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Review article

Functional neural correlates of mindfulness meditations in comparison with psychotherapy, pharmacotherapy and placebo effect. Is there a link?

Chiesa A, Brambilla P, Serretti A. Functional neural correlates of mindfulness meditations in comparison with psychotherapy, pharmacotherapy and placebo effect. Is there a link?

Objective: Mindfulness meditations (MM) are a group of meditation practices which are increasingly receiving attention. The aim of the present work is to review current findings about the neural correlates of MM and compare such findings with other specific and non-specific treatments.
Methods: A literature search was undertaken using MEDLINE, ISI web of knowledge, the Cochrane database and references of retrieved articles. Studies which focused on the functional neural correlates of MM, psychotherapy, pharmacotherapy and placebo published up to August 2009 were screened in order to be considered for the inclusion.
Results: Main findings suggest that long-term MM practice allows a more flexible emotional regulation by engaging frontal cortical structures to dampen automatic amygdala activation. A large overlap exists between cerebral areas activated during MM, psychotherapy, pharmacotherapy and those activated by placebo. However, while MM, psychotherapy and placebo seem to act through a top-down regulation, antidepressants seem to act through a bottom-up process.
Conclusion: MM seem to target specific brain areas related to emotions and emotional regulation. Similar mechanisms have been observed also in other interventions, particularly psychotherapy.

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Introduction

Meditation has been a spiritual and healing practice for more than 5000 years. The word 'meditation' derives from Latin 'meditari', which means 'to engage in contemplation or reflection' and can be defined as both a process and a state. According to the Yoga Sutras, meditation is the act of inward contemplation and the intermediate state between mere attention to an object and complete fusion within it (1). The practice of meditation has been related to significant improvements of health (2) and of mental abilities (3). Among the great variety of existing meditation practices, a growing attention has recently been given to a particular subgroup of meditation practices named 'Mindfulness meditations' (MM) (4).

Mindfulness is currently defined in psychological terms characterised by paying total attention to the present moment with a non-judgmental awareness of the inner and outer experience (5,6). Although the concept of Mindfulness has its origins in many contemplative and philosophical traditions such as Hinduism and Buddhism (7), its practice does not imply to follow any specific philosophical or religious tradition (8). Yet, MM can be considered a component of such ancient practices as Vipassana (9) and Zen meditation (10). In addition, clinically oriented programs designed to organise the original concept of Mindfulness into standardised courses for health, such as Mindfulness based Stress Reduction (MBSR) (11) and Mindfulness based Cognitive Therapy (MBCT) (12) can be considered examples of MM as well.

To date, MM were found to be useful for a great variety of physical and psychiatric disorders as well as for healthy people. In particular, MBSR could be useful for several physical and psychiatric disorders (13–15) as well as for healthy people (16) and MBCT could be able to prevent depression relapses and reduce residual depressive symptoms (17). In addition, Vipassana meditation could be efficacious for the reduction of alcohol and substance abuse in prisoners (18) and Zen meditation could reduce blood pressure (19). It is noteworthy, however, that the majority of current findings does not allow to distinguish specific from non-specific effects of MM (4), implying the necessity for further better designed studies.

Both Vipassana and Zen meditation from one hand and MBSR and MBCT from the other include MM as an active feature of their practice, although with several differences. In any case, the four meditations mentioned above can be grouped together in accordance with the current theoretical framework of meditation that considers such meditations as belonging to the pole of Mindfulness and distinguishes them from other types of meditation practices (2,20,21).

Thanks to the improvements of neuroimaging technologies, there has been in the last decade a wide spread of scientific investigations about the neurobiological correlates of different types of meditations, including MM, by means of different techniques such as Magnetic Resonance Imaging (MRI), functional MRI (fMRI), 18-fluorodeoxyglucose Positron Emission Tomography (PET) and 99mtechnetium hexamethylpropyleneamineoxime Single Photon Emission Computed Tomography (SPECT). Such investigations are particularly important because they provide preliminary evidence about the neurobiological modifications related to meditation practice and they answer the call for more rigorous neurobiological approaches to meditation research.

Findings about the neural correlates of a broad range of meditation practices have already been reviewed elsewhere (20,22) and are not the focus of the present review. Rather, the aim of the present work is to review available findings about the functional neural correlates of MM and compare them with the ones of other types of treatments such as antidepressants, psychotherapy and placebo.

Critical issues related to methodology in neuroimaging studies

Before reviewing neuroimaging findings, there are a number of issues that should be carefully considered in the interpretation of data. First of all, the functional neuroimaging modalities that have been used in meditation, pharmacotherapy, psychotherapy and placebo research vary substantially. They include fMRI, PET and SPECT. These imaging modalities differ with respect to mechanism, image resolution and patient-related limitations (23). Also, fMRI has traditionally been used to probe the brain activation patterns during perceptual or cognitive tasks, whereas PET and SPECT have been usually used to measure baseline brain metabolism. As a consequence, while some studies are performed in subjects during a resting state, others are performed during the execution of a specific task, hence investigating different correlates of psychopathology.

Second, these techniques provide indexes of brain activity by measuring glucose metabolism or cerebral blood flow (CBF). Note, however, that the relationship between glucose metabolism or CBF and neuronal activity remains controversial (24), although very often the term ‘brain activity’ is used interchangeably with ‘metabolic activity’ or ‘haemodynamic activity’.

A further issue that has to be taken into account into the interpretation of reviewed data is that there are many specific differences in rationale, technique and efficacy of the various modalities related to different treatments, particularly psychotherapies, in use today. Such issue is particularly important for placebo treatments as well because recent research showed that placebo effect is not a unitary phenomenon but that there are many types of placebo responses driven by different mechanisms depending on the particular context in which the placebo is given (25,26). Methodological inconsistencies created by the use of single versus multiple therapists, differing numbers of sessions, and further issues (such as, for instance, individual versus group therapy) should also be considered when comparing studies.

Finally, a wide range of patients’ populations are included. While MM and placebo studies were mainly performed in healthy subjects, studies about psychotherapy and pharmacotherapy were exclusively performed in samples of patients suffering from mood and anxiety disorders.

Methods

A literature search was undertaken using MEDLINE, ISI web of knowledge, the Cochrane database and references of retrieved articles. The search included articles indexed in the above mentioned web-based electronic bibliographic databases, published up to August 2009. The search strategy considered only studies published in English. The main search terms were the following: Mindfulness meditation, Vipassana meditation, Zen meditation, MBSR, MBCT, psychotherapy, pharmacotherapy

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and placebo in combination with functional neuroimaging, fMRI, PET and SPECT.

Studies which focused on the functional neural correlates of MM, psychotherapy, pharmacotherapy and placebo were screened by the reviewers in order to be considered for the inclusion. To be included, studies had to specify the used functional neuroimaging technique, the type of practice under examination and which kind of task was used (or its absence). Pertaining to psychotherapy and pharmacotherapy treatments, they had to be well established interventions for the specific disease under investigation. Excluded were: structural neuroimaging studies, studies not reporting details mentioned above, and reviews of the literature. No restriction was used with respect to patient population (e.g. healthy vs. non-healthy subjects), study design (e.g. uncontrolled vs. controlled study) and type of practice/technique under investigation (e.g. psychoanalysis vs. cognitive behavioural therapy (CBT)).

The findings related to psychotherapy focused on approved and well established psychotherapeutic interventions such as CBT and BT for mood and anxiety disorders (27–32), interpersonal therapy (IPT) for major depression (MD) (33) and eye movement desensitisation therapy (EMDR) for post-traumatic stress disorder (34). The focus of the present review with respect to pharmacotherapy regards well established treatments options for MD and anxiety disorders including selective serotonine reuptake inhibitors and serotonine and noradrenaline reuptake inhibitors (35,36).

Finally, the choice of including neuroimaging findings about the placebo effect was motivated by the decision to review commonalities and differences between brain areas activated by non-specific psychological mechanisms related to placebo such as expectancy of a benefit and classical conditioning which are supposed to be common to all treatments (25,37) and those activated by the so-called 'specific treatments' which are supposed to include some specific 'active ingredient' in addition to non-specific mechanisms. This issue is particularly important on account of the recent advances in our understanding of the placebo effect which shifted over the last decades from the impossibility of an inert substance to produce a clinical benefit to the meaning that the patient gives to such substance which is able to produce a measurable effect (38).

The exposure of available findings will mainly focus on three topic brain areas: the prefrontal cortex (PFC), the anterior cingulate cortex (ACC) and the amygdala. Other brain areas are well involved in all such treatments; however, we selected these three areas with the aim to suggest that all investigated treatments can affect brain activity by means of a regulation of these areas, although through different modalities.

Results

Mindfulness meditations

Functional neuroimaging studies about MM showed a consistent activation of the PFC and ACC during meditation (39–42), although with some differences across the studies (Table 1). In an early study, Baerentsen et al. (39) reported the activation of the PFC and ACC during the initiation of Zen meditation. Of note, their observations are in accordance with findings reviewed by Newberg and Iversen (81) which suggested that, during meditation, distracting external events as well as memories represent conflicting events to task goals and that such brain areas, particularly the ACC, may contribute to the maintenance of attention by alerting those systems directly implementing top-down regulation to resolve this conflict (82).

In a following study performed on Vipassana meditators during a period of mindful attention to their breath (40), the authors observed an increased activation of bilateral ACC, in particular, its rostral portion, and of dorsal medial PFC [medial PFC (mPFC)]. The rostral/ventral division of the ACC and the mPFC are activated in emotional processing (83,84) and it could be hypothesised that MM training leads to more cortical processing of emotional conflicts and processes during meditation, possibly reflecting an improved ability for emotional regulation. Interestingly, such explanation is consistent with the observation that subjects with higher dispositional mindfulness show an increased activation of the mPFC during the execution of an affective but not of a cognitive task (85).

The relationship existing between these findings can be better understood if one considers that mindfulness may be conceived as a trait like quality that varies among different individuals (86,87) and that MM practice has been found to increase mindfulness levels (88–91). As a consequence, it could be argued that both subjects with higher dispositional mindfulness levels and those who increased their mindfulness levels through the practice of a MM may more easily engage the mPFC and the ACC during tasks that require emotional regulation.

At the opposite of the previous findings, however, Farb et al. (41) observed a decrease rather than an increase of the activity of the mPFC during meditation. More in detail, the authors observed an increased activation of the mPFC as well as of left language areas during a narrative focus in which subjects had to figure out what some words meant to them, and a decrease of the same areas during

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Table 1. Functional neuroimaging studies

Study	Type and duration of practice	Subjects	Imaging	Main final assessment decreases	Main final assessment increases
			Mindfulness meditations		
Baerentsen et al., 2001 (39)	Zen meditation, 7–23 years of practice	5 healthy long-term meditators	fMRI, onset of meditation	Visual cortex, PCC	PFC, ACC, hyppocampus
Holzel et al., 2007 (40)	Vipassana meditation, 7.9 ± 5.1 years of practice	15 healthy long-term meditators 15 healthy controls	fMRI, meditation and arhitmetic condition	None	Meditation: dorsal mPFC, ACC
Farb et al., 2007 (41)	Mindfulness based stress reduction, 8 weeks	20 healthy novice meditators 16 healthy controls	fMRI, narrative focus (NF) vs. experiential focus (EF)	EF (non-meditators): vmPFC, PCC EF (meditators): mPFC, L dorsolateral amygdala	NF (both groups): R superior frontal gyrus, R precentral gyrus, mPFC, L hippocampus, L caudate EF (non-meditators): L vlPFC, L dlPFC EF (non-meditators): R dlPFC, R ilPFC, R insula, secondary somatosensory cortex
Kozasa et al., 2008 (42)	Zen meditation, at least 6 months	5 healthy meditators after a Zen retreat	fMRI, Stroop effect		R dlPFC, ACC, insula, parietal cortex
Pagnoni et al., 2009 (43)	Zen meditation, at least 3 years	12 healthy long-term meditators 12 healthy controls	fMRI, mindfulness of breathing while distracting by words	L language areas(angular gyrus and superior frontal gyrus) activated for less time after words distraction	
			Psychotherapy and pharmacotherapy		
Brody et al., 1999 (44)	Drug, 8 weeks	16 MD patients treated with paroxetine	PET, resting state	OFC	Ventral PFC
Mayberg et al., 2000 (45)	Drug, 1 and 6 weeks	15 MD patients, 10 treated with fluoxetine, 5 with placebo	PET, resting state	PCC and hippocampus (1st week), subgenual ACC and putamen (6th week), vlPFC, insula, thalamus at both times	dlPFC and hippocampus (6th week), R inferior parietal at both times
Kennedy et al., 2001 (46)	Drug, 6 weeks	13 MD patients 24 healthy subjects	PET, resting state	Dorsal ACC, dorsal PCC, L insula, L hippocampus	L mPFC, vlPFC, dlPFC
Brody et al., 2001a (47)	Psychotherapy and drug, 6 weeks	24 MD patients, 14 treated with IPT, 10 with paroxetine	PET, resting state	IPT: L ventral ACC, Venlafaxine: L middle ACC Both: PFC	Both: insula, L inferior temporal
Brodi et al., 2001b (48)	Psychotherapy and drug, 6 weeks	39 MD patients, 14 treated with IPT, 25 with paroxetine	PET, resting state	In both cases symptoms improvements correlated with reduced metabolism in frontal lobes	
Davidson et al., 2003 (49)	Drug, 2 and 8 weeks	12 MD patients treated with venlafaxine five healthy controls	fMRI, reactivity to positive and negative stimuli		L insula (2nd week), L ACC (8th week)
Fu et al., 2004 (50)	Drug, 8 weeks	19 MD patients treated with fluoxetine 19 healthy subjects	fMRI, vision of sad faces	Pregenual ACC, ventral striatum, cerebellum, L amygdala	
Goldapple et al., 2004 (51)	Psychotherapy and drug, 15–20 sessions	28 MD patients, 15 treated with CBT, 13 with paroxetine	PET, resting state	CBT: PFC, hippocampus Paroxetine: R hippocampus	CBT: dorsal ACC Paroxetine: dlPFC
Anand et al., 2005 (52)	Drug, 6 week	12 MD patients 11 healthy	fMRI, resting state and vision of sad faces		Increased cortico-limbic connectivity meditated by ACC related to improvement
Chen et al., 2007 (53)	Drug, 8 weeks	17 MD patients treated with fluoxetine	fMRI, vision of sad faces		Higher ACC activation at baseline predicted response

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Table 1. Continued

Study	Type and duration of practice	Subjects	Imaging	Main final assessment decreases	Main final assessment increases
Kennedy et al., 2007 (54)	Psychotherapy and drug, 16 weeks	24 MD patients, 12 treated with CBT, 12 with venlafaxine	PET, resting state	CBT: vmPFC, vlPFC Venlafaxine: R posterior subgenual ACC Both: ofc, R thalamus	CBT: subgenual ACC
Fu et al., 2008 (55)	Psychotherapy, 16 weeks	16 MD patients 16 healthy subjects	fMRI, affect recognition task	Amygdala, hippocampus	Dorsal ACC Higher amygdala and hippocampus activity at baseline predicted response
Fumark et al., 2002 (56)	Psychotherapy and drug, 8 weeks	18 patients with social phobia, 6 treated with CBT, 6 with citalopram and 6 in a waiting list	PET, speech with an observing audience	CBT: peri-acqueductal grey Citalopram: thalamus Both active treatments: Amygdala, parahippocampus gyrus	
Paquette et al., 2003 (57)	Psychotherapy, four sessions	12 patients with spider phobia treated with CBT 13 healthy subjects	fMRI, viewing spiders	R dlPFC, para-hippocampal gyrus	R inferior frontal gyrus
Starube et al., 2006 (58)	Psychotherapy, two sessions	28 subjects with spider phobia, 14 treated with CBT, 14 in a waiting list 14 healthy subjects	fMRI, symptoms provocation	ACC, insula, thalamus	
Goosens et al., 2007 (59)	Psychotherapy, 2 weeks	20 subjects with spider phobia treated with exposure therapy 14 healthy subjects	fMRI, symptoms provocation	ACC, amygdala, insula	
Scheinle et al., 2007 (60)	Psychotherapy, one session	26 subjects with spider phobia treated with exposure therapy 25 healthy subjects	fMRI, symptoms provocation	dlPFC, amygdala	Medial ofc, insula
Prasko et al., 2004 (61)	Psychotherapy and drug, 3 months	12 PD patients, 6 treated with CBT, 6 with antidepressants	PET, none	*Both*: R frontal cortex, R temporal	*Both treatments:* L frontal cortex, L temporal
Lindauer et al., 2005 (62)	Psychotherapy, 4 months	20 patients with PTSD, 10 treated with brief ecleptic therapy, 10 in a waiting list 15 traumatised subjects without PTSD	SPECT, audiotaped scripts on trauma	R Middle frontal gyrus	L superior temporal gyrus
Lansing et al., 2005 (63)	Psychotherapy, mean number of sessions 3.83	Six PTSD patients treated with EMDR	SPECT, none	L inferior parietal, occipital	R inferior frontal gyrus, R precentral gyrus
Pagani et al., 2007 (64)	Psychotherapy, 8 sessions	15 PTSD patients treated with EMDR 27 traumatised subjects without PTSD	SPECT, recall of traumatic experiences		ofc
Felmingham et al., 2007 (65)	Psychotherapy, unspecified	Eight PTSD patients treated with exposure therapy	fMRI, recognition of faces	Amygdala	R inferior frontal gyrus, rostral ACC, hippocampus
			Placebo		
Petrovic et al., 2002 (66)	Placebo	Nine healthy subjects	PET, thermal stimulation		ofc, ACC (correlated to higher concentration of opioids in PAG and pons), PAG, pons
Wager et al., 2004 (67)	Placebo	24 healthy subjects	fMRI, anticipation of shock stimulation	R ACC, insula (during stimulation, not during anticipation)	dlPFC, ofc, R ACC, PAG
Petrovic et al., 2005 (68)	Placebo, 2 days after conditioning with a benzodiazepine	15 healthy subjects	fMRI, unpleasant pictures	Inferior occipital gyrus, amygdala	vlPFC, dlPFC, ofc, rostral ACC,
Zubieta et al., 2005, 2006 (69,70)	Placebo	19 healthy subjects	PET, sustained muscle stimulation		dlPFC, pregenual ACC, R anterior insula,
Pariente et al., 2005 (71)	Placebo	14 patients with osteoarthritis treated with placebo or real acupuncture	PET, during placebo acupuncture		dlPFC, rostral ACC, insula,

Table 1. Continued

Study	Type and duration of practice	Subjects	Imaging	Main final assessment decreases	Main final assessment increases
Kong et al., 2006 (72)	Placebo	16 healthy subjects	fMRI, thermal stimulation		dlPFC, rostral ACC, R anterior insula
Bingle et al., 2006 (73)	Placebo	19 healthy subjects	Laser stimulation		Rostral ACC, amygdala, PAG, pons,
Nemoto et al., 2006 (74)	Placebo, 21st day	10 healthy	PET, laser stimulation	L inferior parietal	mPFC, R inferior parietal, posterior parietal cortex
Wager et al., 2007 (75)	Placebo	15 healthy	PET, anticipation of thermal stimulation	PFC, pregenual and subgenual ACC, L amygdala, insula, dorsal PAG	OFC, pregenual ACC, midventral PAG, thalamus (all during pain but not during anticipation)
Lieberman et al., 2004 (76)	Placebo, 21st day	52 IBS patients	PET, intestinal stimulation	Dorsal ACC	R vlPFC
Price et al., 2007 (77)	Placebo	Nine IBS patients	fMRI, intestinal stimulation	Dorsal ACC, L posterior insula, L thalamus, primary and secondary somatosensory cortex	
Craggs et al., 2008 (78)	Placebo	Nine IBS patients	fMRI, intestinal stimulation		dlPFC, dorsal ACC
Mayberg et al., 2002 (79)	Placebo, 1st and 6th weeks	15 MD patients, half of them treated with fluoxetine	PET, resting condition	Both treatments: Subgenual ACC, thalamus, hypothalamus, parietal cortex, parahippocampus	Both treatments: dlPFC, ACC, PCC, posterior insula Only fluoxetine: anterior insula, hippocampus, brainstem
Fumark et al., 2008 (80)	Placebo	25 patients with social phobia	fMRI, public speaking	Amygdala, especially L	

L and R before other words mean left and right, respectively. dlPFC, dorsolateral prefrontal cortex; EF, experiential (mindfulness) focus; IBS, irritable bowel syndrome; mPFC, medial prefrontal cortex; NF, narrative focus; ofc, orbitofrontal prefrontal cortex; PAG, peri-acqueductal grey; PCC, posterior cingulate cortex; PD, panic disorder; PTSD, post-traumatic stress disorder; vlPFC, ventrolateral prefrontal cortex; vmPFC, ventromedial prefrontal cortex.

mindful attention to present thoughts and stimuli. It is worthwhile, however, that significant differences between these two trials (40,41) including expert versus novice meditators, Vipassana versus MBSR meditators as well as the different focus during meditation (the breath vs. mindfulness of thoughts and experiences while observing words) could explain why different findings have been observed.

Despite this finding, significant activations in the PFC were observed both in meditators and in non-meditators during the experiential (mindfulness) focus, even though with specific differences between the two groups (41). During the experiential focus non-meditators showed left dorsolateral PFC (dlPFC) activation, whereas meditators showed an activation of the right dlPFC and inferolateral PFC (ilPFC). Consistent with a dual-mode hypothesis of self-awareness, these results suggested a fundamental neural dissociation in modes of self-representation that support distinct, but usually integrated, aspects of self-reference: the higher order self-reference characterised by neural processes supporting awareness of a self that extends across time (related to left lPFC) and more basic momentary self-reference characterised by neural changes supporting awareness of the psychological present (related to right lPFC) (41). Interestingly, many authors suggested that the latter could represent a return to the neural origins of identity, in which self-awareness in every moment arises from the integration of basic interoceptive and exteroceptive bodily sensory processes (92–94).

Further, the activation of the right dlPFC, along with other areas, has also been implicated in the switching between first and third person perspectives (95) and was associated to a more detached observation state of events characterised by lower emotional reactivity related to reduced amygdala activation (96,97). Consonant with such findings, decreased activity in the left amygdala was observed in meditators during mindfulness focus in the study performed by Farb et al. (41). Note also that a similar pattern of activation of the right dlPFC was observed by Kazosa et al. in a independent sample of Zen meditators as well (42).

A further important finding was reported by Pagnoni et al. (43) about the neural correlates of conceptual processing during Zen meditation. In such study the authors observed that, in comparison to a control group, Zen meditators displayed a reduced duration of the neural response linked to conceptual processing in regions of the default network (98) such as the angular gyrus and the superior frontal gyrus, suggesting that meditative training could foster the ability to control the automatic cascade of semantic associations triggered by a stimulus and, by extension, to voluntarily regulate

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the flow of spontaneous mentation. This result is particularly important if one considers that Farb et al. (41) reported that non-meditators showed a significant activation of left language areas in the PFC, even when they tried to focus their attention on present experience, suggesting the impossibility to dampen their spontaneous mentation. On the other hand, such reduction could be particularly useful for many psychiatric conditions characterised by excessive ruminations (99) such as obsessive compulsive disorder (100), anxiety disorders (101), alcohol dependence (102) and MD (103,104). Interestingly, several findings suggested that MM could be useful for all such disorders (4,17,105–109).

Overall, these findings suggest that, consistently with historical accounts of MM which underscore that mindfulness training allows individuals to treat affective states as 'objects' of attention (110,111), MM practice could be related to a more flexible emotional regulation and to a higher ability to detach from negative states by engaging frontal cortical structures to dampen automatic amygdala activation.

The comparison with other specific and placebo treatments

Current evidence suggests that both anxiety and depressive states could be considered as the result of increased and unmodulated amygdala activity (104,112–115), of a deficit of inhibitory connections to the amygdala meditated by cortical regions such as the orbitofrontal PFC (OFC), mPFC, dlPFC and ACC (96,116–118) or of both (115,119,120). Consistent with this model of mood and anxiety disorders, several studies found that both psychotherapy and pharmacotherapy were able to reverse baseline patterns of activation into two distinct ways. They were found to induce either higher activity of prefrontal areas such as the inferior frontal gyrus (57,63), the medial OFC (60,64), the ventral PFC (44,46), the dlPFC (45,46,51) and the ACC (51,55,65), or lower activation of the amygdala(55,56,60,65) (Table 1). The majority of these studies used a fMRI technique and probed the brain activation patterns during perceptual or cognitive/affective tasks, hence allowing a higher comparability to studies performed on mindfulness meditators. Of note, one can observe that a large overlaps exists between findings in MM studies and those reported in pharmacotherapy and psychotherapy studies.

On the other hand, different and often contrasting results were observed in studies focusing on a resting state in depressed patients and to a lesser extent in other populations of patients. In particular, apart from some studies where an increased activation in some areas of the PFC was observed at rest following a successful treatment with antidepressants (44–46,51), the majority of studies, especially those focusing on psychotherapy, observed decreases in many areas of the PFC including the vlPFC, vmPFC and dlPFC, and of the ACC (44–47,50,51,54,57–60,62). The apparent contrast between these findings and those suggesting that psychotherapy could allow greater frontal activation during emotional tasks could be resolved if one considers that recovery could involve the lowering of tonic resting-state activity, to allow for greater reactivity when executive control is recruited. However this hypothesis has not been verified yet by rigorous neuroimaging studies comparing brain activity at rest and during the execution of a specific task within the context of a single experimental design.

In addition, there is preliminary evidence suggesting that, while psychotherapy could allow a resetting of tonic prefrontal activity and yield greater ability for 'top-down' emotional regulation when it is needed (e.g. when phobic patients are exposed to phobic stimuli), drugs could increase ACC metabolism tonically (48,51). This, in turn, could create a 'bottom-up' effect whereby limbic regions are tonically inhibited during antidepressants administration.

On the basis of reviewed findings, we could preliminary suggest that MM could be more similar to psychotherapy, i.e. they could regulate frontal brain areas to dampen amygdala hyperreactivity specifically when it is necessary, whereas drugs could target amygdala directly. Then, all such treatments could result in a final common state characterised by lower amygdala and prefrontal activity at rest with the latter being able to reverse after MM or psychotherapy when it is required (Fig. 1). Nevertheless, such hypothesis should be verified by neuroimaging studies comparing MM to other interventions for specific disorders and assessing both resting and task related activation at different time points.

Pertaining to the placebo effect, it is noteworthy that almost all studies, independently from the underlying condition, showed a consistent activation of the dlPFC (67–72,78,79), the OFC (66–68,75) and the rostral/ventral ACC (66–73,75,79) during the placebo effect and the anticipation of a negative stimulus. Given that placebo does not exert a therapeutic effect by itself, it could be argued that the expectation of a benefit is able to activate such areas when needed. Furthermore, the notion that similar findings were observed across a great variety of conditions including pain, vision of unpleasant pictures, MD and social phobia suggests that modulatory processes in placebo are not specific for any single condition but are rather a part

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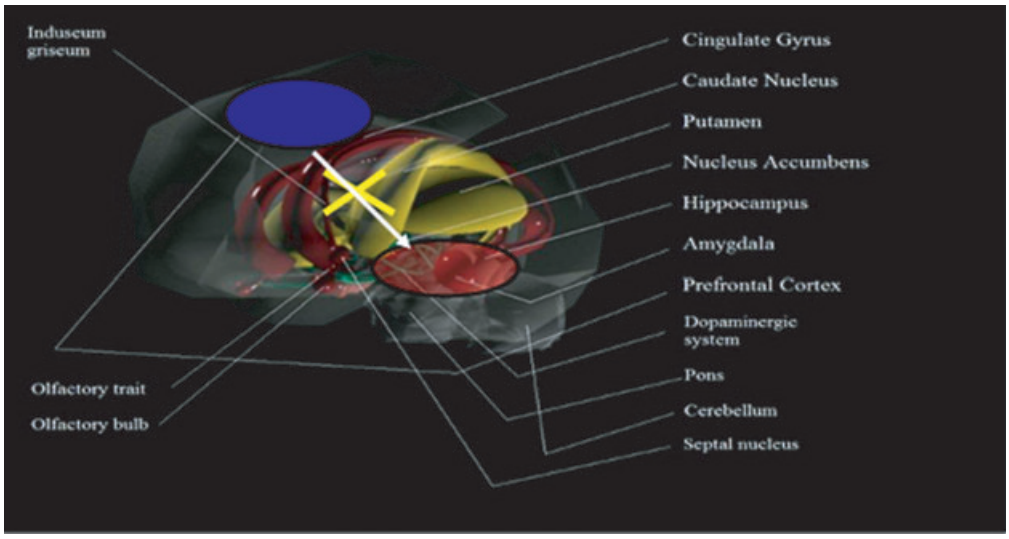
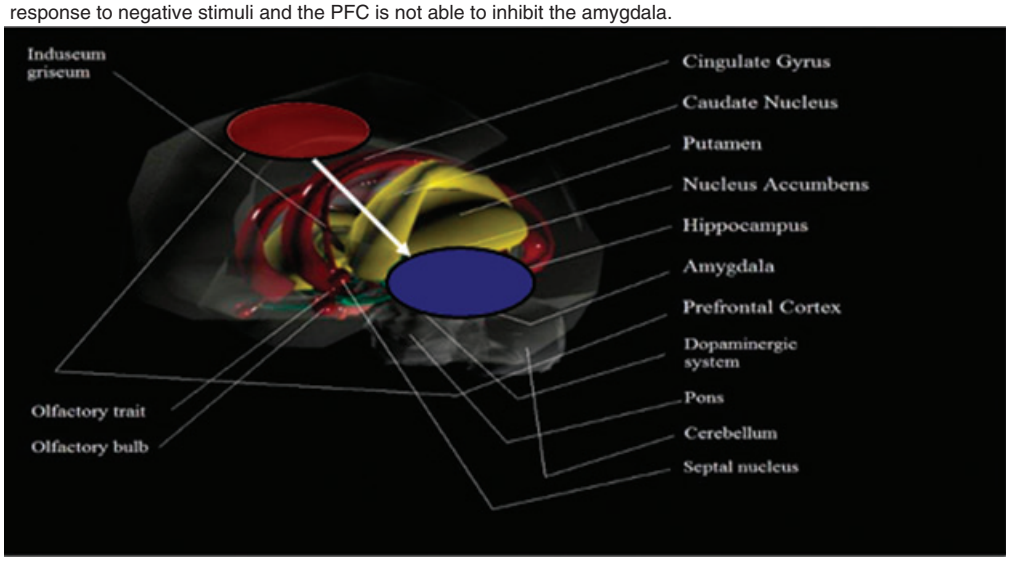
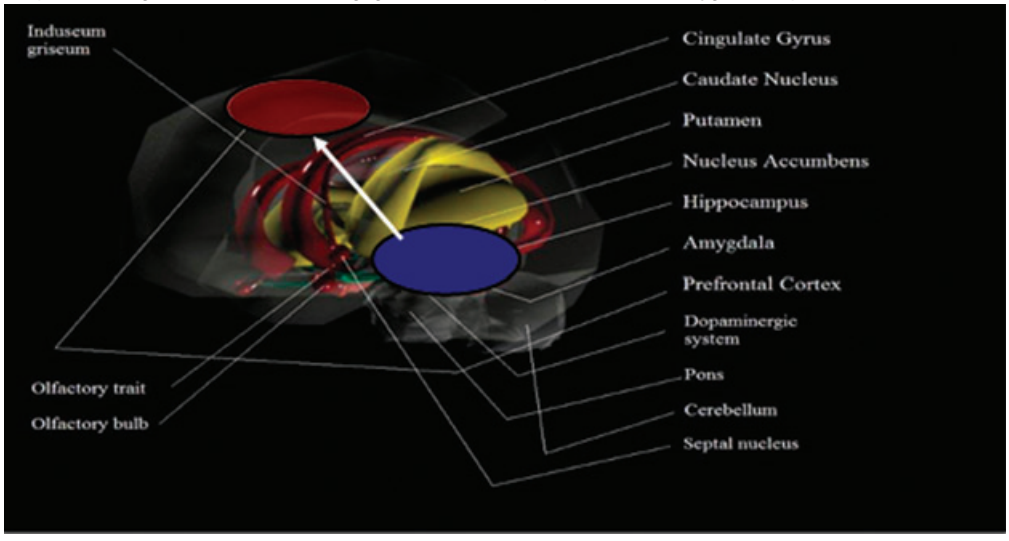


Before meditation or other treatments, high emotional reactivity is observed. The amygdala easily activates in response to negative stimuli and the PFC is not able to inhibit the amygdala.



After meditation or psychotherapy, amigdala activity is usually reduced and whether amygdala activates in response to negative stimuli, PFC is engaged in order to dampen automatic amygdala responses.



After pharmacotherapy, amigdala activityistonically inhibitedand the PFC′s activity is restored.

Fig. 1. Red/clear=hypometabolic area; blue/dark=hypermetabolic area; PFC=prefontal cortex.

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of the mechanisms involved in the regulation of emotional processes in general (26). Consistent with this hypothesis is also the observation that amygdala reactivity can be dampened during the anticipation of a noxious stimulus and in phobic patients after the administration of a placebo (75,80).

Overall, these findings suggest that placebo responses seem mediated by 'top-down' processes dependent on frontal cortical areas that generate and maintain cognitive expectancies, hence suggesting a stronger similarity with MM and psychotherapy rather than with antidepressants. Nevertheless, we should remember that placebo is a phenomenon common to all treatments (25). As a consequence, it is difficult to distinguish the neural correlates of the specific effects of active treatments from the non-specific placebo-like effects (such as the expectancy of a benefit) common to all treatments. This difficulty is particularly evident in the study performed by Mayberg et al. in MD patients where an almost complete overlap between areas activated during the administration of placebo and of fluoxetine was observed (79).

However, while studies performed in meditators and in subjects who underwent a pharmacological or a psychotherapeutic intervention were referred to long-term meditators or to a long-term treatment, respectively (for instance, a 2-months antidepressant treatment), placebo studies often referred to a short period of time (e.g. minutes). As a consequence, while it could be argued that the former observations could be relatively enduring, there is not sufficient evidence to understand to what extent placebo treatments could result in long lasting brain activation patterns.

Discussion

The observations reviewed in the present work suggest that a great overlap could exist between cerebral areas activated during MM, psychotherapy, pharmacotherapy and those activated during the placebo effect, although with some differences. It could be preliminary suggested that while MM, psychotherapy and placebo act through a top-down regulation, antidepressants could act through a bottom-up process. In particular, MM, psychotherapy and placebo could target the PFC which in turn could exert an inhibitory effect on limbic regions such as the amygdala when it is needed (96,121,122), possibly through inhibitory connections from the OFC and ventromedial regions (including the rostral and subgenual cingulate gyri) to the amygdala (123,124). On the other hand antidepressants could target amygdala directly modulating specific emotional information processing mediated by the amygdala such as repetitive negative thinking in depressed patients (28). Note also that structural neuroimaging studies in long-term Vipassana and Zen meditators showed that MM practice could be related to enduring macroscopic modifications of brain areas including the PFC (125), the anterior insula (125,126) and the putamen (127). Further, there is a partial overlap between thicker brain areas in long-term meditators and brain areas activated in functional neuroimaging studies (41–43) and it could be argued that the repeated activation of specific brain areas could lead to long-term macroscopic brain modifications. Notably, such explanation is consistent with observations that when a task that requires attention is consistently directed towards a behaviourally relevant sensory stimulus, robust changes in sensory cortical maps are observed (128–130) and that the entity of changes in specific brain areas seems to be related to meditation experience (125).

Despite the preliminary nature of these findings, it is noteworthy that they could have an important clinical impact. First of all, they preliminary support a neurobiological basis for the usefulness of MM in several clinical conditions that are only partial responsive to current treatments options such as anxiety and mood disorders. Even though no specific neuroimaging study on MM has yet been performed in clinical samples, it is noteworthy that several clinical trials about MM have already provided preliminary evidence about their efficacy on all such conditions (13,17,131).

In addition, our findings underscore that the mechanisms underlying MM could share some similarities with other treatments, in particular psychotherapy, in that they engage frontal cortical structures to dampen exaggerated limbic responses to negative stimuli when it is needed, although specific neuroimaging studies of MM addressing such issue in psychiatric populations of patients are still lacking. Finally, our findings point out to the necessity of a more deep investigation of the comparison between the neurobiological modifications induced by specific treatments and those induced by non-specific treatments or placebos. Such investigation could allow to more deeply dissect the overlapping specific and non-specific effects of the so-called 'specific treatments' in general and could be helpful, along with clinical trials designed to compare MM to active non-specific treatments such as educational support groups, in distinguishing specific from non-specific effects of MM in particular.

Other limitations have to be considered in the interpretation of our findings. First of all, the fact that studies about MM have been performed in healthy subjects could raise concerns about their applicability to psychiatric populations of patients. However,

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as reported above, preliminary data suggest that MM could be useful for disorders such as MD and anxiety disorders, and neuroimaging data on these populations of patients are warranted. Second, a great number of interventions and of active drugs with different rationales and mechanisms of actions were included. However, on account of the preliminary nature of the present review, this could represent a strength rather than a limitation in that we tried to compare MM to a large number of treatments in order to open new directions for future comparative research.

Also, we mainly focused on three brain areas while it is known that further cerebral areas are involved in the response to meditation, psychotherapy, pharmacotherapy and placebo (20,26,132). Nonetheless, the aim of the present work was only to suggest a possible model of the mechanisms through which MM could be effective and to review possible similarities of our model with other treatment options. As a consequence we also excluded those interventions or conditions which main targets were not the PFC, the ACC or the amygdala such as Parkinson's disease and schizophrenia (26,133). Further, while we generally referred to MM as a unitary group of meditative practices, it is worthwhile that specific differences exist across different MM (134). As a consequence, while available studies mainly focused on long-term Vipassana and Zen meditators, further research is needed to investigate the neural correlates of MBSR and MBCT practice.

A final concern could derive from the decision to use neuroimaging findings to explain the correlates of normal physiology or psychopathology of the individual. Note, however, that neuroimaging studies could suggest possible brain areas where future studies could assess potential changes in neurotransmitter metabolites to determine which system is likely to be involved. Concurrently, molecular imaging will be needed to determine where exactly these changes take place and further research should aim at integrating functional imaging with molecular techniques such as radioligand imaging or biochemical analysis of metabolites in order to elucidate the molecular mechanisms of MM and its commonalities and differences with psychotherapy, pharmacotherapy and placebo.

In conclusion, our findings suggest that MM practice could allow a more flexible emotional regulation and a higher ability to detach from negative states by engaging frontal cortical structures to dampen automatic amygdala activation. Also, a great overlap could exists between cerebral areas activated during MM, psychotherapy, pharmacotherapy and those activated by expectancy in placebo studies. However, it could be preliminary suggested that while MM, psychotherapy and placebo act through a top-down regulation, antidepressants could act through a bottom-up process. Accordingly, further research is needed to replicate findings observed in healthy subjects in clinical populations of patients, to compare MM with other specific and non-specific treatments and to better investigate the neurochemical correlates of MM.

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References

1. Taylor E. Introduction. In: Murphy M, Donovan S, Sausalito CA, eds. The physical and physiological effects of meditation. Institute of Noetic Science, 1999.
2. Ospina MB, Bond K, Karkhaneh M et al. Meditation practices for health: state of the research. Evid Rep Technol Assess (Full Rep) 2007; 1–263.
3. Barinaga M. Buddhism and neuroscience. Studying the well-trained mind. Science 2003;**302**:44–46.
4. Chiesa A, Serretti A. A systematic review of neurobiological and clinical features of mindfulness meditations. Psychol Med 2009:1–14.
5. Kabat-Zinn J. Wherever you go, there you are: mindfulness meditation in everyday life. New York: Hyperion, 1994.
6. Marlatt GA, Kristeller JL. Integrating spirituality into treatment: resources for practitioners. In: Miller WR, ed. Mindfulness and meditation. Washington: American Psychological Association, 1999.
7. Buddhaghosa B. Vissuddhimagga (The Path of Purification). Seattle: Shambala, 1976.
8. Kabat-Zinn J. Indra's net at work: the mainstreaming of Dharma practice in society. York Beach, ME: Samuel Weiser, 2000.
9. Ahir DC. Vipassana: a universal Buddhist meditation technique. New Delhi: Sri Satguru Publications, 1999.
10. Mizuno K. Essentials of Buddhism. Tokyo: Kosei Publishing Company, 1972.
11. Kabat-Zinn J. Full catastrophe living: using the wisdom of your body and mind to face stress, pain and illness. New York: Dell Publishing, 1990.
12. Segal ZJ, Williams MG, Teasdale JD. Mindfulness based cognitive therapy for depression: a new approach to preventing relapses. New York: Guildford Press, 2002.
13. Bishop SR. What do we really know about mindfulness-based stress reduction? Psychosom Med 2002;**64**:71–83.
14. Proulx K. Integrating mindfulness-based stress reduction. Holist Nurs Pract 2003;**17**:201–208.
15. Allen NB, Chambers R, Knight W. Mindfulness-based psychotherapies: a review of conceptual foundations, empirical evidence and practical considerations. Aust N Z J Psychiatry 2006;**40**:285–294.
16. Chiesa A, Serretti A. Mindfulness-based stress reduction for stress management in healthy people: a review and meta-analysis. J Altern Complement Med 2009;**15**: 593–600.

17. Coelho HF, Canter PH, Ernst E. Mindfulness-based cognitive therapy: evaluating current evidence and informing future research. J Consult Clin Psychol 2007;**75**: 1000–1005.
18. Chiesa A. Vipassana meditation: systematic review of current evidence. J Altern Complement Med 2010;**16**:37–46.
19. Chiesa A. Zen meditation: an integration of current evidence. J Altern Complement Med 2009;**15**:585–592.
20. Cahn BR, Polich J. Meditation states and traits: EEG, ERP, and neuroimaging studies. Psychol Bull 2006;**132**: 180–211.
21. Goleman D. The meditative mind: the varieties of meditative experience. New York: Perigee Books ed., 1988.
22. Rubia K. The neurobiology of Meditation and its clinical effectiveness in psychiatric disorders. Biol Psychol 2009;**1**:1–11.
23. Dougherty DD, Rauch SL, Rosenbaum JF. Essentials of neuroimaging for clinical practice. Washington: American Psychiatric Association, 2004.
24. Giove F, Mangia S, Bianciardi M et al. The physiology and metabolism of neuronal activation: in vivo studies by NMR and other methods. Magn Reson Imaging 2003;**21**:1283–1293.
25. Price DD, Finniss DG, Benedetti F. A Comprehensive Review of the placebo effect: recent advances and current thought. Annu Rev Psychol 2008;**59**:565–590.
26. Faria V, Fredrikson M, Furmark T. Imaging the placebo response: a neurofunctional review. Eur Neuropsychopharmacol 2008;**18**:473–485.
27. Rupke SJ, Blecke D, Renfrow M. Cognitive therapy for depression. Am Fam Physician 2006;**73**:83–86.
28. Derubeis RJ, Siegle GJ, Hollon SD. Cognitive therapy versus medication for depression: treatment outcomes and neural mechanisms. Nat Rev Neurosci 2008;**9**:788–796.
29. Otto MW, Deveney C. Cognitive-behavioral therapy and the treatment of panic disorder: efficacy and strategies. J Clin Psychiatry 2005;**66**(Suppl. 4):28–32.
30. Rowa K, Antony MM. Psychological treatments for social phobia. Can J Psychiatry 2005;**50**:308–316.
31. Jonsson H, Hougaard E. Group cognitive behavioural therapy for obsessive-compulsive disorder: a systematic review and meta-analysis. Acta Psychiatr Scand 2009;**119**:98–106.
32. Choy Y, Fyer AJ, Lipsitz JD. Treatment of specific phobia in adults. Clin Psychol Rev 2007;**27**:266–286.
33. De Mello MF, De Jesus Mari J, Bacaltchuk J, Verdeli H, Neugebauer R. A systematic review of research findings on the efficacy of interpersonal therapy for depressive disorders. Eur Arch Psychiatry Clin Neurosci 2005;**255**:75–82.
34. Shepherd J, Stein K, Milne R. Eye movement desensitization and reprocessing in the treatment of post-traumatic stress disorder: a review of an emerging therapy. Psychol Med 2000;**30**:863–871.
35. Cipriani A, Furukawa TA, Salanti G et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. Lancet 2009;**373**:746–758.
36. Zohar J, Westenberg HG. Anxiety disorders: a review of tricyclic antidepressants and selective serotonin reuptake inhibitors. Acta Psychiatr Scand Suppl 2000;**403**: 39–49.
37. Benedetti F. Mechanisms of placebo and placebo-related effects across diseases and treatments. Annu Rev Pharmacol Toxicol 2008;**48**:33–60.
38. Pollo A, Benedetti F. Placebo response: relevance to the rheumatic diseases. Rheum Dis Clin North Am 2008;**34**:331–349.
39. Baerentsen KB, Hartvig NV, Stodkilde-Jorgensen H, Mammen J. Onset of meditation explored with fMRI. Neuroimage 2001;**13**:297.
40. Holzel BK, Ott U, Hempel H et al. Differential engagement of anterior cingulate and adjacent medial frontal cortex in adept meditators and non-meditators. Neurosci Lett 2007;**421**:16–21.
41. Farb NAS, Segal ZV, Mayberg HS et al. Attending to the present: mindfulness meditation reveals distinct neural modes of self reference. Soc Cogn Affect Neurosci 2007;**2**:313–322.
42. Kozasa EH, Radvany J, Barreiros MA, Leite JR, Amaro E. Preliminary functional magnetic resonance imaging Stroop task results before and after a Zen meditation retreat. Psychiatry Clin Neurosci 2008;**62**:366.
43. Pagnoni G, Cekic M, Guo Y. "Thinking about Not-Thinking": neural correlates of conceptual processing during zen meditation. PLoS Med 2008;**3**:e383–e392.
44. Brody AL, Saxena S, Silverman DH et al. Brain metabolic changes in major depressive disorder from pre- to post-treatment with paroxetine. Psychiatry Res 1999;**91**: 127–139.
45. Mayberg HS, Brannan SK, Tekell JL et al. Regional metabolic effects of fluoxetine in major depression: serial changes and relationship to clinical response. Biol Psychiatry 2000;**48**:830–843.
46. Kennedy SH, Evans KR, Kruger S et al. Changes in regional brain glucose metabolism measured with positron emission tomography after paroxetine treatment of major depression. Am J Psychiatry 2001;**158**:899–905.
47. Brody AL, Saxena S, Stoessel P et al. Regional brain metabolic changes in patients with major depression treated with either paroxetine or interpersonal therapy: preliminary findings. Arch Gen Psychiatry 2001a;**58**:631–640.
48. Brody AL, Saxena S, Mandelkern MA, Fairbanks LA, Ho ML, Baxter LR. Brain metabolic changes associated with symptom factor improvement in major depressive disorder. Biol Psychiatry 2001b;**50**:171–178.
49. Davidson RJ, Irwin W, Anderle MJ, Kalin NH. The neural substrates of affective processing in depressed patients treated with venlafaxine. Am J Psychiatry 2003; **160**:64–75.
50. Fu CH, Williams SC, Cleare AJ et al. Attenuation of the neural response to sad faces in major depression by antidepressant treatment: a prospective, event-related functional magnetic resonance imaging study. Arch Gen Psychiatry 2004;**61**:877–889.
51. Goldapple K, Segal Z, Garson C et al. Modulation of cortical-limbic pathways in major depression: treatment-specific effects of cognitive behavior therapy. Arch Gen Psychiatry 2004;**61**:34–41.
52. Anand A, Li Y, Wang Y et al. Antidepressant effect on connectivity of the mood-regulating circuit: an FMRI study. Neuropsychopharmacology 2005;**30**:1334–1344.
53. Chen CH, Ridler K, Suckling J et al. Brain imaging correlates of depressive symptom severity and predictors of symptom improvement after antidepressant treatment. Biol Psychiatry 2007;**62**:407–414.

54. Kennedy SH, Konarski JZ, Segal ZV et al. Differences in brain glucose metabolism between responders to CBT and venlafaxine in a 16-week randomized controlled trial. Am J Psychiatry 2007;**164**:778–788.
55. Fu CH, Williams SC, Cleare AJ et al. Neural responses to sad facial expressions in major depression following cognitive behavioral therapy. Biol Psychiatry 2008;**64**: 505–512.
56. Furmark T, Tillfors M, Marteinsdottir I et al. Common changes in cerebral blood flow in patients with social phobia treated with citalopram or cognitive-behavioral therapy. Arch Gen Psychiatry 2002;**59**:425–433.
57. Paquette V, Levesque J, Mensour B et al. "Change the mind and you change the brain": effects of cognitive-behavioral therapy on the neural correlates of spider phobia. Neuroimage 2003;**18**:401–409.
58. Straube T, Glauer M, Dilger S, Mentzel HJ, Miltner WH. Effects of cognitive-behavioral therapy on brain activation in specific phobia. Neuroimage 2006;**29**: 125–135.
59. Goossens L, Sunaert S, Peeters R, Griez EJ, Schruers KR. Amygdala hyperfunction in phobic fear normalizes after exposure. Biol Psychiatry 2007;**62**:1119–1125.
60. Schienle A, Schafer A, Hermann A, Rohrmann S, Vaitl D. Symptom provocation and reduction in patients suffering from spider phobia: an fMRI study on exposure therapy. Eur Arch Psychiatry Clin Neurosci 2007;**257**: 486–493.
61. Prasko J, Horacek J, Zalesky R et al. The change of regional brain metabolism (18FDG PET) in panic disorder during the treatment with cognitive behavioral therapy or antidepressants. Neuro Endocrinol Lett 2004;**25**:340–348.
62. Lindauer RJ, Gersons BP, Van Meijel EP et al. Effects of brief eclectic psychotherapy in patients with posttraumatic stress disorder: randomized clinical trial. J Trauma Stress 2005;**18**:205–212.
63. Lansing K, Amen DG, Hanks C, Rudy L. High-resolution brain SPECT imaging and eye movement desensitization and reprocessing in police officers with PTSD. J Neuropsychiatry Clin Neurosci 2005;**17**:526–532.
64. Pagani M, Hogberg G, Salmaso D et al. Effects of EMDR psychotherapy on 99mTc-HMPAO distribution in occupation-related post-traumatic stress disorder. Nucl Med Commun 2007;**28**:757–765.
65. Felmingham K, Kemp A, Williams L et al. Changes in anterior cingulate and amygdala after cognitive behavior therapy of posttraumatic stress disorder. Psychol Sci 2007;**18**:127–129.
66. Petrovic P, Kalso E, Petersson KM, Ingvar M. Placebo and opioid analgesia – imaging a shared neuronal network. Science 2002;**295**:1737–1740.
67. Wager TD, Rilling JK, Smith EE et al. Placebo-induced changes in FMRI in the anticipation and experience of pain. Science 2004;**303**:1162–1167.
68. Petrovic P, Dietrich T, Fransson P, Andersson J, Carlsson K, Ingvar M. Placebo in emotional processing – induced expectations of anxiety relief activate a generalized modulatory network. Neuron 2005;**46**:957–969.
69. Zubieta JK, Bueller JA, Jackson LR et al. Placebo effects mediated by endogenous opioid activity on mu-opioid receptors. J Neurosci 2005;**25**:7754–7762.
70. Zubieta JK, Yau WY, Scott DJ, Stohler CS. Belief or Need? Accounting for individual variations in the neurochemistry of the placebo effect. Brain Behav Immun 2006;**20**:15–26.
71. Pariente J, White P, Frackowiak RS, Lewith G. Expectancy and belief modulate the neuronal substrates of pain treated by acupuncture. Neuroimage 2005;**25**: 1161–1167.
72. Kong J, Gollub RL, Rosman IS et al. Brain activity associated with expectancy-enhanced placebo analgesia as measured by functional magnetic resonance imaging. J Neurosci 2006;**26**:381–388.
73. Bingel U, Lorenz J, Schoell E, Weiller C, Buchel C. Mechanisms of placebo analgesia: rACC recruitment of a subcortical antinociceptive network. Pain 2006;**120**:8–15.
74. Nemoto M, Mito T, Brinigar WS, Fronticelli C, Koehler RC. Salvage of focal cerebral ischemic damage by transfusion of high O2-affinity recombinant hemoglobin polymers in mouse. J Appl Physiol 2006;**100**:1688–1691.
75. Wager TD, Scott DJ, Zubieta JK. Placebo effects on human mu-opioid activity during pain. Proc Natl Acad Sci U S A 2007;**104**:11056–11061.
76. Lieberman MD, Jarcho JM, Berman S et al. The neural correlates of placebo effects: a disruption account. Neuroimage 2004;**22**:447–455.
77. Price DD, Craggs J, Verne GN, Perlstein WM, Robinson ME. Placebo analgesia is accompanied by large reductions in pain-related brain activity in irritable bowel syndrome patients. Pain 2007;**127**:63–72.
78. Craggs JG, Price DD, Perlstein WM, Nicholas Verne G, Robinson ME. The dynamic mechanisms of placebo induced analgesia: evidence of sustained and transient regional involvement. Pain 2008;**139**:660–669.
79. Mayberg HS, Silva JA, Brannan SK et al. The functional neuroanatomy of the placebo effect. Am J Psychiatry 2002;**159**:728–737.
80. Furmark T, Appel L, Henningsson S et al. A link between serotonin-related gene polymorphisms, amygdala activity, and placebo-induced relief from social anxiety. J Neurosci 2008;**28**:13066–13074.
81. Newberg AB, Iversen J. The neural basis of the complex mental task of meditation: neurotransmitter and neurochemical considerations. Med Hypotheses 2003;**61**: 282–291.
82. Van Veen V, Carter CS. The anterior cingulate as a conflict monitor: fMRI and ERP studies. Physiol Behav 2002;**77**:477–482.
83. Bush G, Luu P, Posner MI. Cognitive and emotional influences in anterior cingulate cortex. Trends Cogn Sci 2000;**4**:215–222.
84. Phan KL, Wager T, Taylor SF, Liberzon I. Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. Neuroimage 2002;**16**:331–348.
85. Creswell JD, Way BM, Eisenberger NI, Lieberman MD. Neural correlates of dispositional mindfulness during affect labeling. Psychosom Med 2007;**69**:560–565.
86. Baer RA, Smith GT, Hopkins J, Krietemeyer J, Toney L. Using self-report assessment methods to explore facets of mindfulness. Assessment 2006;**13**:27–45.
87. Brown KW, Ryan RM. The benefits of being present: mindfulness and its role in psychological well.being. J Pers Soc Psychol 2003;**84**:822–848.

https://doi.org/10.1111/j.1601-5215.2010.00460.x Published online by Cambridge University Press

88. Lau MA, Bishop SR, Segal ZV et al. The Toronto mindfulness scale: development and validation. J Clin Psychol 2006;**62**:1445–1467.
89. Cohen-Katz J, Wiley S, Capuano T, Baker D, Shapiro S. The effects of mindfulness based stress reduction on nurse stress and burnout: a qualitative and quantitative study. Holist Nurs Pract 2005;**19**:26–35.
90. Shapiro S, Brown KW, Biegel G. Teaching self-care to care-givers: effects of mindfulness-based stress reduction on the mental health of therapists in training. Train Educ Prof Psychol 2007;**1**:105–115.
91. Carmody J, Reed G, Kristeller J, Merriam P. Mindfulness, spirituality, and health-related symptoms. J Psychosom Res 2008;**64**:393–403.
92. Damasio AR. The feeling of what happens: body and emotion in the making of consciousness. Iowa city: Harcourt Trade, 1999.
93. Craig AD. Human feelings: why are some more aware than others? Trends Cogn Sci 2004;**8**:239–241.
94. Panksepp J. Affective consciousness: core emotional feelings in animals and humans. Conscious Cogn 2005;**14**: 30–80.
95. Ruby P, Decety J. How would you feel versus how do you think she would feel? A neuroimaging study of perspective-taking with social emotions. J Cogn Neurosci 2004;**16**:988–999.
96. Ochsner KN, Bunge SA, Gross JJ, Gabrieli JD. Rethinking feelings: an FMRI study of the cognitive regulation of emotion. J Cogn Neurosci 2002;**14**:1215–1229.
97. Kalisch R, Wiech K, Critchley HD et al. Anxiety reduction through detachment: subjective, physiological, and neural effects. J Cogn Neurosci 2005;**17**:874–883.
98. Mason MF, Norton MI, Van Horn JD, Wegner DM, Grafton ST, Macrae CN. Wandering minds: the default network and stimulus-independent thought. Science 2007; **315**:393–395.
99. Brosschot JF, Gerin W, Thayer JF. The perseverative cognition hypothesis: a review of worry, prolonged stress-related physiological activation, and health. J Psychosom Res 2006;**60**:113–124.
100. Clayton IC, Richards JC, Edwards CJ. Selective attention in obsessive-compulsive disorder. J Abnorm Psychol 1999;**108**:171–175.
101. Hofmann SG. Cognitivefactors that maintain social anxiety disorder: a comprehensive model and its treatment implications. Cogn Behav Ther 2007;**36**:193–209.
102. Borders A, Barnwell SS, Earleywine M. Alcohol-aggression expectancies and dispositional rumination moderate the effect of alcohol consumption on alcohol-related aggression and hostility. Aggress Behav 2007;**33**:327–338.
103. Teasdale JD, Segal Z, Williams JM. How does cognitive therapy prevent depressive relapse and why should attentional control (mindfulness) training help? Behav Res Ther 1995;**33**:25–39.
104. Siegle GJ, Steinhauer SR, Thase ME, Stenger VA, Carter CS. Can't shake that feeling: event-related fMRI assessment of sustained amygdala activity in response to emotional information in depressed individuals. Biol Psychiatry 2002;**51**:693–707.
105. Kuyken W, Byford S, Taylor RS et al. Mindfulness-based cognitive therapy to prevent relapse in recurrent depression. J Consult Clin Psychol 2008;**76**:966–978.
106. Kabat-Zinn J, Massion AO, Kristeller J et al. Effectiveness of a meditation-based stress reduction program in the treatment of anxiety disorders. Am J Psychiatry 1992;**149**:936–943.
107. Miller JJ, Fletcher K, Kabat-Zinn J. Three-year follow-up and clinical implications of a mindfulness meditation-based stress reduction intervention in the treatment of anxiety disorders. Gen Hosp Psychiatry 1995;**17**:192–200.
108. Koszycki D, Benger M, Shlik J, Bradwejn J. Randomized trial of a meditation-based stress reduction program and cognitive behavior therapy in generalized social anxiety disorder. Behav Res Ther 2007;**45**: 2518–2526.
109. Fairfax H. The use of mindfulness in obsessive compulsive disorder: suggestions for its application and integration in existing treatment. Clin Psychol Psychother 2008;**15**:53–59.
110. Analayo. Satipatthana: the direct path to realization. Birmingham: Windhorse Publications, 2003.
111. Kapleau P. The three pillars of Zen: teaching, practice and enlightenment. Boston: Bacon Press, 1965.
112. Abercrombie HC, Schaefer SM, Larson CL et al. Metabolic rate in the right amygdala predicts negative affect in depressed patients. Neuroreport 1998;**9**: 3301–3307.
113. Drevets WC. Prefrontal cortical-amygdalar metabolism in major depression. Ann N Y Acad Sci 1999;**877**: 614–637.
114. Evans KC, Wright CI, Wedig MM, Gold AL, Pollack MH, Rauch SL. A functional MRI study of amygdala responses to angry schematic faces in social anxiety disorder. Depress Anxiety 2008;**25**:496–505.
115. Eren I, Tukel R, Polat A, Karaman R, Unal S. Evaluation of regional cerebral blood flow changes in panic disorder with Tc99m-HMPAO SPECT. Psychiatry Res 2003;**123**:135–143.
116. Davidson RJ. Affective style, psychopathology, and resilience: brain mechanisms and plasticity. Am Psychol 2000;**55**:1196–1214.
117. Mayberg HS. Limbic-cortical dysregulation: a proposed model of depression. J Neuropsychiatry Clin Neurosci 1997;**9**:471–481.
118. Davidson RJ. Affective neuroscience and psychophysiology: toward a synthesis. Psychophysiology 2003;**40**: 655–665.
119. Siegle GJ, Thompson W, Carter CS, Steinhauer SR, Thase ME. Increased amygdala and decreased dorsolateral prefrontal BOLD responses in unipolar depression: related and independent features. Biol Psychiatry 2007;**61**:198–209.
120. Bremner JD. Neuroimaging studies in post-traumatic stress disorder. Curr Psychiatry Rep 2002;**4**:254–263.
121. Mayberg HS, Liotti M, Brannan SK et al. Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. Am J Psychiatry 1999;**156**:675–682.
122. Ochsner KN, Ray RD, Cooper JC et al. For better or for worse: neural systems supporting the cognitive down- and up-regulation of negative emotion. Neuroimage 2004;**23**:483–499.
123. Ray JP, Price JL. The organization of projections from the mediodorsal nucleus of the thalamus to orbital and medial prefrontal cortex in macaque monkeys. J Comp Neurol 1993;**337**:1–31.

https://doi.org/10.1111/j.1601-5215.2010.00460.x Published online by Cambridge University Press

124. Ghashghaei HT, Barbas H. Pathways for emotion: interactions of prefrontal and anterior temporal pathways in the amygdala of the rhesus monkey. Neuroscience 2002;**115**:1261–1279.
125. Lazar SW, Kerr CE, Wasserman RH et al. Meditation experience is associated with increased cortical thickness. Neuroreport 2005;**16**:1893–1897.
126. Holzel BK, Ott U, Gard T et al. Investigation of mindfulness meditation practitioners woth voxel-based morphometry. Soc Cogn Affect Neurosci 2008;**3**:55–61.
127. Pagnoni G, Cekic M. Age effects on gray matter volume and attentional performance in Zen meditation. Neurobiol Aging 2007;**28**:1623–1627.
128. Recanzone GH, Merzenich MM, Jenkins WM, Grajski KA, Dinse HR. Topographic reorganization of the hand representation in cortical area 3b owl monkeys trained in a frequency-discrimination task. J Neurophysiol 1992;**67**:1031–1056.
129. Bao S, Chang EF, Woods J, Merzenich MM. Temporal plasticity in the primary auditory cortex induced by operant perceptual learning. Nat Neurosci 2004;**7**:974–981.
130. Bangert M, Altenmuller EO. Mapping perception to action in piano practice: a longitudinal DC-EEG study. BMC Neurosci 2003;**4**:26–39.
131. Baer RA. Mindfulness training as a clinical intervention: a conceptual and empirical review. Clin Psychol Sci Pract 2003;**10**:125–143.
132. Linden DE. How psychotherapy changes the brain – the contribution of functional neuroimaging. Mol Psychiatry 2006;**11**:528–538.
133. Roffman JL, Marci CD, Glick DM, Dougherty DD, Rauch SL. Neuroimaging and the functional neuroanatomy of psychotherapy. Psychol Med 2005;**35**:1385–1398.
134. Ivanovski B, Malhi GS. The psychological and neurophysiological concomitants of mindfulness forms of meditation. Acta neuropsychiatrica 2007;**19**:76–91.

https://doi.org/10.1111/j.1601-5215.2010.00460.x Published online by Cambridge University Press