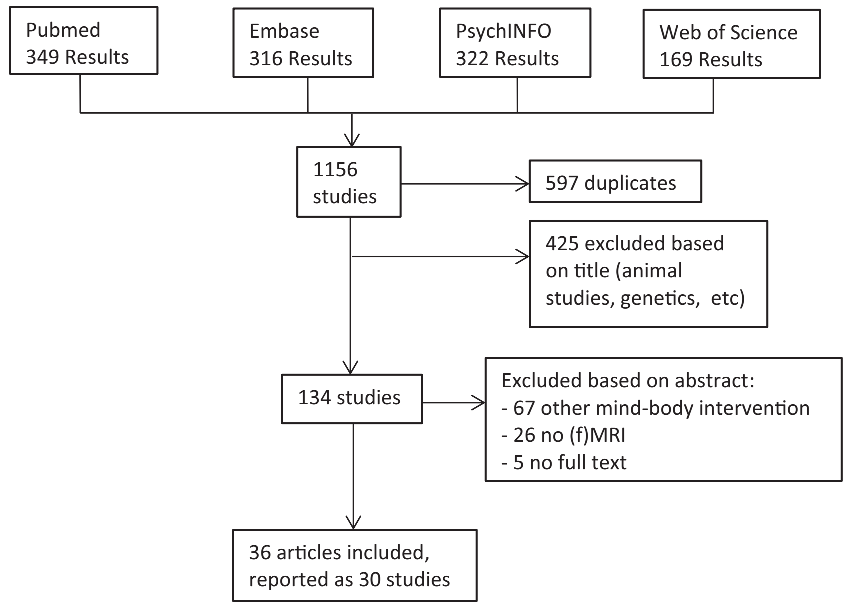

Fig. 1. Flowchart of the literature search (Search performed June 2016).

cross-sectional studies. An overview of rejected studies along with reasons for their rejections is available upon request.

3.2. Quality assessment

The results of the quality assessment are shown in Table 2. The proportion of inter-rater agreement was moderate (75%), the scores shown in the table are consensus scores. Of all studies, 11 studies were unclear about participant selection, although the groups compared were demographically not significantly different. Furthermore, in four of the RCTs randomization and allocation concealment were not obtained, which increases risk of selection bias. The method of measuring baseline characteristics and outcomes was reliable and with the exception of one study there was no risk of reporting bias. There was no indication of attrition bias in the longitudinal studies, as group demographics were still alike after drop-out occurred.

3.3. Study characteristics

Study characteristics are summarized in Table 1. Seven RCTs and four intervention cohort studies performed functional or structural MRI brain scans of MBSR participants (Farb et al., 2007; Goldin, Ramel, & Gross, 2009; Goldin, Ziv, Jazaieri, Hahn, & Gross, 2013; Holzel et al., 2010; Holzel et al., 2013; Ives-Deliperi, Solms, & Meintjes, 2011; Kilpatrick et al., 2011; Kirk et al., 2016; Pickut et al., 2013; Roland et al., 2015; Smart, Segalowitz, Mulligan, Koudys, & Gawryluk, 2016; Wells et al., 2012). Six RCTs, four cohort studies, and five cross-sectional studies investigated what effect aspects of the MBSR program have on the brain assessing certain fMRI tasks. Tasks that were performed were Feeling vs. Thinking, Affect Labeling vs. Gender labeling, Affect matching vs Face matching, and Reappraising emotions vs Reacting to emotional stimuli (Allen et al., 2012; Braden et al., 2016; Creswell, Way, Eisenberger, & Lieberman, 2007; Desbordes et al., 2012a; Doll, Holzel, Boucard, Wohlschlager, & Sorg, 2015; Doll et al., 2016; Haase et al., 2016; Herwig, Kaffenberger, Jancke, & Bruhl, 2010a; King et al., 2016; Modinos, Ormel, & Aleman, 2010; Smoski et al., 2015; Strawn et al., 2016; Way, Creswell, Eisenberger, & Lieberman, 2010; Yang et al., 2016).

Observing vs suppressing (for instance participants learned to label affects, reappraise emotions or focus on their breath). And finally, one cohort and three cross-sectional studies (Friedel et al., 2015; Kong, Wang, Song, & Liu, 2016; Murakami et al., 2012; Taren, Creswell, & Gianaros, 2013) measured the correlation between pre-disposition to mindfulness and brain activity or structure. Predisposition was measured using the Mindful Attention Awareness Scale (MAAS) (Brown & Ryan, 2003) and the Five Facet Mindfulness Questionnaire (FFMQ) (Baer, Smith, Hopkins, Krietemeyer, & Toney, 2006). These are validated questionnaires that assess the following aspects: living in the present moment, observing, non-judgment, awareness, non-reactivity to inner experiences, and acceptance. These qualities can be present in a person without following the MBSR program, for instance due to education, personality or culture. We first report the results of full MBSR training, after which supportive studies investigating aspects of the training are discussed. To keep interpretation of the results of the studies comprehensively, we have placed the comparison condition in Table 1, instead of in the text. The results are reported per structure that has been described in earlier meta-analyses on traditional meditation (see also Table 3). In addition to these regions of interest, the amygdala was reported so many times that we added this region to our outcomes. The areas are also shown in Fig. 2.

3.4. Prefrontal cortex

Overall, prefrontal cortex (PFC) shows increased activity after MBSR (Farb et al., 2007), particularly dorsolateral and dorsomedial (Goldin et al., 2009, 2013). The PFC also shows increased functional connectivity with the salience network (Menon, 2015), the superior temporal gyrus, the visual cortex, the amygdala, the hippocampus and the posterior cingulate cortex (Kilpatrick et al., 2011; Roland et al., 2015; Wells et al., 2013). Specifically, there was negative functional connectivity with the amygdala, where the PFC seemed to down-regulate the amygdala responses (Holzel et al., 2013). Mindfulness-based tasks were positively associated with activation in areas of ventrolateral, medial, dorsolateral and orbitofrontal PFC (Braden et al., 2016; Creswell et al., 2007; Herwig, Kaffenberger, Jancke, & Bruhl, 2010b; Modinos et al., 2010; Murakami et al., 2015; Way et al., 2010; Zeidan et al., 2015). Also,

Table 1
Study characteristics.

Author (year)	Outcome	Design	Participants (N)	Mindfulness condition	Comparator condition	Task (if applicable)
Farb et al. (2007, 2010, 2013)	fMRI	RCT	Healthy (36)	MBSR (20)	WL (16)	Narrative vs experiential focus
Ives-Deliperi et al. (2011)	fMRI	Cohort	Healthy (10)	Post-MBSR	Population norms	Random numbers vs Open monitoring
Goldin et al. (2009) and Goldin and Gross (2010)	fMRI	Cohort	Social anxiety (14)	Post-MBSR	Pre-MBSR	Distraction vs breath focus
Holzel et al. (2013)	fMRI	RCT	Generalized Anxiety Disorder (26)	Post-MBSR	SME (11)	Labeling facial expressions
Kirk et al. (2016)	fcMRI	RCT	Healthy (51)	MBSR (27)	Muscle Relaxation (24)	Economic decisions
Kilpatrick et al. (2011)	fcMRI	RCT	Healthy (32)	MBSR (17)	WL (15)	Pay attention to sounds of scanner
Roland et al. (2015)	fcMRI	Cohort	Tinnitus (13)	Post-MBSR	Pre-MBSR	N.A.
Wells et al. (2013)	Both	RCT	Alzheimer (13)	MBSR (8)	TAU (5)	N.A.
Smart et al. (2016)	MRI	RCT	Alzheimer (8)	Post-MBSR (8)	Pre-MBSR	N.A.
Holzel et al. (2010, 2011)	MRI	Cohort	Stressed (26)	Post-MBSR MBSR (16)	Pre-MBSR WL (17)	N.A.
Pickut et al. (2013)	MRI	RCT	Parkinson (27)	MBSR (14)	TAU (13)	N.A.
Supportive studies						
King et al. (2016)	fMRI	RCT	PTSD (23)	16 week MBET (14)	Group therapy (9)	N.A.
Haase et al. (2016)	fMRI	RCT	Marines (35)	MMFT (19)	Usual fitness training (16)	Processing with restricted breathing
Allen et al. (2012)	fMRI	RCT	Healthy (38)	6 week MT	Group reading	N.A.
Desbordes et al. (2012a, 2012b)	fMRI	RCT	Healthy (36)	8 week MT, CBCT	Health discussion group	Facial expressions
Braden et al. (2016)	fMRI	RCT	Back pain (23)	4 week MBSR (12)	Reading group (11)	Sadness induction
Haase et al. (2015)	fMRI	Cohort	Motocross athletes (7)	Post 6 week MT	Pre 6 week MT	Processing with restricted breathing
Yang et al. (2016)	fcMRI	Cohort	Healthy (13)	Post 40 week MBSR	Pre 40 week MBSR	Rest vs. meditation
Doll et al. (2015, 2016)	fMRI	Cohort	Healthy (26)	Attention to Breath	Passive observing	Aversive pictures
Strawn et al. (2016)	fMRI	Cohort	Children with anxiety (9)	Post 12 week MBCT	Pre 21 week MBCT	Processing task with emotional and neutral distractors
Smoski et al. (2015)	fMRI	Cross-sectional	Depression (37)	Remitted depressed (18)	Healthy (19)	Reappraisal vs. emotional acceptance
Herwig et al. (2010a, 2010b)	fMRI	Cross-sectional	Healthy (27)	'Feel'	'Think', 'Wait'	Think or Wait vs Feel
Creswell et al. (2007), Way et al. (2010)	fMRI	Cross-sectional	Healthy students (27)	Affect labeling Affect matching	Gender labeling Face matching	Gender vs Affect Labeling Face vs Affect matching
Modinos et al. (2010)	fMRI	Cross-sectional	Healthy students (18)	Reappraising emotions	Reacting to emotions	Reacting vs Reappraising
Murakami et al. (2015)	fMRI	Cross-sectional	Healthy (21)	Observing	Suppressing	Emotional visual stimuli
Zeidan et al. (2015)	Both	RCT	Healthy (75)	4-day MT	Placebo, sham-MT, book listening	Pain inducement
Friedel et al. (2015)	MRI	Cohort	Adolescents (82)	MAAS at age 19	MAAS at age 16	N.A.
Murakami et al. (2012)	MRI	Cross-sectional	Healthy (19)	FFMQ high score	FFMQ low score	N.A.
Taren et al. (2013)	MRI	Cross-sectional	Healthy (145)	MAAS high score	MAAS low score	N.A.
Kong et al. (2016)	MRI	Cross-sectional	Healthy (290)	MAAS high score	MAAS low score	N.A.

(f)(c)MRI: (functional) (connectivity) Magnetic Resonance Imaging, RCT: Randomized Controlled Trial, MBSR: Mindfulness Based Stress Reduction, WL: Waiting List, N.A.: Not applicable, SME: Stress Management Education, TAU: Treatment As Usual, MBET: Mindfulness Based Exposure Training, MMFT: Mindfulness-based Mental Fitness Training, MT: Mindfulness Training, CBCT: Cognitive Behavioral Compassion Training, FFMQ: Five Facet Mindfulness Questionnaire, MAAS: Mindful Awareness Assessment Scale.

amount of practice predicted increased medial and dorsolateral PFC activation during mindful emotional processing (Allen et al., 2012). One study found that acceptance rather than reappraising sad images, was associated with less PFC activation (Smoski et al., 2015). No structural changes were reported.

3.5. Insula

The insular regions are reported in two MBSR studies, one showing less activity (Ives-Deliperi et al., 2011), and one showing more activity (Holzel et al., 2013). Seven studies, however, reported increased activity in relation to mindfulness-based tasks (Creswell et al., 2007; Haase et al., 2015; Haase et al., 2016; Herwig et al., 2010b; Modinos et al., 2010; Murakami et al., 2015; Zeidan et al., 2015). Dispositional mindfulness was positively associated with activation in the left insula and right anterior volume (Kong et al., 2016; Murakami et al., 2012), and less cortical thinning in the left anterior insula (Friedel et al., 2015). Amount of practice during MBSR predicted right anterior insula and frontoinsular activation during negative emotional processing (Allen et al., 2012). One study showed that compared to muscle relaxation, the MBSR group had greater ability to effectively regulate the anterior insula and thereby promote a more cooperative decision making style (Kirk et al., 2016). In healthy adults, greater activation in left insula while accepting than while reappraising sad images was associated with greater intensity of negative affect

Table 2
Quality analysis of RCTs and non-RCTs.

Author (year)	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other
	Sequence generation	Allocation concealment					
Farb et al. (2007)	+	?	+	+	NA	+	
Holzel et al. (2013)	+	+	+	+	+	+	
Kirk et al. (2016)	?	?	+	+	?	–	
Kilpatrick et al. (2011)	+	–	–	+	+	?	
Wells et al. (2013)	+	?	+	+	+	+	
Smart et al. (2016)	–	+	+	+	+	+	
Pickut et al. (2013)	+	+	+	+	+	+	
King et al. (2016)	?	?	+	+	+	+	
Allen et al. (2012)	+	?	+	+	+	+	
Braden et al. (2016)	–	?	+	?	?	+	
Desbordes et al. (2012a, 2012b)	+	+	+	+	?	+	Subgroup of CALM study
Zeidan et al. (2015)	+	?	?	+	?	+	
Haase et al. (2016)	–	?	+	+	+	+	

Non-RCTs	Selection bias	Comparability	Outcome assessment	Follow-up	
Ives-Deliperi et al. (2011)	+	NA	+	NA	No control group
Goldin et al. (2009) and Goldin and Gross (2010)	+	+	+	+	
Roland et al. (2015)	+	NA	+	+	No control group
Holzel et al. (2010)	+	NA	+	NA	No control group
Yang et al. (2016)	+	NA	?	+	No control group
Doll et al. (2015, 2016)	?	NA	+	NA	No control group
Strawn et al. (2016)	?	NA	+	+	No control group
Smoski et al. (2015)	?	+	+	NA	
Herwig et al. (2010a, 2010b)	?	NA	+	NA	No control group
Creswell et al. (2007) and Way et al. (2010)	?	NA	+	NA	No control group
Modinos et al. (2010)	?	NA	+	NA	No control group
Murakami et al. (2015)	?	NA	+	NA	No control group
Murakami et al. (2012)	?	NA	+	NA	No control group
Taren et al. (2013)	?	NA	+	NA	No control group
Kong et al. (2016)	+	NA	+	NA	No control group
Haase et al. (2015)	–	NA	+	NA	No control group
Friedel et al. (2015)	+	+	+	+	

+ low risk; ? unknown risk/not mentioned; – high risk; NA not applicable; CALM Compassion and Attention Longitudinal Meditation. RCTs were assessed with the Cochrane Collaboration tool for assessing Risk of Bias, the non-RCTs using the Newcastle-Ottawa Scale.

post-acceptance, suggesting that this activation either reflected less effective emotion regulation, or reflected heightened emotional awareness rather than regulation (Smoski et al., 2015).

3.6. Cingulate cortex

The cingulate cortex also shows disparate results. In two MBSR studies less activity was reported (Goldin et al., 2013; Ives-Deliperi et al., 2011), while in four MBSR studies increased functional connectivity with the prefrontal cortex, the left temporal cortex, the parietal cortex and visual cortex were found (Kilpatrick et al., 2011; Roland et al., 2015; Wells et al., 2013), as well as increased cingulate volume (Holzel et al., 2011). Eight supportive studies report increased activation (Allen et al., 2012; Braden et al., 2016; Haase et al., 2015, 2016; Herwig et al., 2010b; Strawn et al., 2016; Zeidan et al., 2015), of which one during mindfulness-based tasks (Modinos et al., 2010). Compared to baseline, traumatized veterans showed increased connectivity between the posterior cingulate and the dorsal anterior cingulate and left dorsolateral PFC, which was correlated to decreased trauma-symptoms (King et al., 2016). No structural changes were reported.

3.7. Hippocampus

The hippocampus shows more activity and more volume in four MBSR studies (Goldin, 2011; Holzel et al., 2011; Pickut et al., 2013), including less Parkinson-related atrophy (Wells et al., 2013). Three supportive studies underline the increase in activity and volume (Creswell et al., 2007; Kong et al., 2016; Murakami et al., 2012), but one does not (Taren et al., 2013).

3.8. Amygdala

In two MBSR studies the right amygdala showed less activity compared to controls (Goldin et al., 2013; Holzel et al., 2013), the left amygdala in one study (Farb et al., 2007). Only in Parkinson patients more right amygdala volume was found (Pickut et al., 2013), though it was not clear whether volume in Parkinson patients increased or whether volume in controls decreased more. MBSR-induced stress reduction was associated with right amygdala volume decrease (Holzel et al., 2010). Three supportive studies report less amygdala activity in association with mindfulness tasks: mindfulness training was associated with less right amygdala activity, where compassion training was associated with more right amygdala activity (Desbordes et al., 2012b). When comparing ruminating to observing ones feelings, the left amygdala is more active during the ‘think’-condition and, notably, deactivated during the ‘feel’-condition (Herwig et al., 2010b). Affect labeling showed less bilateral amygdala activity compared to the control task gender labeling (Creswell et al., 2007; Way et al., 2010). Two studies report negative functional connectivity with the prefrontal cortex (Holzel et al., 2013; Modinos et al., 2010). While suppression showed a positive association with the dorsolateral PFC, observing showed a negative correlation with the medial PFC (Murakami et al., 2015). When reappraising emotions, the left amygdala was negatively correlated with dorsolateral PFC activation in more mindful individuals (Creswell et al., 2007). Dispositional

Table 3
Results.

Author (year)	Prefrontal cortex	Insula	Cingulate cortex	Hippocampus	Amygdala	Other
Farb et al. (2007, 2010, 2013)	More activity (4928 mm^3)				Less activity (576 mm^3 L)	More activity somatosensory cortex
Ives-Deliperi et al. (2011)	Less activity	Less activity anterior	Less activity anterior			Less activity in temporal lobe, precuneus
Goldin et al. (2009), Goldin and Gross (2010) and Goldin, Ziv, Jazaieri, and Gross (2012)	More activity dorsomedial		Less activity posterior	More activity	Less activity (1180 mm^3 R) Earlier deactivation	More activity inferior and superior parietal lobule, cuneus, precuneus, middle occipital gyrus
Holzel et al. (2013)	More activity, Improved connectivity amygdala	More activity			Less activity (784 mm^3 R)	
Kirk et al. (2016)		Increased coupling between left septal region and right posterior insula				
Kilpatrick et al. (2011)	Increased connectivity salience network		Stronger anticorrelation visual cortex			
Roland et al. (2015)	Increased connectivity temporal gyrus (647 mm^3 L), visual cortex (224 mm^3)		Frontal (242 mm^3 L, 354 mm^3 R), left temporal and parietal cortex (540 mm^3)			No changes in default network
Wells et al. (2013)	Increased connectivity hippocampus		Increased connectivity prefrontal	242 mm^3 less atrophy	No subcortical changes	
Smart et al. (2016)						More total brain volume change
Holzel et al. (2010, 2011)			More volume posterior	More volume (L)	Correlation stress reduction and volume decrease (13 mm^3 R)	More volume temporo-parietal junction, cerebellum
Pickut et al. (2013)				More volume (229 mm^3 R; 54 mm^3 L)	More volume (8 mm^3 R)	More volume caudate nucleus (260), thalamus (57), temporal lobe (30) and left occipital lobe (174); cerebellum in TAU (128)
King et al. (2016)	Increased connectivity with posterior		Increased connectivity anterior with posterior			
Haase et al. (2016)		Increased activation anterior (R)	Increased activation anterior			
Allen et al. (2012)	More activity dorsolateral, frontal gyrus	More activity Posterior (L) anterior (R)	More activity cingulate gyrus			Amount of practice predicted increased frontoinsular activation
Desbordes et al. (2012a, 2012b)					MT: less activity (R) CBCT: more activity (R)	Whole-brain analysis: no significant differences in any of the groups
Braden et al. (2016)	Increased activity (L)		Increased activity anterior			Correlation anterior cingulate (L) and sad valence ratings r = 0.65
Haase et al. (2015)	Decreased connectivity with posterior cingulate	Increased activation anterior	Increased activation anterior, decreased connectivity between anterior and posterior			
Yang et al. (2016)	Decreased connectivity anterior cingulate		Decreased connectivity anterior – posterior			Decreased connectivity anterior cingulate with occipital, temporal, cuneus. Increased with cerebellum, parietal.
Doll et al. (2015, 2016)	Increased activation				Less activity	More intrinsic functional connectivity between default mode network and salience network
Strawn et al. (2016)		Increased activation	Increased activation anterior			Increased activation thalamus and nucleus
Smoski et al. (2015)	Acceptance: less activation dorsolateral than Reappraisal	Acceptance: greater activation than Reapp				Greater activation to accept than reappr in left insula was associated with greater intensity of negative affect post-accept. Accept was associated with less effective subjective regulation than reappr

(continued on next page)

Table 3 (*continued*)

Author (year)	Prefrontal cortex	Insula	Cingulate cortex	Hippocampus	Amygdala	Other
Herwig et al. (2010a, 2010b) more activity	Think: anterior, dorsolateral Feel: superior, medial, inferior	Think: L Feel: R	Think: Posterior Feel: middle gyrus		Think: more activity (L) Feel: less activity (L)	Think: parietal, occipital cortex. Feel: temporal, somatosensory cortex, intraparietal sulcus.
Creswell et al. (2007), Way et al. (2010)	More activity medial (63,004 mm^3); ventrolateral (4910 mm^3); dorsolateral (2675 mm^3)	More activity (5380 mm^3 L)		More activity	Less activity ($r = -0.60$ LR) (10,752 mm^3 R; 908 mm^3 L)	More activity thalamus
Modinos et al. (2010)	More activity dorsolateral, inferior gyrus		More activity anterior		Negative correlation dorsolateral PFC ($r = -0.50$ L)	More activity temporal gyrus, angular gyrus, cerebellum
Murakami et al. (2015)	Increased activation frontal gyrus (L)	Increased activation anterior			Suppress: DLPFC (pos L) Observe: MPFC (neg L)	Middle temporal gyrus, inferior parietal lobule, putamen
Zeidan et al. (2015)	Greater activation orbitofrontal	Greater activation anterior	Greater activation anterior			Greater activation subgenual
Friedel et al. (2015)	No correlation	Less prior cortical thinning				
Murakami et al. (2012)		More volume anterior (R)		More volume (R)	More volume (R)	
Taren et al. (2013)				Less volume ($r = -0.2$ R)	Less volume ($r = -0.2$ R)	Caudate (L $r = -0.22$; R $r = -0.19$), nucleus accumbens (L $r = -0.20$)
Kong et al. (2016)	Orbitofrontal 768 mm^3; inferior frontal -1024 mm^3	920 mm^3		Parahipp gyrus 880 mm^3		

L: left, R: right, TAU: treatment as usual, MT: mindfulness training, CBCT: compassion based cognitive therapy, (DL)/(M)PFC: (dorsolateral)/(medial) prefrontal cortex.

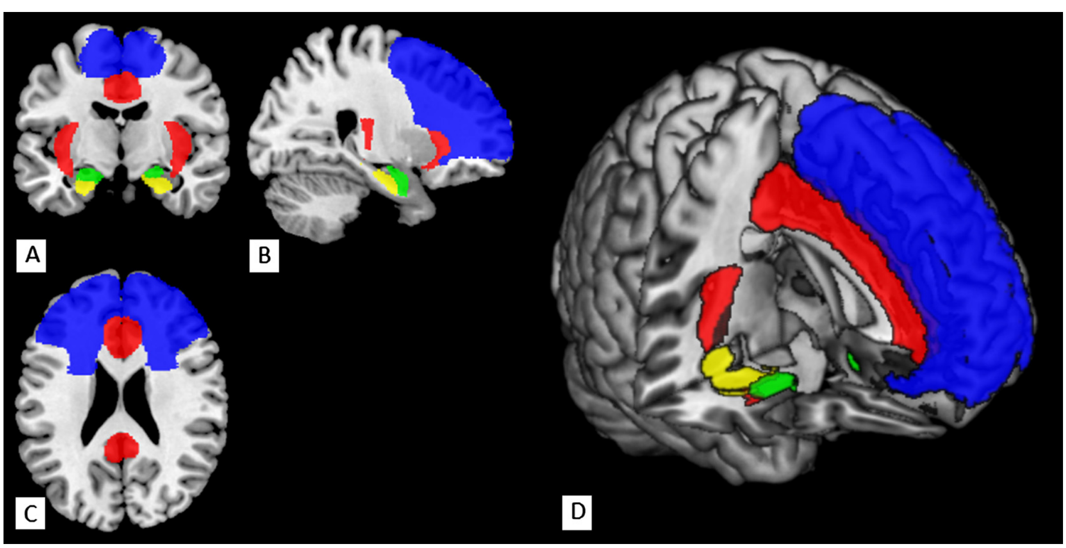

Fig. 2. Based on Hammers ROIs[1]. Coronal (A), Sagittal (B), Axial (C) and 3D (D) view of gray matter areas involved in MBSR. Prefrontal cortex (blue) and Hippocampus (yellow) show increased activation, the Amygdala (green) shows decreased activation. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

mindfulness was positively associated with bilateral amygdala deactivation. The structural supportive studies report a positive association between right amygdala volume and the describing facet of the FFMQ (Murakami et al., 2012), and a negative association with overall mindfulness (Taren et al., 2013).

3.9. Other results

This section reports regions not indicated by traditional meditation neuroimaging studies as affected consistently. More activity or volume in relation to MBSR or mindfulness-based tasks was found in the parietal cortex (somatosensory, precuneus), temporal cortex (middle and superior gyrus), occipital cortex (cuneus, middle gyrus), cerebellum, and basal ganglia (caudate nucleus, thalamus and putamen), though most structures were only reported once. One study reported less activity in temporal lobe and the precuneus compared to population norms (Ives-Deliperi et al., 2011), and another study reported no changes in the default mode network (Roland et al., 2015). Another study reported less volume in the cerebellum (Pickut et al., 2013).

4. Discussion

In this study we systematically reviewed the evidence of effect of secular mindfulness on function and structure of the brain, hence aiming to understand the neurobiological explanation of this increasingly popular stress reduction training. Long-term meditation has been associated with structural and functional differences in the prefrontal cortex, the sensory cortices and insula, the hippocampus, and the cingulate cortex (Fox et al., 2014; Holzel et al., 2007; Manna et al., 2010; Tomasino et al., 2012), associated with emotion regulation and response control (Fox et al., 2014; Luders et al., 2009; Tomasino, Fregona, Skrap, & Fabbro, 2013; Vestergaard-Poulsen et al., 2009). Only one MBCT study was found, therefore the interpretation of results was mainly focused on the neuronal working mechanisms of MBSR. After 8 weeks of MBSR training, participants demonstrated similar changes in the PFC, the hippocampus, insula and the cingulate cortex, associated with attention regulation, self-referential processing, and perspective taking, all stimulated in both long-term meditation and MBSR exercises. Based on the task-based studies, the insula shows increased activation, but the MBSR studies showed no consensus. The insula is associated with perception, motor control, self-awareness, interoception, and interpersonal experience (Kolb & Wishaw, 2009), and with linking behavioral outcomes to motivation (which results in learning) (Hayden & Platt, 2010). It could be that this area needs longer practice to be affected, or that these functions are too diverse to refer to the insula as a whole, or that the insula is activated regardless of valence of stimuli (positive or negative) when connecting sensory information to emotions (Cunningham, Raye, & Johnson, 2004; Maddock, Garrett, & Buonocore, 2003).

In addition to these four prior appointed regions, the amygdala seems to play a larger role in the neuronal working mechanism of MBSR, than it does in traditional meditation. The amygdala is related to the fight-or-flight reaction: it adds emotional value to sensory input (Kolb & Wishaw, 2009) and functions as a pre-conscious warning system (Craigmyle, 2013). If a threat is significant, the amygdala responds within milliseconds and activates the sympathetic nervous system (Bouret, Duvel, Onat, & Sara, 2003), prior to conscious awareness of the stimuli (Mormann et al., 2008). When the situation allows for cortical processing, the PFC can regulate the amygdala, either increasing or decreasing its activity (Ohman, 2005). MBSR seems to be associated with more efficient PFC inhibition of amygdala responses, improving emotion regulation. Different aspects of the training (reappraising emotions, affect labeling and breath focus exercises) are associated with increased prefrontal activity, hippocampal activity and less amygdala activity, suggesting a neuronal explanation that provides support for the stress-reducing effects of the training found in traditional meditation research. While in line with these results a negative association was found between amygdala volume and overall mindfulness as measured with the MAAS ($N = 145$), a positive association was found between right amygdala volume and the describing facet of the FFMQ ($N = 19$). It is possible that as in this group the other factors (observing, acting with awareness, nonjudging of, and nonreactivity to inner experiences) were not associated with amygdala differences, describing in itself may not be a very stress-reducing activity.

It may be logical that MBSR participants show more effect in the amygdala than long-term meditators, as the room for improvement may be larger. Monks or nuns are not expected to experience a lot of stressful events in their monastery, and if they do, their long experience will enable them to cope mindfully. Western participants, however, are more likely to experience stress in daily life, and their amygdala might therefore have a higher baseline activity. The down-regulation of the amygdala underlines the stress-reducing effect of MBSR with a neuronal map.

There are several limitations that should be taken into account. First, unfortunately no quantitative meta-analysis was possible in this sample of studies, due to the wide variety of outcome measures and participants. The inclusion of studies examining populations that have brain pathology (e.g., Alzheimer's and Parkinson's disease) make interpretation of findings hard enough. Second, the functions of each of the mentioned brain structures are still assumptions, and too much deducting should be discouraged as the significance of found changes is controversial. Also, correlational fMRI studies using self-reported measures should be interpreted with caution as they often overestimate the correlation, and they report means of just the subset of voxels exceeding chosen thresholds (Vul, Harris, Winkielman, & Pashler, 2009). The three correlational fMRI studies in this review did not explain their calculation method sufficiently to assess whether this is a risk, although one study reported $r = -0.88$, which might indicate overestimation (Creswell et al., 2007). Third, to ascribe these neuronal effects solely to the training is precarious: MBSR is a multifaceted group program and some positive effects may result from components not specific to meditation or mindfulness, such as social interaction within the group, or gentle stretching exercises. A fourth limitation is the design of many of the included studies: small study populations with a large inter-study heterogeneity make comparison difficult, and increase the risk of small study bias. Only three non-RCTs had a control group (Friedel et al., 2015; Goldin & Gross, 2010; Smoski et al., 2015). Longer prospective studies will be necessary to determine if MBSR and MBCT training also results in long-term changes in brain activity and structure. Finally, in this field there is a high risk of publication bias.

In summary, the findings suggest that the 8-week MBSR training evokes similar brain responses to traditional long-term meditation styles. The connectivity between prefrontal cortex, hippocampus and amygdala indicates a neuronal working mechanism of how this secular training induces emotional and behavioral changes.

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