The Neurobiology of Meditation and Mindfulness

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Abstract Neurobiological effects of meditation and mindfulness can be detected in the brain as functional and also structural alterations in grey and white matter, particularly in areas related to attention and memory, interoception and sensory processing, or self- and auto-regulation (including control of stress and emotions). On the molecular level, dopamine and melatonin are found to increase, serotonin activity is modulated, and cortisol as well as norepinephrine have been proven to decrease. These findings are reflected in functional and structural changes documented by imaging techniques such as fMRI or EEG. They may be relevant for medicine and health care, especially with reference to therapeutic strategies for behavior change and life-style modification, or in association with stress regulation and the treatment of addiction. Neuronal mechanisms of mindfulness can be divided into four areas: attention regulation, body awareness, emotion regulation and self-perception.

Abbreviations

ACC	Anterior cingulated cortex
BDNF	Brain-derived neurotrophic factor
E	Epinephrine
EEG	Electroencephalogram
fMRI	Functional magnetic resonance imaging

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NE Norepinephrine
PCC Posterior cingulated cortex
PFC Prefrontal cortex

Introduction

Meditation and mindfulness techniques are gaining importance in medicine and health care, because they have been shown to be effective in various clinical conditions (see Ernst et al. 2009; Fjorback et al. 2011; Grossman et al. 2004; Vøllestad et al. 2012). As a consequence, research has been focused on potential mechanisms of action and first reports on models for the underlying molecular principles and their neurobiological foundations are evolving. The new paradigm of a brain that regulates itself and adapts to stimuli from the environment but also from the internal milieu of the individual consciousness it supports, is useful for understanding these processes. At the center of the interest lies a potential for physiological, psychological, and neurobiological stress reduction (e.g., Esch et al. 2003, 2013; Esch and Stefano 2010; Jung et al. 2010, 2012; Manoch et al. 2009; Marchand 2012; Mohan et al. 2011; Stefano et al. 2005, 2006). Stress is an important factor for morbidity and mortality (e.g., see Rosengren et al. 2004; Russ et al. 2012), and thus methods for stress reduction are gaining importance as well. Knowledge about the facts and connections we already know, particularly with regard to current neuroscience, could be helpful for physicians, therapists and health professionals. Therefore, a summary of the most important neurobiological findings regarding meditation is presented here.

Biological Principles of Meditation and Mindfulness

Meditation can be defined as willfully and purposefully regulating one's own attention, either for the purpose of relaxation, exploring oneself or personal growth and transcendence (see the chapter by Schmidt). Meditation can operationally be divided into two categories: Either one is focusing attention on a *changing* object such as physical sensations in the body scan, progressive muscle relaxation, autogenic training, or movements in yoga, tai chi, qigong, or mental content as in guided imagery, or mindfulness meditation proper. Or an *unchanging* or repetitive object is constantly held in focus, such as in mantra meditations like Transcendental meditation (TM) or Benson meditation, breathing meditation like Zazen, ostinato drumming, rhythmic dancing, jogging/flow, etc. (see Benson and Klipper 2000; Ott 2010; Petermann and Vaitl 2009). However, in practice both categories frequently overlap, and normally the ability to keep one's attention focused on a steady object is the precondition for the capacity to constantly attend to moving objects. As a common ground, all techniques are usually conducted with an attitude of intentionally directed or focused concentration and attention, which is called ‘mindful awareness’ or ‘mindfulness’. As a consequence, they have the potential to elicit the so-called ‘relaxation response’ (Benson and Klipper 2000; Esch et al. 2003). This physiological reaction is the biological – that is, natural – antagonist of stress, thus antagonizing the ‘stress response’. This property is, supposedly, responsible for some of the observed clinical, medical or therapeutic effects of meditation, particularly in stress-associated diseases like cardiovascular, immune, proinflammatory or neurodegenerative diseases, including anxiety and depression (for an overview see, e.g., Esch et al. 2003 or Stefano et al. 2005).

Mindfulness refers to the specific or formal practice of mindfulness training and meditation (e.g., Ernst et al. 2009), as well as to the outcome of such a training, the general capacity to be mindful, or being fully present. Jon Kabat-Zinn, who brought the principles of mindfulness to Western medicine, describes it as a specific kind of paying attention characterized by a non-judgmental, purposeful and continuing awareness of all mental and physical or bodily states and processes, from one moment to the next. It is the awareness that arises from paying attention on purpose, in the present moment, and without evaluating or judging what comes to mind (Kabat-Zinn 1990). Under stress frequently automatic mental patterns are formed and are part of the cognitive stress response. Such patterns can be observed as automatic negative thoughts or constant rumination, especially about the past or assumptions about the future, and as the tendency of the mind to wander away in boring or challenging as well as stressful situations. If mindfulness is practiced systematically, such automatic chains can be broken. A person skilled in meditation can intentionally suppress automatic thoughts by actively keeping the mind in the present, for instance, through staying with the actual experience as it happens here and now, or through focusing on the breath. This alone can be enough to reduce psychological and physiological stress (see, for example, Ernst et al. 2008; Esch and Esch 2013; Esch and Stefano 2010; Esch et al. 2013; Stefano et al. 2005). While being mindful, we usually experience that our lives are not instantaneously threatened, that is, in the real present, right here and now, there is no life-threatening danger, and consequently there is actually no specific ‘reason’ to be stressed or alarmed (Esch 2002, 2003, 2008; Thees et al. 2012). This active and intentional turn towards the non-stressful present moment is an innate capacity or attitude, like an inner ‘mindset’ that humans possess, biologically, and that can be facilitated and trained by systematic mental practice like mindfulness meditation (cf., Rossano 2007).

For a uniform and more exact definition of mindfulness for scientific purposes, Bishop et al. developed a working model consisting of two aspects (Bishop et al. 2004): the first aspect is represented by self-regulation of attention, i.e. actively regulating attention towards an awareness of the present and the experiences therein, and the second by the sustained and active maintenance of an attitude of abiding curiosity, openness, and acceptance in the face of these very experiences. Thereby, qualities such as acceptance are developed, that is, non-judging and ‘letting go’, as well as presence and ‘connectivity’: contact with the momentary inner sensual, mental and bodily experiences on the one hand, and an empathic and attentive ‘outreach’ to the surrounding world and environment on the other hand. Together with the capacity to ‘grow from the inside’ and to better deal and cope with challenges and stress, these aspects resemble very much what is also known from Positive Psychology and happiness research as requirements or ingredients for a successful or happy and healthy life, i.e. high level of satisfaction with one’s life and self-contentment, including resiliency (e.g., see Esch 2011). Thus, it is not surprising that the underlying concepts and different models widely overlap. This is particularly due to a shared neurobiology between the diverse concepts, and most importantly the likely relevance of brain mechanisms that involve endogenous reward and motivation processes which are imbedded in the brain for nearly all these models and processes. They also share aspects of attention regulation – from self- and auto-regulation to an activation of regions in the brain that correlate with empathic and compassionate behaviors, also embracing regions with mirror neuron activity (Esch and Stefano 2011; see below).

Kabat-Zinn (1990) differentiates two ways of practice necessary to make mindfulness become a steady and integral part of daily life: Formal mindfulness training, such as sitting or walking meditation, consists of specific exercises and techniques to stabilize the state of attentive and mindful awareness in the present moment. Informal practice, on the other hand, includes maintenance and persistence of mindfulness as a ‘state of being’ during daily routines and activities such as dish washing, shopping, speaking, brushing the teeth, etc. These informal practices serve to integrate a mindful attitude into a way of living. In principle, both forms can be trained and both are, rather confusingly, sometimes called ‘mindfulness meditation’. However, usually the term ‘meditation’ refers to the more formal aspects of mindfulness training, e.g., body scan, observing and bringing attention to the breath, etc. Yet this complex training, typically delivered within a structured process, e.g. a mind-body program or a behavioral group intervention, usually contains at the same time formal and informal practices, as critical and important ingredients. Here, the informal aspects particularly relate to the experience and activities of daily life. Thus, mindfulness training such as Mindfulness Based Stress Reduction (MBSR) training, or mind-body medical training including mindfulness as a core element are now successfully offered and practiced within medicine and the health care system, or within other settings, including kindergarten, schools, occupational health, or even nursing homes (e.g., see Ernst et al. 2008; Esch and Esch 2013; Mendelson et al. 2010).

Such multifaceted programs train participants in critical elements of mindfulness meditation, aiming at reducing physical or mental ailments and distress, or increasing self-efficacy (Ernst et al. 2009). In this context, Kabat-Zinn and colleagues see their work as a complementary or mind-body medical approach within behavioral medicine, where patients and participants, in contrast to conventional medicine, are usually not separated along indications or different diseases, indicating different treatments, except where such programs have been adapted for specific groups. Hence, in mindfulness training, the element of mindfulness is key, more or less regardless of the actual indication. And yet assumed health effects of being mindful and thereby reducing stress lie at the center of all measures as a common ‘denominator’ (Salzberg and Kabat-Zinn 2000). In fact, for this generic method across diseases, mobilizing inner salutogenic resources and potentials, and modifying illness-prone behavior patterns appears to be critical (Ernst et al. 2009; Esch 2010). In this way, mindfulness meditation relates to the inner capability to self-help, self-care or heal. Thus, the biological principle of self- and auto-regulation is the center piece and target that is, originally, rather independent of external circumstances and conditions. In that sense, mindfulness-based approaches help individuals to regain their auto-regulative capacities that have been lost, e.g., through repeated challenges of stress.

Neuroscience of Mindfulness and Mindfulness Meditation

At the center of mindfulness-based approaches is the deliberate focus of attention on feelings and sensations perceptible in the present moment. The feelings are observed, but not evaluated or actively changed. For example, through mindful observation of breathing, posture, tension, pain etc., self-perception is trained and a connection can be made to 'alienated' parts of the body (Kabat-Zinn 1990). In addition, to primarily psychological approaches at explaining it, physiological and, in particular, neuroscience and brain-related effects and mechanisms of action of meditation and mindfulness are increasingly being examined today.

Scientific Evidence

According to the model of frontal alpha-symmetry of cortical activation, a relative increase in left-anterior brain activity is associated with positive feelings and improved immune function (Davidson 1998). Based on this assumption, Davidson et al. (2003) sought and found evidence of significantly stronger activation of left frontal areas of the brain, associated with a greater increase in antibody titer after a flu shot in participants at the end of a mindfulness course in comparison with those on the waiting list. The extent of the increase in cortical activity correlated with the increase in the antibody titer. This again indicates in this context the inseparability of mind and body and the cross-linking of the systems involved, as well as the continuity between central and peripheral processes. In other studies, a regional increase in the activity of numerous specific areas of the brain, such as motivation and reward areas and regions that control attention and the 'emotionality' of physiological (physical) responses, like the orbitofrontal cortex, interoception, like the insular cortex, and (central) autonomic functions, as well as controlling and evaluating emotions and linking them to memory formation, like the hippocampus, was found in participants during or after meditation (Critchley et al. 2001; Davidson 1998; Esch et al. 2004a; Hölzel et al. 2007, 2011a; Kang et al. 2013; Lazar et al. 2005; Linden 2000; Newberg et al. 2001; Newberg and Iversen 2003; Vestergaard-Poulsen et al. 2009). However, it appears that global brain activity tends to be reduced in experienced meditators (Lazar et al. 2000). It could be said that this reflects increased 'efficiency' (Esch and Stefano 2010). Newberg and Iversen (2003) identified a neurophysiological pattern of changes that occurred during meditative states that included certain key cerebral structures and hormonal and autonomic reactions, indicating changes in cognition, sensory perception, as well as affect (affective state), and an overall (i.e., brain-rooted) influence on endocrine-hormonal and autonomic activity. There are also increased functional – and structural – asymmetries, in particular lateralization and a tendency to shift activity 'forward', a so called 'anteriorization' seem to be relevant (see Davidson et al. 2003; Kang et al. 2013; Newberg et al. 2010; Yu et al. 2011). Creswell et al. (2007) found that subjects with a higher level of self-attributed mindfulness display greater prefrontal cortical activation and deactivation of the amygdala when naming emotions. Recent studies confirm this finding and correlate it with structural plastic adaptation effects in the area of the amygdala, which was 'shrinking' during a typical 8-week mindfulness training event (Desbordes et al. 2012; Hölzel et al. 2010). At the same time, there is a positive correlation between the structural and thus objective changes in the brain on the one hand, and the subjective perception of stress on the other hand: stress is perceived to a lesser extent or is coped with better (Hölzel et al. 2010). These findings confirm the assumption that mindfulness potentially has a positive effect on neuronal pathways that regulate affect and emotions (see below).

To summarize the *structural* effects of meditation on the brain, it can be stated that in those who meditate regularly (in comparison with control groups), the thickness of various areas of the cortex potentially increases. This can be specifically observed in those areas associated with attention and memory, interoception, and sensory processing as well as with self-regulation and auto-regulation (see Hölzel et al. 2008, 2011a; Kang et al. 2013; Lazar et al. 2005; Newberg et al. 2010; Pagnoni and Cekic 2007; Wang et al. 2011).

With respect to *functional* changes in brain activity, Lutz et al. (2004) show that many years of meditation lead to an increase in high-frequency, synchronized gamma waves in the EEG during a certain kind of meditation that involved the cultivation of compassion. Such a pattern also occurs during increased attention and functional learning processes and is associated with higher order conscious and cognitive processes, among other things. In this particular study, however, the coherence and synchronization of the high-frequency 40 Hz oscillation covered an extraordinarily large part of the brain. Cahn et al. (2010) confirmed these observations. Apparently, gamma activation in particular is an indication of the 'quality of meditation', i.e., the quality and experience of the person practicing it. But relevant changes in the EEG can also be observed after a relatively short period of practice. In addition to the alpha and gamma waves described, changes in the beta band and especially in the theta band can occur – here again in the relevant regions of the brain (Aftanas and Golocheikine 2001, 2002; Baijal and Srinivasan 2010; Cahn et al. 2012; Hinterberger et al. 2011; Jacobs et al. 1996; Kerr et al. 2011; Kjaer et al. 2002; Kubota et al. 2001; Lagopoulos et al. 2009; Yu et al. 2011). However, it can generally be assumed that there are significant differences in the EEG and physiology of the brain between long-term and short-term meditators or novices. Therefore, experience, individual length of practice, and also personal characteristics, as well as differences in the meditation techniques used must be considered (see, e.g., Brefczynski-Lewis et al. 2007; Farb et al. 2007). From an EEG perspective and for the experimental differentiation and estimation of the quality of the individual meditation experience, we can use the theta band (pronounced frontal, near midline) for depth or relaxation, connotation of ‘inner reflection’ and ‘self-contemplation’ on the one hand. The gamma band in the parietal or parieto-occipital and temporal region, i.e. more lateral, seems to refer to the experience of ‘dissolution of boundaries’ or transcendence, and also the ‘quality of compassion’, including the perception of unity and coherence, on the other hand. Finally, the occurrence of synchronicity or synchronization in the regions mentioned, including a spatial expansion of those synchronous waves and frequencies beyond the places of origin seems to be a ‘good’ signature. Characteristic increases in those bands are found regularly in experienced meditators; the alpha changes described above are usually observed only in beginners, as they are associated nonspecifically with relaxation and the closing of the eyes.

It is clear that, depending on individual ‘expertise’ and also on the momentary state of mood or general trait, and the meditator’s initial state of happiness, meditation can be associated with short peaks or exceptional moments or even ‘rapture’ but also with sustained feelings of deep joy, satisfaction, and ‘inner peace’ (Esch 2011; Esch and Stefano 2004, 2005). Today some of the neuromolecular correlates of these feelings are known, such as the involvement of dopamine and others (Esch and Stefano 2010; see below). Thus, these subjective feelings undoubtedly have objectifiable neurobiological correlates. For example, in an extreme case, the gamma oscillations can even extend to the ‘whole’ brain and generate very high amplitudes (i.e., involving many neurons) thus displaying strong synchronicity, which probably gives the subjective impression of fusion of subject and object or conveys a ‘mystical experience’, and is sometimes also termed *global binding* (Lutz et al. 2004; Ott 2010). In such moments, spatial representation of the ‘ego’ and proprioceptive input from the body (i.e., the subjective body image) are modified (see the chapter of Farb in this volume). Although these states are actually observed only in long-term meditators, analogous states can possibly occur in the area of pharmacotherapy as well as ‘side effects’, in drug use, or in psychopathologies as so called productive symptoms (Esch 2011). The consequences of these states – adverse effects, contraindications or desired aspects in therapeutic utilization – of a mindfulness- or meditation-based process are currently the subject of considerable controversy (see Lustyk et al. 2009).

Classification System for Mechanisms of Action

Britta Hölzel and Ulrich Ott propose the following system for the assessment and classification of the neuronal mechanisms of action of mindfulness (see Hölzel et al. 2011b).

Attention Regulation

Mindfulness techniques can help to focus or broaden attention. On the one hand, regular practice makes it easier to focus and keep attention on an object, to notice more quickly when thoughts drift away, and to deal with disruptions more effectively, by either blocking them out or accepting them. On the other hand, it is easier to disperse attention or broaden the 'light beam of consciousness' (Esch 2011), expanding the window of the present as it were and thus noticing more if desired. This can be confirmed in several ways in an experimental setting (e.g., van Leeuwen et al. 2009), but can also be seen in everyday life in heightened perception and awareness of breathing and a reduced tendency to be distracted. In the brain, as mentioned, the prefrontal cortex (PFC) and the anterior cingulated cortex (ACC) are especially involved. True to the slogan *use it or lose it*, over time, attention training, as it seems, also results in a slower aging process of the brain (compared with control persons, non-meditators; e.g., Pagnoni and Cekic 2007). This is probably caused by the functional and structural differentiation and morphological strengthening of networks in the areas of the brain described, as well as by the overall improvement in connectivity, involving not only increased density or size of the grey matter, but of the white matter as well (see Esch 2011; Esch and Stefano 2010; Kang et al. 2013; Luders et al. 2011; Ott 2010). Cultivating a 'beginner's mind' that remains in the present could also slow down the aging of the brain. This seems to be associated with a reduction in baseline activation of the so called default mode network (e.g., see Pagnoni et al. 2008). This statement is surely speculative due to the complexity of the findings. However, we know that with improved attention, memory is generally 'strengthened', and the functions, as well as the activity in the prefrontal working memory and in the declarative memory associated with the hippocampus, including the general ability to learn and remember, are improved (see Hölzel et al. 2010, 2011a; Mohan et al. 2011; Zeidan et al. 2010). Hence, meditation training may induce learning that is not stimulus- or task-specific, but process-specific, e.g. pattern recognition, and thereby may result in enduring changes in mental function (Desbordes et al. 2012).

Body Awareness

It is generally true that mindfulness meditation increases functional and structural activity in the somatosensory and insular cortex. It can therefore be assumed that, over time, meditation improves the ability for interoception as well as exteroception (Esch 2011), refining body awareness, in particular, through greater differentiation of 'inner maps' (Ott 2010). The cingulum is also involved in this process, where relevant aspects of the current experience and detected 'errors' are filtered and thus recognized more rapidly. This means that the person who meditates on a regular basis feels 'good', because he or she is in close contact with his or her own feelings. This in turn leads to improved 'intuition' and a 'gut feeling' that is in fact associated with an enhanced representation of feelings from the inner body. Motion and skills memory and the corresponding areas in the dorsal striatum are also strengthened (see Newberg et al. 2010; Pagnoni and Cekic 2007). But it is likely that this improved ability to achieve 'attunement' is useful not only in order to recognize more quickly what is happening in one's *own* body, e.g., whether stress must be modulated, or what would constitute useful or appropriate reactions and actions (Esch and Stefano 2010; Hölzel et al. 2010). These also include effectively recognizing warning signals in time. In addition, mindfulness may also be useful for coming into closer contact with *others*. This is so, because the regions for 'body awareness' activated by mindfulness include areas and modalities that are needed for resonance with others as well (see also Siegel 2007). In addition to the classic mirror neuron areas, e.g., in the PFC, the associated areas in the temporal lobe and in the region of the temporoparietal junction should be mentioned as well (Hölzel et al. 2011a; Kang et al. 2013). Empathy and compassion, that is the emotional ability to empathize, but also the cognitive ability to perceive the perspective of the other (see *Theory of Mind*), are presumably reinforced (e.g., Desbordes et al. 2012). Hence, compassion and altruism, which can be trained through meditation and involve, among others, the prefrontal or orbitofrontal brain, also activate relevant dopaminergic midbrain structures and enhance the overall PFC-limbic (dopaminergic) connectivity (see below).

Emotion Regulation

In neurobiology today we distinguish three levels of the limbic system or, functionally speaking, of the limbic auto-regulation, which is responsible for endogenous control of emotion and motivation (see also Esch 2011). The lower and middle levels that are involved in generating, and usually unconsciously 'evaluating', affects and emotions, through structures such as the amygdala, are generally difficult to control consciously. However, the upper limbic level has the ability to influence the regulation of emotions (and, maybe with stronger limitations, affects). It is sometimes also termed 'paralimbic' and comprises part to the prefrontal cortex, namely, in addition to the ACC, the orbitofrontal cortex and, in my view, parts of the insula as well (Esch 2011). This area of motivation and function of auto-regulation, which can be seen as a 'bridge' between the cortex and the limbic system or, figuratively speaking, between reason and cognition on the one hand, and affects and emotions on the other hand, can be strengthened by practicing mindfulness (Creswell et al. 2007; Esch and Stefano 2010; Hölzel et al. 2010, 2011a; Wang et al. 2011). Arguably, it may be easier to recognize and actively break the 'downwards spiral' or the vicious cycle between negative cognitions and the emotions linked with them, or vice versa, if those bridging functions are strong (see Ott 2010). In other words: a technique that activates these regions may also have a central influence on integrative processes in the brain, because it connects mind and reason, with affect and soma, or physiology. Thus, the *mind-body connection* becomes real, can be experienced and measured. In addition, self-regulation, the modulation of emotions and perceived stress is improved. These processes become neuronally objectifiable, controllable, and locatable. Interestingly, in the center of this assumedly enhanced connectivity between the PFC and limbic areas are those areas that 'subjectively' contribute to the experience of connectedness, affiliation, and acceptance. In other words, mindfulness training possibly leads to a systematic desensitization of negative affects and emotions, and at the same time to an increase in compassion, openness, and equanimity. Thereby, in addition to the inhibitory effect on the amygdala, the hippocampus is strengthened and the temporoparietal junction (see *Embodiment, Perspective Taking*) and the posterior cingulated cortex (PCC) are activated. This can be interpreted as relativizing the significance of contents and promoting recognition of what is important (see also Desbordes et al. 2012; Hölzel et al. 2011a; Khalsa et al. 2009; Ott 2010). However, findings concerning the PCC are still inconsistent (Kang et al. 2013). What can be seen in any event is that, in principle, affective circuits and 'autonomic' functions linked with them can be shaped by training, similar to attention (Newberg et al. 2010). Thus, it is possible to actively integrate higher neuronal structures, thus inhibiting inappropriate or 'undesired' automatic patterns and reactions to unpleasant stimuli like stress. In this way, new behavior patterns can arise, including those that lead to a reduction in or improved regulation of stress. It is also possible that other functions can be improved such as better coping with pain (see also Gard et al. 2012; Schmidt et al. 2011).

Self-Perception

Studies have shown that practicing mindfulness can potentially lead to a more 'refined' self-perception. This means that ideas of the self and the self image on the one hand, and actual self-perception on the other hand can be better distinguished (see, e.g., Farb et al. 2007 and the chapter by Farb in this volume). Similar processes have already been observed in the context of pain modulation. Here, the practitioner learns *not* to identify with thoughts, perceptions, and feelings ('you are not the pain', 'pain and suffering are not one'). This attitude is also termed *de-centering* or *dis-identification* and can possibly be trained by mindfulness, which leads to a more mindful and distanced handling of stressful thoughts, emotions, psychosocial or mental stress, reduces 'over-identifying with the ego' (negative ego beliefs), and so prevents the occurrence of negative consequences (Ernst et al. 2009; Linden 2000; Plews-Ogan et al. 2005; Schmidt et al. 2011; Teasdale et al. 1995, 2002; Walach et al. 2007; Williams et al. 2000). This would then be, in the truest sense of the words, a 'self-efficacy experience' or experience of authentic internal control (see, e.g., Sonntag et al. 2010). Neurobiologically, it appears to be less a process of primarily cognitive control ('I do not want to have any more pain' or 'I can cope with it'), but in fact a change in pain processing (Gard et al. 2012) ('I feel less pain', 'The pain I feel is not bothering me'). Mindfulness again appears to be a means of modulating self and pain perception and pain anticipation (physical, but also regarding 'experiencing unfairness' and mental pain) by involving the sensory and interoceptive areas, such as the ACC and the insula. Such positive control experiences can generally help the individual in assuming responsibility for his or her own health (Esch 2002, 2003; Sonntag et al. 2010). Some authors also state that the constructs of the ego on the one hand and the self on the other are experienced more clearly and separately from one another when, with the help of mindfulness training, for example, inner evaluations like judgments or appraisal are reduced and, instead, autonomy, self-awareness, authenticity, and integrity are experienced, and simultaneously, feelings of coherence, connectedness and consistency arise (Esch 2011; Ott 2010). Here, it is important to state that in the relevant literature, the self includes aspects of self-attribution, such as self-reference, ego image, and corresponding ‘appraisal structures’, that is, an egocentric perspective, neuronally attributed more to midline structures in the brain including the medial PFC, as well as the non-judgmental focus on the present experience *of* the self, for which more lateral structures, including in the insula and the somatosensory cortex, are activated (Farb et al. 2007; Lazar 2011). Sometimes the ‘allocentric perspective’ is also mentioned in the context of this lateralization or activation of the lateral networks (see Hanson 2009 and the chapter by Austin in this volume).

Although mindfulness, obviously, has a tendency to strengthen the ‘self’ in contrast with the ego, and to reduce the tendency to judge and evaluate experiences, it appears that, in the context of the various aspects of the self, particularly the *flexible* and nuanced *handling* and recognition of the different modes, and the possibility of ‘switching back and forth’ are trained (see Farb et al. 2007; Malinowski 2012; Ott 2010). The fact that the *default mode*, detectable near the midline structures, or *resting state network*, which is associated with ‘leisure’ and inner reflection , as well as with self-related ‘daydreaming’, is modulated by meditation and mindfulness also fits with this auto-regulatory approach (Lazar 2011; McAvoy et al. 2008; Ott 2010; Pizoli et al. 2011; Schnabel 2010). On the one hand it is said that mindfulness is that which would arise, or be ‘left over’, if we would not do or think anything, the ‘natural condition of our mind’ (Walach 2010) as a *resting state*, on the other hand, mindfulness also appears to be able to inhibit the activity in the *default mode network*, i.e. to prevent daydreaming (Ott 2010). We need to await the results of further studies, but we can probably assume that a common denominator may be that mindfulness improves self-perception ability as well as increases psychological, inner flexibility. Very likely this is achieved in the context of an improved ability to regulate one’s own brain activity. Mindfulness thus ultimately results in more degrees of freedom in behavior control (see, e.g., Malinowski 2012). An associated feeling of increased internal control (‘I can’) potentially strengthens self-efficacy and the feeling of ‘inner strength’ (see also Esch 2003, 2010; Sonntag et al. 2010). This could be important for the healthcare system and in particular for medical lifestyle modification or addiction treatment. In addition, mindfulness has a positive effect on resonance circuits in the brain regarding attunement and empathy through mirror neurons, which then in turn functionally integrate near-midline and lateral networks (see Esch 2011; Siegel 2007). So it is certainly correct to emphasize the aspect of integration as the central ‘pivotal element’ of the observed effects in the context of brain-related adaptation reactions in practitioners of mindfulness.

The classification system of the mechanisms of action of mindfulness can also be understood as an interwoven pyramid of various states, which – in the sense of a continuum of practice or experience, but also in the course of a therapeutic process – are potentially followed through during meditation. A certain hierarchy, e.g. depending on the individual meditation quality or practitioner's experience, can be construed (Esch 2011; Ott 2010). Thus, regulating attention is a prerequisite for other exercises and further 'steps'. Body awareness and the acceptance associated with it, as a result of which the body or the mind is no longer, for example, perceived as an 'enemy' or merely as sick, is in turn an important prerequisite for an integral healing process. The regulation of emotion, which is also about alternative behaviors and coping with pain, sorrow, stress, anxiety, depression, addiction, craving, etc., in other words about breaking negative vicious circles and emotional and cognitive self-regulation, is undoubtedly a part of this, especially in the context of an in-depth psychotherapeutic approach. Finally, in this process it is important to scrutinize one's own ego beliefs, not necessarily in order to question them, but to acknowledge them, and to identify and activate potentials and resources that may be blocked by unfavorable attributions. So one may succeed in taking the subject out of a mode of turmoil and disharmony, i.e., out of the *reactive mode* and finally to transfer it to a *resting* or *responsive mode* (c.f., Hanson 2009). This can then give rise to happiness (Esch 2011; Hanson 2009). In the end, a transcendental or spiritual experience may arise, sometimes called 'resolution of the ego', or an experience of unity. In this experience a primarily cognitive and clearly defined self-perception, which would be spatially and sensually contained, does no longer exist, but rather a perception of an utterly unlimited connectedness accompanied by deep compassion. However, these states also appear to depend greatly on the individual's prior experience or predispositions – as well as on the meditation method practiced. This is reflected in the fact that the areas for spatial-sensory location or the spatial memory tend to be down-regulated in some methods, at least in long-term meditators, while up-regulated, but then relatively consistently, in others.

Neuromolecular Aspects of Meditation

For several years attempts have been made to discover, aside from the macroscopic and morphological changes in the function and structure of the brain and central nervous system, changes and mechanisms at the molecular level that correspond with the observations made in the context of practicing mindfulness and meditation. In many areas, however, little progress has been made due to the difficulty of examining the human brain in real time during meditation while making valid and reliable measurements at the same time. Moreover, many methods are still in the experimental stage, so relatively well substantiated methods and conclusive models are used to merge the findings from various areas to an overall picture (see, e.g., Esch and Stefano 2010).

In any event, there is presumably involvement of the central limbic and mesolimbic or mesostriatal mechanisms. Thus, the brain's motivation and reward systems – with dopamine as the leading messenger substance – appear to be involved (overview see Esch et al. 2004b; Esch and Stefano 2004). So it is not surprising that various authors were able to directly prove the presence of dopamine both in the brain and in plasma in connection with meditation (e.g., Jung et al. 2010; Kjaer et al. 2002). There have also been repeated reports of the involvement of enzymes for the production and release of norepinephrine (NE) and epinephrine (E), therefore establishing a direct connection with stress physiology and with stress modulation at the molecular level (e.g., Jung et al. 2012). Other factors sensitive to stress are apparently also involved, such as the brain-derived neurotrophic factor (BDNF), although there are, as so often in this context, genetic predispositions (e.g. polymorphisms) that make a response more likely (see also Esch and Stefano 2010; Jung et al. 2012).

Lower values are found for plasma NE in meditators in comparison with control persons (e.g., Infante et al. 2001). The enzyme systems responsible for this (see above) are also involved in dopamine and morphine metabolism, although the real-time involvement of endogenous morphine during meditation has not been reliably proven yet, probably for the reasons mentioned above (see, e.g., Mantione et al. 2008, 2010a, b). The situation is also somewhat unclear with respect to serotonin. It appears that meditation has a positive effect on the modulation of peripheral and central serotonin levels, with a tendency to raise them, but this effect is not consistently verifiable (Bujatti and Riederer 1976; Liou et al. 2010; Solberg et al. 2004; Walton et al. 1995; Yu et al. 2011). This may be due to circadian rhythms and interaction with other hormone systems, as there is, for instance, a 'competition' between melatonin and tryptophan.

By contrast, meditation increases peripheral melatonin levels (Liou et al. 2010; Solberg et al. 2004) and reduces cortisol levels (Brand et al. 2012; Esch et al. 2007; Walton et al. 1995) quite reliably. At the same time it can be seen that sympathetic *responsivity* is reduced (e.g., Hoffman et al. 1982) in favor of increased parasympathetic tone (Bujatti and Riederer 1976). Interestingly, in this context it has long been known and quite thoroughly proven that stress – especially chronic stress – lowers acetylcholine levels by increasing acetylcholinesterase activity and activating the respective genes (Evron et al. 2005), which again illustrates the stress/anti-stress regulation mechanism at the molecular level. Also, relaxation/meditation training activates discriminative gene patterns (Dusek et al. 2008). Both, acetylcholine and morphine increase the activity of the constitutive nitric oxide-producing enzymes (overview, e.g., Stefano and Esch 2005), which is presumably one reason why elevated nitric oxide levels have been found in the breath of meditators (e.g., Dusek et al. 2006; Mantione et al. 2007). Interestingly, constitutive nitric oxide has an anti-inflammatory effect, e.g., by inhibiting the pro-inflammatory nuclear transcription factor NFkappaB, and chronic stress does the opposite and induces inflammation (Esch et al. 2002). This could represent a neurobiological core element of the stress-modulating capacity of meditation and associated health benefits (Esch and Stefano 2010; Stefano and Esch 2005). However, this last point is still speculative.

In summary, it can be established that meditation can counteract stress at the mental, physical, physiological, and molecular level. Some of these effects are subjective by definition, but can definitely be objectified using suitable methods. Regarding the improvement in mood and affect and subjective feelings of relaxation, happiness or 'simply' pleasure that have sometimes been reported by meditators, it can be assumed that the endogenous motivation and reward systems are involved and a direct relationship with self-regulation can thus again be assumed.

Conclusions and Outlook

Meditative experiences and mindfulness are rooted not only in psychology, but in neuroscience and neurobiology as well. They can be detected at the level of the brain in the area of functional, but also structural changes in grey and white matter, especially in those areas and networks associated with attention and memory, interoception, and sensory processing as well as with self- and auto-regulation. This includes emotion and stress regulation to which, in addition to the integration of central autonomic regions, the limbic system and endogenous motivation and reward centers belong. Anxiety and ‘sensitivity to stress’ can be reduced and the ability to learn and remember is presumably improved.

At the level of neurobiological auto-regulation and molecular control, it has been proven that dopamine and melatonin are increased and cortisol and norepinephrine are reduced during meditative states, i.e., classic stress hormones are inhibited. However, increases in serotonin, nitric oxide, acetylcholine, and endogenous morphine are still speculative, which is due in part to the complexity and difficulties with measuring methods. Thus, there is a need for further research. But in any case, the findings are already interesting for medicine and the healthcare system, especially for therapeutic behavior change, lifestyle modification, and addiction treatment. They can also be used to address the issue of and appraise the risks and ‘side effects’ of meditation.

Some authors relate meditation/mindfulness in this context to elements of motivation physiology and biology. The *approach system* and the *avoidance system* must be differentiated here (e.g., Esch 2011; Hanson 2009; McColl and Singer 2012; Sauer et al. 2011). Avoidance and aversion also includes the fight-or-flight and stress response, and approach or appetite also includes binding and reward perception and the anticipation of it (e.g., Bisaz and Sullivan 2012; McCall and Singer 2012). The binding or affiliation system is also described as a social relief and welfare system, and at the neurobiological level presumably includes a central role of oxytocin signaling pathways, a connection that awaits further study (Esch and Stefano 2005; Groppe et al. 2013; McCall and Singer 2012). The desire and reward system, on the other hand, is also described as the *wanting* or *pleasure system* and it incorporates dopamine and opioidergic signal pathways as central neurotransmitters (Esch and Stefano 2004; Singer 2010). Thereby, there is a bridge to the aversion system, e.g., when there are pharmacological, but also mental or psychosocial withdrawal symptoms. In such a situation the stress hormones assume a dominant role. Thus all of these systems are connected neurobiologically and neuromolecularly, and mindfulness is believed to be able to return a ‘system in turmoil’, i.e., when regulation is in the reactive mode, and stress, allostasis, and depletion prevail, to the *responsive mode*, with the primary function of down-regulation or even homeostasis and the goal of regeneration, restoration and 'recharge', associated with feelings of inner peace, non-wanting or 'quiescence' (McCall and Singer 2012).

There is apparently a correlation between motivation regulation and self-regulation on the one hand, and controlling affects and emotions and stress regulation on the other – and all of these aspects appear to respond quite well to mindfulness therapy. Moreover, in a broader sense, mindfulness leads functionally and systemically to an increase in the degrees of 'freedom', i.e., internal flexibility, since adaptation to reality, perceived control, self-efficacy, and self-management skills are strengthened. This is expressed neurobiologically, in the brain, e.g., by an increase in asymmetry in EEG and fMRI findings: neurological imaging shows asymmetric activity shifting and lateralization, and in addition frequently 'anteriorization'. Especially, the relevant networks are activated via mindfulness practice, and this ultimately means that there is a network potential for growth, but also for acceptance, affiliation, and happiness or deep inner satisfaction. Of course, outcomes are speculative.

Chronic stress over the lifetime has been proven to lead to degenerations in parts of the PFC, leading, among others, to a decrease in the ability to regulate emotions, but also to deteriorated executive functions and a reduced performance of the working memory in the dorsolateral PFC. Furthermore, there may also be degeneration in the hippocampus, which is very stress-sensitive, while the amygdala may gain in size, with presumed effects such as elevated anxiety, or continuously feeling stressed. These are developments that the regular practice of meditation and mindfulness, including compassion training, appear to counteract, potentially, although there are still many questions with respect to therapeutic approaches.

In conclusion, we state again that the neuronal mechanisms of action of mindfulness can be systematically classified in four areas: attention regulation, body awareness, emotion regulation, and self-perception. Britta Hölzel and Ulrich Ott propose this classification and it appears to be useful and practicable.

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