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BRAIN EFFECTS OF MINDFULNESS IN THREE MODALITIES: FUNCTIONAL ACTIVATION AND CONNECTIVITY DURING TASK AND REST

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2. ABBREVIATIONS

ACC - anterior cingulate cortex
AI - anterior insula
aMCC - anterior medial cingulate cortex
aPE - aversive prediction error
ATB - attention to breath
BOLD - blood oxygen level dependent
BPD - borderline personality disorder
CEN - central executive network
CS - conditioned stimulus
CPZ - chlorpromazine
dACC - dorsal anterior cingulate cortex
DLPFC - dorsolateral prefrontal cortex
DMN - default mode network
DMPFC - dorsomedial prefrontal cortex
FA - focused attention
FMI - Freiburg Mindfulness Inventory
fMRI - functional magnetic resonance imaging
FWE - family wise error
HC - healthy controls
iFC - intrinsic functional connectivity
ICA - independent component analysis
ICN - intrinsic connectivity network
intra-iFC - intrinsic functional connectivity within networks
inter-iFC - between networks intrinsic functional connectivity
MAAS - Mindful Attention and Awareness scale
MBSR - mindfulness based stress reduction
MD - major depression
MNI - Montreal Neurological Institute
mPFC - medial prefrontal cortex
OM - open monitoring
P - prediction
PCC - posterior cingulate cortex
PE - prediction error
PFC - prefrontal cortex
PI - posterior insula
PPI - psycho-pysiological interaction
PV - passive viewing
ROI - region of interest
rs-fMRI - resting state-functional magenteic resonance imaging
SN - salience network
SVA - small volume analysis
TPJ - temporo-parietal junction
US - unconditioned stimulus
VLPFC - ventrolateral prefrontal cortex
VMPFC - ventromedial prefrontal cortex
VTA - ventral tegmental area

3. ABSTRACT

Mindfulness, i.e., attention to present moment experience without judgment, has beneficial effects on different aspects of behavior and cognition. For example, it improves psychopathological symptoms related to emotion regulation, anxiety and interpersonal functioning. However, very little is known about the neural correlates of these effects. Existing neuroimaging experiments have shown that both mindfulness and psychiatric disorders manifest as distinct, but partly overlapping patterns in brain activation and functional connectivity in various networks of the brain. Therefore, understanding of the neural correlates of mindfulness and its effect on emotion regulation and learning may elucidate how mindfulness affects cognition, particularly in case of psychiatric disorders. The present dissertation aims at investigating the neural correlates of mindfulness effects on emotion regulation and learning. To this end, I report the results of studies investigating the effect of mindful focused attention to breath on brain activations and functional connectivity during (1) exposure to stimuli with negative valence and (2) classical conditioning. Furthermore, I report studies that investigated (3) the correlates of mindfulness disposition in the brain's intrinsic network architecture and (4) compared it with changes in this architecture in patients with borderline personality disorder, who are known to profit from mindfulness-based treatment. The included studies allow for the following conclusions: (1) mindful focused attention leads to reduced activation of the amygdala during stimulation with aversive pictures and (2) reduced prediction error related signaling in right putamen during conditioning. (3) Trait mindfulness is associated with the functional connectivity between key cognitive networks, i.e., the default mode, salience and central executive networks. (4) Borderline patients showed aberrant within- and between-network connectivity among default mode and salience network which overlapped with effects of mindfulness in dorso-medial prefrontal cortex. These results provide evidence for a potential neural pathway of how mindful focused attention affects emotional processing and learning. Furthermore the results suggest neural mechanisms by which mindfulness may support the treatment of psychiatric disorders, with the example of borderline personality disorder, presumably by improving emotion regulation abilities, rumination tendency and relearning of maladaptive behavior.

4. OVERVIEW

The present Ph. D. dissertation was written in semi-cumulative form. It comprises a general introduction, which is followed by the reports of four brain imaging experiments in form of manuscripts for publication. At the time of thesis submission, one of these papers had been submitted to “NeuroImage” (paper one), one is prepared for submission (paper two), one is under review in “Frontiers in Human Neuroscience” (paper three) and one has been published in “Frontiers in Human Neuroscience”(paper four). The joint discussion summarizes and interprets the findings beyond the scope of the individual manuscripts.

5. INTRODUCTION

The concept of mindfulness has spread from Buddhist tradition into psychotherapy and neuroscience. The aim of this thesis is to connect these fields of research by investigating the neural correlates of mindfulness in the context of its uses in psychotherapy. To this end, the introduction will shed light on the neural effects of *mindfulness* in the context of *emotion regulation* and *learning*, and then take a systems view on the *intrinsic brain networks* that are involved in mindfulness and borderline personality disorder as an example of an affective brain disease.

Since a model of regulation of emotions cannot stand without a theory about emotional processing, I will first present a recent neuroscientific model of emotions and outline traditional approaches for emotion regulation. Next, I will compare these strategies with those provided by mindfulness practice. The role mindfulness plays in psychotherapy is closely related to relearning of emotional responses and regulation strategies. Therefore, the second part of the introduction is dedicated to the neuroscientific basis of classical conditioning and the possible mechanisms how mindfulness may influence learning. The third part will introduce an intrinsic brain network perspective on the processes involved in mindfulness and show, why the study of network interactions may be beneficial in explaining neural effects of mindfulness especially in the context of affective disorders.

5.1 PRACTICAL DEFINITION OF MINDFULNESS AND ITS PSYCHOLOGICAL EFFECTS

A group of leading scientists in the field has developed a practical definition and operationalization for mindfulness (Bishop, Lau, & Shapiro, 2004) that can be generalized to different traditions of mindfulness practice. In this description, mindfulness is seen as a self-regulatory mechanism that monitors attention and orients it towards present experience without judgment. Mindfulness encompasses the way *how* something is done rather that *what* exactly is done. Thus, mindfulness is a meta-awareness skill that can be achieved by mental training. As this training looks back on over two millennia of tradition, multiple techniques to develop this skill have been proposed and are still taught. However, all techniques include instructions on how to allocate attention that can be subdivided into two categories: focused attention (FA) on one object only or open monitoring (OM) of present experience (A. Lutz, Slagter, Dunne, & Davidson, 2008). FA is mostly used to teach novices as it trains the essential skill in mindfulness: staying in the present moment without judgment of good or bad. It involves three crucial abilities of regulating attention: monitoring the focus of attention, disengaging from distracting objects of attention and redirecting attention back to the initial object of attention. With sufficient training, these skills are becoming more and more effortless. In addition, the urge to act on emotions or thoughts, termed emotional reactivity, is reduced with training (e. g., Britton, Shahar, Szepsenwol, & Jacobs, 2012) and substituted with mere observation.

FA has been subject to more extensive research than OM. This may be due to the fact that in contrast to FA, OM is more vaguely defined as sustaining the monitoring feature of attention without engaging it towards a specific object. In other words, OM entails sustaining moment to moment awareness to any experience in the present (A. Lutz, Slagter, et al., 2008). Research into the psychological effects of mindfulness has shown increases in attentional performance, especially selective attention (C. G. Jensen, Vangkilde, Frokjaer, & Hasselbalch, 2012) that might be related to more effective usage of brain resources (Slagter et al., 2007). However, a meta analysis on the psychological effects of mindfulness concluded that the attentional effects were only moderate in magnitude, and that meditation has even stronger effects on personal relationships and emotion regulation (Sedlmeier et al., 2012).

5.2 MINDFULNESS IMPROVES EMOTION REGULATION

Mindfulness has been shown to have beneficial effects on emotion regulation. Emotion regulation describes a variety of strategies that influence the generation of emotions and how these are experienced and expressed (Gross & Thompson, 2007). Evidence for a beneficial effect of mindfulness on emotion regulation is available from both correlational studies using questionnaires (Hill & Updegraff, 2012; Sedlmeier et al., 2012) and those using experimentally controlled conditions (e. g., Arch & Craske, 2006; J. Lutz et al., 2013). The beneficial effects of mindfulness include increased emotional differentiation (Hill & Updegraff, 2012), improved reappraisal skills (Sedlmeier et al., 2012), relaxation (reviewed in Hölzel et al., 2011), and decreased emotional reactivity after meditation (Arch & Craske, 2006). Given these effects of mindfulness on emotion regulation it is unsurprising that psychotherapists included mindfulness practice in a number of structured psychotherapy manuals for disorders of emotion regulation (e. g., for borderline personality disorder, see Linehan, 1993a, for bipolar disorder, see Williams et al., 2008 and for depression, see Luoma, Hayes, & Walser, 2007). In order to understand emotion regulation, it is necessary to get a grip on the processes that underlie emotional processing in general, which I will review next.

5.3 EMOTIONS AS SITUATED CONCEPTUALIZATION

The framework of emotion regulation is embedded into a model of emotion generation. Although most research into emotion regulation has been based on the process model of emotion generation (Gross, 1998), the most extensive model that can be related to the current findings in neuroscience has been formulated by Lindquist and colleagues in a “constructivist model of emotion generation” (for a review, see Lindquist, Wager, Kober, Bliss-Moreau, & Barrett, 2012, Fig.1). The advantage of the constructivist model of emotion generation is that it accounts for the complexity of the emotional experience. In the model, emotions are based on four so called “psychological primitives”, which are smaller building blocks of cognitive functioning: (1) core affect, (2) situated conceptualization of core affect, (3) language and (4) executive attention. Each of these psychological primitives is defined by the processes it implements and by various associated brain regions. While affect in psychology is a term used for anything emotional, core affect describes the mental representations of bodily changes that can be experienced as positive or negative feelings with some degree of arousal. Core affect is associated with brain regions that, among other things, implement visceral control and are involved in processing of salience related to the internal homeostasis: the amygdala, medial orbitofrontal cortex, insula, anterior cingulate cortex, thalamus, hypothalamus, bed nucleus of stria terminalis, basal forebrain and the periaqueductal gray (Lindquist et al., 2012). In short, core affect attaches a label of bodily value to an object. The second psychological primitive, situated conceptualization then connects this label to prior history and experience with the object, in order to categorize it or make meaning of it. As such, this system comprises regions involved in memory and personal value like ventromedial prefrontal cortex (VMPFC), dorsomedial PFC (DMPFC), medial temporal lobe (hippocampus, entorhinal cortex, parahippocampal cortex), and posterior cingulate cortex (PCC) /retrosplenial area, also called the default mode network (e. g., Raichle et al., 2001). Through these regions and in combination with the fourth psychological primitive, executive attention, an object and its associated core affect are combined with prior experience. These effortless and automatic processes result in one experience that could have the quality of a physical symptom (e. g., a rumbling stomach), a feeling (e. g., tiredness), or a discrete emotion (e. g., surprise vs. fear). In other words, conceptualization will produce cognitive appraisals that trigger emotions. In addition, the situated conceptualization network will make inferences about what may have triggered an emotion that has been identified in another person, enabling us to experience empathy or produce a theory of mind (for a neuroscientific review, see Schurz, Radua, Aichhorn, Richlan, & Perner, 2014). The third process in the model, language or emotional words, works closely together with the conceptualization process in order to make emotional categories of what is a very complex phenomenological process, i.e., emotions. This process involves the right anterior temporal lobe and ventro-lateral PFC (VLPFC). While the anterior temporal lobe combines heteromodal information into a representation of a complex category, the VLPFC is associated with semantic processing and categorization of objects. As such, emotional words serve as placeholders for a combination of various experiences, memories and core affects. The fourth psychological primitive, executive attention guides and enhances certain interoceptive feelings and representations of external objects to create a moment of here and now, sustaining the combination of external objects, core affect, and situated conceptualization into one concept of an emotion. Executive attention recruits the dorso-lateral PFC (DLPFC) and VLPFC (reviewed in Lindquist et al., 2012) with lateral parietal regions (Corbetta & Shulman, 2002). In summary, different aspects of emotions are represented in a variety of brain regions. The experience of an emotion is produced by executive attention effortless combining representations of an object with a core affect, and previous experience into an abstract concept.

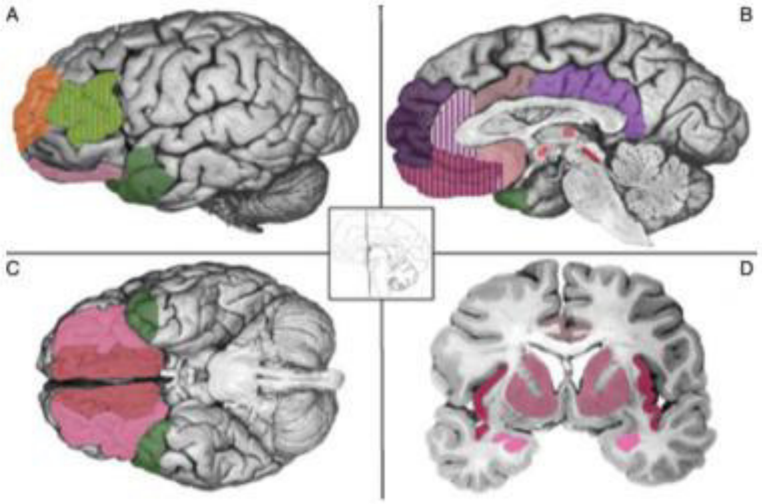

Figure 1. The constructivist model of emotion generation.

The figure shows brain regions that are hypothesized to be involved in the generation of emotion through four psychological primitives. Core affect (pink): amygdala, insula, medial orbitofrontal cortex, anterior cingulate cortex, thalamus, hypothalamus, bed nucleus of the striaterminalis, basal forebrain and periaequedictal grey. Conceptualization (purple): ventromedial prefrontal cortex, dorsomedial prefrontal cortex, medial temporal lobe, posterior cingulate cortex/retrosplenial area. Language (green): ventrolateral prefrontal cortex & anterior temporal lobe. Executive attention (orange): dorso-lateral prefrontal cortex & ventrolateral prefrontal cortex. Image taken from Lindquist et al. (2012), reprinted with the permission of Cambridge university press 2012.

5.4 EMOTION REGULATION AND ITS INTERACTION WITH MINDFULNESS

5.4.1 TYPES OF BENEFICIAL EMOTION REGULATION STRATEGIES

The most prominent beneficial strategies in the literature have been cognitive in nature, such as reappraisal and distraction. In studies evaluating the effectiveness of emotion regulation strategies, reappraisal and distraction are generally contrasted with expressional suppression, that has been shown to be associated with higher emotional, social and cognitive costs (Gross & John, 2003; Gross, 2002). The neural correlates of cognitive emotion regulation strategies have been investigated in a number of studies (e. g., Kanske, Heissler, Schönfelder, Bongers, & Wessa, 2011; McRae et al., 2010; for a review, see Ochsner, Silvers, & Buhle, 2012; Thiruchselvam, Blechert, Sheppes, Rydstrom, & Gross, 2011). Based on these studies, the authors of a recent meta-analysis propose in the “heuristic model of emotion regulation” that cognitive regulation is achieved through a three-step-process that first, signals the need to regulate, then down regulates an emotion and finally, generates a new, regulated, emotional state (Kohn et al., 2013, Fig. 2). In their heuristic model of emotion regulation an emotion is signaled from subcortical regions through anterior medial cingulate cortex (aMCC) into ventro-lateral prefrontal cortex (VLPFC) and insula cortex. These structures evaluate salience and signal the need to regulate to dorso-lateral prefrontal cortex (DLPFC). Then, DLPFC is thought to induce a reenaction of the emotional scene through imagination of motoric, somatosensory and language processing and coherent verbalization via pre-motor areas, angular gyrus and superior temporal gyrus. This new emotional scene leads to a generation of a new emotion in striatum and amygdala either directly or guided through aMCC (Kohn et al., 2013). Thus, this mechanism could represent a general pathway of emotion regulation or be restricted only to cognitive strategies. To investigate this, studies have used also mindfulness based emotion regulation strategies.

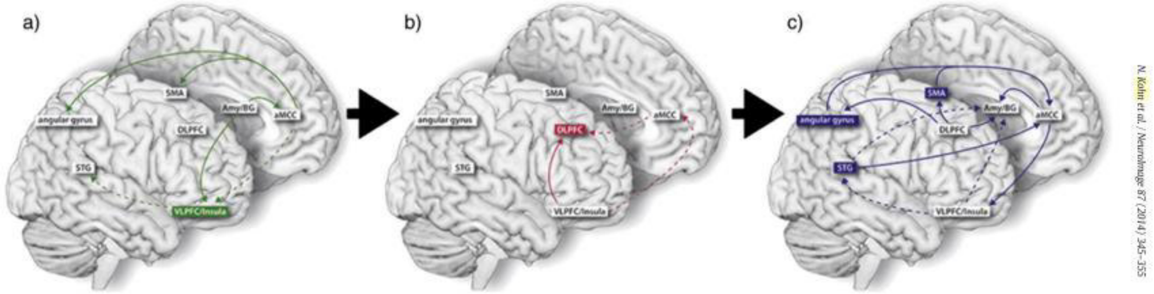

Figure 2. The heuristic model of emotion regulation (Kohn et al., 2013).

Regulation proceeds in three steps. a) VLPFC and insula signal the need for regulation. b) DLPFC induce a reenaction of the emotional scene through motor, sensorymotor and language processing areas, c) striatum and amygdala generate a new regulated emotional state. Image taken from Kohn et al. (2013), reprinted with permission of Elservier.

5.4.2 MINDFULNESS BASED EMOTION REGULATION STRATEGIES

Studies that evaluate mindfulness based strategies have appeared in recent years focusing on trait mindfulness, measured by self-rating questionnaires (Creswell, Way, Eisenberger, &

Lieberman, 2007; Modinos, Ormel, & Aleman, 2010; Schulze et al., 2011), following mindfulness training (Farb et al., 2007; Goldin & Gross, 2010; Hölzel et al., 2013; Taylor et al., 2011) and during non-judgmental awareness of the present moment (J. Lutz et al., 2013). As described earlier, mindfulness provides two definable strategies that can be used as regulation strategies in emotional situations: focused attention (FA) and open monitoring (OM). Emotion regulation based on mindfulness seems to affect emotion regulation on multiple levels. Strategies may have a relaxing effect on the organism (Baer, 2003), might serve as retrieval cue for other cognitive strategies like reappraisal (Treanor, 2011), and can ultimately change one´s attitude towards emotions altogether as described in detail below (reviewed in Chambers, Gullone, & Allen, 2009). Initially, focused attention, for example, on the sensations of breathing, might help disengaging attention from an aversive feeling or a negative thought, thereby facilitating emotion regulation. This strategy can, for instance, be used when first confronted with an aversive stimulus in order to calm one´s mind. Later, reappraisal strategies might come into play. Once a meta-awareness of one´s thoughts is established, other viewpoints of an emotional situation become apparent, which can allow for refocusing on the emotional stimulus for open monitoring practice. This is supported by an improved ability for reappraisal that is associated with dispositional mindfulness (Modinos et al., 2010) and that seems to go hand in hand with mindfulness ability (Garland, Gaylord, & Fredrickson, 2011; Garland, Gaylord, & Park, 2009).

Another effect of mindfulness training lies in the reduction of expressional suppression which by itself could positively affect well-being as it can be replaced by more beneficial strategies (Chambers et al., 2009). Mindfulness training also improves emotional differentiation and reduces negative emotional liability (Hill & Updegraff, 2012). Finally, long-term mindfulness training changes one´s attitude towards emotions: by default most emotions are seen as a phenomenon that requires us to act upon it. However, observing rather than acting upon one´s emotions, can teach that emotions will arise and disappear without any action required. Through this experience, the meditator can understand that emotions do not have to be acted upon, but are simply a phenomenon of the mind. Instead, one can decide which emotions are helpful to one´s goals and only strengthen those selectively (Chambers et al., 2009). These multi-layered effects are difficult to control for as mindfulness is only complete if it entails all its aspects, i. e., control of attention to monitoring of thoughts, sensations and feelings, and development of a non-reactive and observant attitude towards emotions. Multiple tools for measuring different facets of mindfulness have been developed and are currently in use (e. g., Brown & Ryan, 2003; Murakami et al., 2012; Stro, Michalak, & Heidenreich, 2011; Walach, Buchheld, Buttenmüller, Kleinknecht, & Schmidt, 2006). These questionnaires, together with functional magnetic resonance imaging have been used in attempts to understand the neural correlates of the construct of mindfulness during meditation and its effect on emotion regulation, which will be reviewed in the next paragraphs.

5.4.3 NEURAL CORRELATES OF MINDFULNESS

Research on mindfulness is faced with a number of problems that have led to different approaches in identifying brain regions involved in mindfulness. First and foremost, there is no gold-standard control condition for any mindful state. This problem worsens with increasing expertise in mindfulness, as it is assumed that highly trained individuals do not fall back into a "normal" mode of brain function since their brains already have undergone plastic changes related to mindfulness training (Hölzel et al., 2008). Studies indicate that there is a difference in brain activation for beginners and experts (Brefczynski-Lewis, Lutz, Schaefer, Levinson, & Davidson, 2007; Brewer et al., 2011; Taylor et al., 2011). Therefore, researchers have tried to study mindfulness naïve subjects or those with only moderate amount of training. In addition to studying beginners and experts, other studies have tried to define a personal trait or skill in mindfulness through questionnaires and correlated those scores with brain activation and behavior.

5.4.3 NEURAL CORRELATES OF MINDFULNESS MEDITATION IN BEGINNERS

A number of studies investigated the neural correlates of mindfulness in beginner meditators. As described above, the technique in teaching mindfulness to novices involves FA to one stimulus, for instance the sensations of breathing. Focused attention in novices is related to activation of a large network of regions including fronto-parietal attention network, regions of the medialPFC, insula and subcortical areas (Brefczynski-Lewis et al., 2007; Dickenson, Bferkman, Arch, Liebermann, & Lieberman, 2013; Farb, Segal, & Anderson, 2013; Hasenkamp, Wilson-Mendenhall, Duncan, & Barsalou, 2012). There is also evidence, for a deactivation of areas of the default mode network during FA (Farb et al., 2013). Dickenson et al. (Dickenson et al., 2013) found that focused breathing compared to mindwandering activated a network of structures located in the temporoparietal junction (TPJ), insula, the DMPFC, and dorsal anterior cingulate cortex (dACC), together with deactivation of regions of the default mode network (DMN, for a review, see Buckner, Andrews-Hanna, & Schacter, 2008), mainly the medial PFC. Similarly, when non-meditators were asked to concentrate on a visual stimulus, they activated a big network of regions including fronto-parietal cortices, the insula, thalamic nuclei, basal ganglia, and the cerebellum (Brefczynski-Lewis et al., 2007). In addition, Farb and colleagues (2013) found that after 10 days of intense meditation training, participants deactivated DMPFC during FA and showed changed connectivity between the posterior insula and DMPFC during focus on body sensations. In a methodologically interesting study, Hasenkamp and colleagues (2012) were able to show that meditation involves four different phases that each is associated with activation of different brain regions. Focus on the sensation of breathing was associated with activation in DLPFC. During mind wandering, participants showed activation of the DMN. Awareness of mind wandering was associated with activation of areas of the salience network (Seeley et al., 2007), and shifting attention back to the sensation of breathing required activation of the inferior parietal and DLPFC. Together, these data indicate that focused attention in beginners is associated with activation of parietal and frontal areas involved in the direction of attention, together with the insula, the ACC and subcortical structures.

5.4.4 NEURAL CORRELATES OF MEDITATION IN EXPERT MEDITATORS

Expert meditators are people who have been practicing meditation from 1.5 to 60 years. Most studies recruited their subjects from monasteries or other institutions that implement meditation in their daily lives. For these individuals, meditation is one of the most trained activities and therefore presumably an easy state to achieve and sustain. Less brain regions seem to be necessary and activation is usually seen in subcortical regions. For example, Bearentsen and colleagues (2010) found that the onset of meditation was characterized by activation of the putamen and the supplementary motor area together with a deactivation of occipital regions. During sustained meditation, a network of regions in the right hemisphere showed deactivations including the insula, middle temporal gyrus, and precentral gyrus. The authors concluded that the onset of meditation was implemented in cortico-striatal-thalamico-cortical loops. Interestingly, the authors also found a network involved in attentional control that showed increased functional connectivity during meditation (Baerentsen et al., 2010). Another study by Guleria, Kumar, Kishan, and Khetrapal (2013) investigated meditation based on mantra citation compared to visual identification of shapes. Results showed increased activation of left DLPFC, inferior frontal gyrus, supplementary motor area and the precuneus. The authors interpreted their activation as control of attention and working memory (Guleria et al., 2013). Similarly, Brefczynski-Lewis et al. (2007) found an inverted u-shaped curve of brain activity in areas involved in sustained attention as a function of meditation expertise. It is difficult however, to compare studies of expert meditators as the traditions and techniques of meditation differ from each other. The details in technique might have less impact on activations in beginners than in experts, because beginners are faced with more basal problems like sustaining attention.

With a higher consistency, studies have found deactivations of regions belonging to the DMN (Brefczynski-Lewis et al., 2007; Brewer et al., 2011; Hasenkamp et al., 2012; Ives-Deliperi, Solms, & Meintjes, 2011). For example, Brefczynski-Lewis et al. (2007) found deactivations of the default mode network during concentration meditation (similar to FA). Similarly, Ives-Deliperi et al. (2011) found decreases in activation regions of the DMN for OM meditation compared to random generation of numbers. In detail, they found deactivations in both anterior and posterior midline structures of the DMN, which are related to mind wandering, together with an activation of the PCC. Brewer and colleagues (2011) found that experienced meditators deactivated regions within the DMN independently of the used meditation technique. However, in contrast to most other studies, Hölzel et al. (2007) found greater activation of medial PFC /anterior cingulate regions in experienced meditators compared to non-meditators when comparing meditation with an arithmetic task. Hasenkamp et al. (2012) found that expert meditators showed a decreased likelihood of mind wandering during focused attention together with decreased activation in prefrontal, insula and subcortical regions during shifting of attention back to the sensations of breathing. In addition, they found that for experts, the VMPFC showed a quick return to baseline activation after a switch of attention was initiated, while beginners showed sustained activation even after initiation of a switch. The VMPFC is involved in processing of personal value (Legrand & Ruby, 2009). The authors speculated that the return to baseline in activation of this region might be related to the non-judgmental stance in mindfulness that for beginners is often hard to maintain after realization of mind wandering (Hasenkamp et al., 2012). In summary, although studies show a remarkable amount of inconsistencies, expertise in meditation is characterized by a deactivation of areas of the DMN and the insula that could be related to reduced judgmental processing, together with more efficient top-down control of sustained attention in prefrontal regions.

5.4.5 NEURAL CORRELATES OF PRACTICE TIME AND EXPERTISE

In an attempt to bridge the findings from beginners and experts and follow the trajectory in the development of expertise, some studies have tried linking brain activations with mindfulness practice time. In an activation likelihood estimation meta-analysis, the authors distinguished between beginners and expert meditators (Tomasino, Fregona, Skrap, & Fabbro, 2012). Their analysis indicated the superior parietal lobule as overlapping area between beginners and experts. In addition, beginners showed activation of the superior medial gyrus and inferior parietal lobule, while experts relied on activation in supplementary motor area and supramarginal gyrus, which supports the hypothesis of reduced need for executive control in experts. In addition, Brefcynski-Lewis et al. (2007) found an expertise related negative correlation between hours of practice and brain activation in a number of regions, including inferior frontal gyrus, middle frontal gyrus and DLPFC, bilateral insula, posterior superior temporal gyrus and left globus pallidus during meditation. The authors interpreted these results as an indication of increased processing efficiency due to increased proficiency with time. Interestingly, the authors also presented distracting sounds during meditation and found that activation in medial PFC and amygdala was negatively correlated with hours of practice. These results underline the interpretation of regions involved in executive functions and attention regulation showing plasticity effects related to skill-learning for mindfulness (Brefczynski-Lewis et al., 2007). Similarly, Hasenkamp and colleagues (2012) found a negative correlation between mindfulness practice and activation in a variety of regions during the shift of attention from mind wandering back to the sensation of breathing. This might indicate a greater ease for the reallocation of attention with practice. In summary, results suggest that with expertise, activations within regions involved in executive and attentional control show a reduction of activation during meditation, allowing for a longer, more effortless and less distractible form of meditation.

5.4.6 NEURAL CORRELATES OF TRAIT MINDFULNESS

As noted above, meditation practice results in skill-learning related plasticity. Yet, the concept of mindfulness does not only relate to meditation practice, but can also be measured using self-rating questionnaires (Brown & Ryan, 2003; Murakami et al., 2012; Stro et al., 2011; Walach et al., 2006). However, the results should be interpreted with caution, since experts from the philosophical field of mindfulness have criticized these attempts at measuring mindfulness as incomplete and far from Buddhist understandings, advising towards interview approaches instead (Grossman & Van Dam, 2011). Nevertheless, a number of studies have used questionnaires to find correlates of mindfulness ability or trait mindfulness. Interestingly, these correlations are generally found in areas involved in emotional processing, like medial PFC and the amygdala during a variety of tasks. Creswell et al. (2007) found more widespread activation of prefrontal regions together with reduced activation of the amygdala associated with higher trait mindfulness during affect labeling. Similarly, Frewen and colleagues (2010) observed a correlation of trait mindfulness with activation of the amygdala and medial PFC during emotional imagery. In another experiment, Modinos et al. (2010) found that trait mindfulness was related to activation of the DMPFC during reappraisal of negative emotional stimuli and Brown and colleagues (2013) found lower late positive potentials, a marker of emotional arousal, in more mindful individuals in response to emotional pictures. In addition, Way and colleagues (2010) found that trait mindfulness was negatively correlated with activation of areas involved in self-referential processing and the amygdala. Together, these data indicate that trait mindfulness is associated with lower emotional reactivity and improved emotion regulation ability that could be mediated by lower amygdala responsively and increased activation of the medial PFC.

5.4.7 NEURAL CORRELATES OF MINDFUL EMOTION REGULATION

One of the strongest effects of mindfulness training is an increase in emotional competence (Sedlmeier et al., 2012). For example, Burg and Wolf (2012) devised a task that tests the ability to stay focused on the present moment. They found that this ability correlated with decreased frequency of brooding rumination. As outlined above, mindfulness strategies can be divided into FA and OM, which both have been shown to effectively regulate emotions (Arch & Craske, 2006; J. Lutz et al., 2013). These regulation effects have also been studied using fMRI. Studies mostly report neural differences before and after an 8 week training course in mindfulness based stress reduction (MBSR) and employ FA together with aversive emotional stimulation. Overall, studies report regulatory activations in the right insula and medial PFC or the ACC (Farb et al., 2007; P. Goldin, Ziv, Jazaieri, & Gross, 2012; Zeidan et al., 2011, but see Haase et al., 2014) and some a reduction in amygdala activation for novices and a reduction in DMN activation for experts (Desbordes et al., 2012; Taylor et al., 2011). For example, Farb and colleagues (2010) studied sadness provoking films and found that participants that had followed an 8 week course of MBSR were resistant against sadness related deactivations in insula, right lateral PFC, subgenual ACC and activations in language areas, and the precuneus. The authors also noted a correlation between strength of deactivation of the right insula and depression scores. These results suggest that mindfulness training alters the cortical reactions to sadness including more interoceptive and less language processing. In addition, soldiers that were exposed to an aversive breathing load, in which a devise makes it harder and uncomfortable to breathe in order to induce stress, showed reduced right insula and ACC activation (Haase et al., 2014). These studies emphasize the role of the insula and the ACC, two hubs of the salience network, which is hypothesized to play a role in alerting attention to stimuli with importance for homeostatic salience (Seeley et al., 2007). Another study, involved breath focused meditation in the presence of painful stimulation (Zeidan et al., 2011). After four days of minimal mindfulness training, activation in the orbitofrontal cortex was associated with reductions in pain unpleasantness. Additionally, the same authors found that activation in a network of medial frontal, orbitofrontal, and dorso-medial frontal regions was associated with a reduction in anxiety after breathing meditation (Zeidan, Martucci, Kraft, McHaffie, & Coghill, 2014). These studies indicate the involvement of medial PFC and orbitofrontal cortex in emotional processing during FA meditation.

In an influential study, Farb et al. (2007) investigated the neural correlates of two distinct forms of self reference: narrative and experiential focus. Narrative focus was defined as the default setting of the mind, while experiential focus emphasizes current experience and is promoted by mindfulness training. Results suggest that experiential focus is associated with a deactivation of midline structures and activation of a right lateralized attention network together with visceral processing regions like the right insula. In addition, they noted that the narrative focus was characterized by a coupling between the right insula and medial PFC that was reduced during experiential focus in participants that had participated in MBSR training. Other studies reported an additional deactivation within the amygdala for novices that was related to lower aversive valence scores (Desbordes et al., 2012; Taylor et al., 2011).Thus, it seems that mindfulness related emotion regulation is linked to deactivations in the amygdala and activations in insula, DMPFC and orbitofrontal cortex, which might be associated with experiential focus.

As noted above, the neural correlates of mindfulness seem to change with the amount of practice. This observation seems to hold true also for effects on emotion regulation. For example, in one study, experienced meditators showed deactivation within the hubs of the default mode network when presented with emotions during a mindful state, while beginners showed activation in a fronto-parietal network together with amygdala suppression (Taylor et al., 2011). How can we explain this difference in brain activations between experts and novices? One possible answer was given in a review on attentional allocation during mindful emotion regulation (Chiesa, Serretti, & Jakobsen, 2013).The authors suggested that novices use top-down attentional control during mindfulness, while experts rely on bottom-up attentional mechanisms. The notion of amygdala deactivation however is still an object of debate, because mindfulness strictly teaches observant attention even to negative experiences instead of avoidance. Amygdala deactivation might be a transient effect only seen in novices that may be due to strong top-down control of attention and focus of attentional resources on perceptional input with continuous monitoring of mind wandering (Brefczynski-Lewis et al., 2007; Hölzel et al., 2011). According to this idea, continuous practice could lead to more efficient monitoring, leaving additional resources for the full experience of emotions. In summary, the neural correlates of focused attention revolve around deactivation of the amygdala with activations in fronto-parietal regions and right insula in beginners and deactivation of the DMN in experts.

OM is a strategy that is generally employed only by advanced mindfulness practitioners as it requires greater skill in monitoring of mind wandering. Only one study has investigated the neural correlates of emotion regulation effects of OM in meditation naive subjects and also found amygdala deactivation (J. Lutz et al., 2013). However, no study has directly investigated the neural correlates of emotion regulation of aversive pictures by FA in early mindfulness practitioners during the acquisition of their focused attention skill. In paper one, I report a study, which tried to elucidate the neural processes that underlie these emotion regulatory effects of FA in participants receiving only two weeks of 20 minutes daily training in FA.

5.5 LEARNING EFFECTS OF MINDFULNESS MEDITATION

Another aspect of the emotional experience and its regulation is learning. Regulation strategies are learned throughout life from one´s parents and peers (Gross & Thompson, 2007). For example, a mother might reinterpret an emotional situation for her child in order to change its emotions, thereby teaching cognitive change (“I know you are scared of that barking dog, but it was just barking at the pigeons over there, not at you.”). A supportive and accepting philosophy of parents towards emotions has been shown to positively affect children´s emotional coping efficacy (Gross & Thompson, 2007). Effective emotional coping and emotion regulation strategies are associated with lower incidents of affective disorders like depression and anxiety disorders, while patients suffering from an affective disorder mostly employ ineffective regulation strategies like rumination and avoidance (Aldao, Nolen-Hoeksema, & Schweizer, 2010).

Mindfulness training has been shown to have a beneficial effect on anxiety and other emotion regulation disorders (Baer, 2003; Goldin & Gross, 2010; Hofmann, Sawyer, Witt, & Oh, 2010). While one of these effects is improved emotional competence as described above, it has been hypothesized that mindfulness training can alter learning related processes, for example, being a retrieval cue for emotion regulation strategies and extinction cues (Hölzel et al., 2011; Treanor, 2011). Additionally, a recent review summarized current evidence that shows how mindfulness and extinction processes overlap, but pointed out that evidence is still scarce (Tang, Hölzel, & Posner, 2015). Only one study exist that investigated the neural effects of mindfulness training on learning (Kirk, Montague, Mascaro, & Montague, 2015). Thus, questions remain about how mindfulness may interact with learning and which processes exactly are targeted by mindfulness. The next paragraphs will deal with an imaging perspective of the neuroscience behind the most basic learning processes and the possible interactions between mindfulness and learning.

5.5.1 PREDICTION ERRORS AS THE BASIS OF LEARNING AND LEARNING OF EMOTION REGULATION

One major component of learning is the ability to predict future states of the world. This remarkable ability possessed by both animals and humans alike has been thought to be the task of the telencephalon (Friston, 2005). According to this theory, the brain tries to reduce surprises by predicting sensory inputs and comparing the predictions to actual sensory information resulting in an prediction error signal that shapes learning for future events (den Ouden, Kok, & de Lange, 2012). Evidence in favor of this theory has been found in perception and action as well as in language, memory, cognitive control and motivational value processing (reviewed in den Ouden et al., 2012). One of the most basic learning processes is classical conditioning, in which a conditioned stimulus (CS), for instance a bell, is associated with an unconditioned stimulus (US), for example, food. Researchers have been trying to predict learning related processes using computational models (reviewed by Niv & Schoenbaum, 2008). The Rescorla-Wagner model (Rescorla & Wagner, 1972) is one of the oldest and simplest models for classical conditioning that is still used in neuroscience today. The model assumes that an organism tries to predict future rewards and punishments from previous experience. Probabilities of events (Predictions, V) are computed based on earlier made prediction errors (PE) and real events (R). PEs are computed based on the Rescorla-Wagner rule shown in formula 1 and 2.

$$\text{Formula 1: } V_t = P_{t-1} \times U_t$$

$$\text{Formula 2: } P_t = P_{t-1} + \lambda(R_t - V_t) \times U_t,$$

In these formulas, V_t is the predicted outcome of trial t and R_t is the actual outcome of trial t. The parameter U stands for different CS that can be provided in an experiment. Furthermore, P_t stands for the update of prediction at trial t, which depends on the prediction error (PE_t in formula 3) from the previous trial t-1 multiplied by the learning rate (λ). The learning rate determines how much information is retained from one trial to another, thus determining the speed of learning. The PE of trial t is the difference between the prediction (V_t) and the real outcome (R_t), described in formula 3:

Formula 3: $PE_t = (R_t - V_t)$.

The model can explain learning during acquisition, extinction, and a variety of learning phenomena like blocking (Kamin, 1969), overshadowing (Reynolds, 1961) and conditioned inhibition (Konorski, 1949; Rescorla & Lolordo, 1965). The most important parameter in models that predict learning is the PE that gives the difference between a prediction and the actual outcome. This difference (PE) will then change future predictions in order to make them more accurate. Using these learning models, imaging experiments have been able to identify brain regions that implement specific mathematical processes namely, computations related to the prediction error.

5.5.2 BRAIN REGIONS CODING PREDICTION ERRORS

Prediction error signals have been found in almost every brain region (reviewed by Niv & Schoenbaum, 2008). However, the main structures implied in reward and punishment prediction error signaling during conditioning are the striatum and the anterior PFC (for a meta-analysis, see J. Garrison, Erdeniz, & Done, 2013). The striatum, for instance, coded the prediction error for visual prediction of a discrimination task (den Ouden, Daunizeau, Roiser, Friston, & Stephan, 2010) and coded incidental learning of predictive auditory cues in a visual detection task (den Ouden, Friston, Daw, McIntosh, & Stephan, 2009). During classical conditioning, conditioned stimuli can be paired either with a reward or punishment. Prediction error signals belonging to these events have been shown to be coded by three different sources of cells in rats (Bromberg-Martin, Matsumoto, & Hikosaka, 2010). Activation of these cells within the substantia nigra and tegmentum is related to prediction errors indicating either reward, punishment or both (i.e., salience; Bromberg-Martin et al., 2010; Lammel et al., 2012; Lammel, Ion, Roeper, & Malenka, 2011; Lammel, Lim, & Malenka, 2014; Volman et al., 2013). Furthermore, corresponding fMRI experiments have found similar activations for PE signaling in humans within the striatum

(Delgado, Li, Schiller, & Phelps, 2008; J. Garrison et al., 2013; J. Jensen et al., 2007; Metereau & Dreher, 2013). These studies indicate that a possible modulation of prediction errors will probably be apparent within the striatum signaling PE signals related to reward, punishment and salience.

5.5.3 MODULATION OF PREDICTION ERRORS

Assuming that mindfulness training might influence learning related processes, this should be apparent in PE signaling during classical conditioning in the striatum. Indeed, fMRI experiments have shown that other emotion regulation strategies can modulate PE signals within the striatum (Delgado, Gillis, & Phelps, 2008; Staudinger, Erk, Abler, & Walter, 2009; Staudinger, Erk, & Walter, 2011). In their study, Delgado, Gillis & Phelps (2008) used a classical conditioning paradigm training subjects to expect a monetary reward following a blue square but not following a yellow square. Further, subjects were asked to either simply attend or regulate their emotions related to the squares (their expectation). During the regulation condition, both skin conductance measurements and PE signaling within the striatum were reduced compared to the attend condition. Their data indicate that emotional distancing from a conditioned stimulus can influence learning related computations within the striatum (Delgado, Gillis, et al., 2008). In another recent experiment, Kirk, Montague, Mascaro and Montague (2015) showed that mindfulness also can modulate reward PE signals during conditioning. However, similar evidence is missing for punishment related data (i.e., for an aversive PE) especially for mindfulness based emotion regulation strategies. In paper two, I report an experiment, in which we posed the question whether mindful attention to breath can influence aversive PE related signaling within the striatum during aversive classical conditioning.

5.6 RESTING STATE NETWORKS INVOLVED IN MINDFULNESS TRAINING

As described above, mindfulness training has been shown to recruit a number of brain regions. These include mainly prefrontal, parietal and subcortical brain areas (Creswell et al., 2007; Dickenson et al., 2013; Frewen et al., 2010; Hasenkamp et al., 2012). For example, Dickenson et al. (2013) found activations in DMPFC, ACC, insula, and TPJ during a controlled focused breathing task. This pattern of wide spread brain regions warrants a model of brain function that focuses on the interplay between brain networks rather than individual brain regions (Bullmore &

Sporns, 2009). Neural networks have been identified that serve as the neural basis for a variety of cognitive processes, for example, the executive attention network (Corbetta & Shulman, 2002) or the default mode network (Raichle et al., 2001). These findings combined with the advent of the resting state analysis of brain function have led to the definition of a number of intrinsic networks that show a similar pattern during rest and goal directed behavior (Smith et al., 2009).These intrinsic brain networks are usually defined by coherent synchronized ongoing activation during rest in frequencies below 0.1 Hertz and form functional connectivity networks when analyzed by correlational methods (Raichle et al., 2001). Resting state networks have shown changes in connectivity related to learning (Lewis, Baldassarrea, Committeria, Romania, & Corbetta, 2009) and in psychopathology (e. g., in depression, see Sheline, Price, Yan, & Mintun, 2010, or borderline personality disorder, Doll et al., 2013). As such, resting state connectivity may serve as a biomarker for changes in brain function (Greicius, 2008).

Recently, meditation by attention to breath has been shown to involve different brain states, that are associated with distinct cognitive processes and patterns of brain activations (Hasenkamp et al., 2012). These brain activations were located within three different brain networks that can be identified also during resting state: the central executive attention network (Dosenbach et al., 2007) was associated with focus on the breath, the default mode network was associated with mind wandering and the salience network (Seeley et al., 2007) was activated during awareness of mind wandering. A resting state analysis of the same subjects revealed differences in functional connectivity in meditators with high vs. low experience in meditation (Hasenkamp & Barsalou, 2012). The authors described increases in connectivity for individuals with more experience within attentional networks and between lateral parietal attention regions and medial prefrontal cortex (Hasenkamp & Barsalou, 2012). The mean mindfulness experience of groups in the studies cited above ranged between 450 to 3066 h of meditation, i.e., participants were clear experts in mindfulness. Few studies have investigated connectivity changes in mindfulness within the default mode, salience and central executive networks (Berkovich-Ohana, Glicksohn, & Goldstein, 2013; Hasenkamp & Barsalou, 2012; Kilpatrick et al., 2011; Shaurya Prakash, De Leon, Klatt, Malarkey, & Patterson, 2013; Taylor et al., 2013). These studies reported increased connectivity within the medial PFC (Hasenkamp & Barsalou, 2012), and between medial PFC and the posterior insula (Brewer et al., 2011). However, most studies focused on within network connectivity. Only two studies systematically reported between network connectivity changes related to mindfulness (Froeliger et al., 2012; Kilpatrick et al., 2011). This is surprising since recent results indicate between network interactions as critical for the transitions between states of focus and mind-wandering during FA meditation for expert meditators (Hasenkamp & Barsalou, 2012). In the study reported in paper three, we reasoned that changes in connectivity might already be present after much less experiences and thus analyzed resting state brain connectivity after only two weeks of 20 minutes daily training in attention to breath.

5.7 CHANGED RESTING STATE CONNECTIVITY IN PSYCHIATRIC DISORDERS – EXEMPLIFIED IN BORDERLINE PERSONALITY DISORDER

Borderline personality disorder (BPD) is a pervasive disorder that affects social relations, self image, impulsive behavior, emotional processing and their regulation (Leichsenring, Leibing, Kruse, New, & Leweke, 2011). It is associated with substantial suffering for the patients (Oldham, 2007) and produces immense treatment costs (Torgersen, 2005). Mindfulness is one essential part of the dialectic behavioral therapy that has been proven effective in the treatment of borderline personality disorder (Kliem, Kröger, & Kosfelder, 2010). The therapy comprises modules that teach the observant and non judgmental attitude of mindfulness using attentional exercises that focus on the perception of body and mind (Linehan, 1993b). As described above, mindfulness is associated with changes in connectivity network architecture. Similarly, borderline personality disorder has been shown to be characterized by changes in connectivity networks within the DMN, CEN (Wolf et al., 2011). It has been suggested that the network architecture of connectivity networks may be a biomarker of psychiatric disorders (Greicius, 2008). However, the connectivity within the SN and the inter-iFC between above mentioned key cognitive networks, i.e., DMN, SN and CEN, has not been investigated. In paper four, I report a study that investigated this question focusing a unifying theory of resting state networks that are affected in affective disorders (Menon, 2011). A better understanding of the interactions of these networks may not only help the comprehension of the mechanisms behind borderline personality disorder, but also how mindfulness may support the treatment of this disorder.

5.8 SUMMARY AND AIMS OF THE THESIS

In summary, mindfulness is an old tradition that only recently has caught the attention of cognitive neuroscientists. The aim of this dissertation is to provide a comprehensive and in depth investigation of brain processes involved in mindfulness for novices in order to generate predictions and hypotheses pertaining to the efficacy of mindfulness in the treatment of affective disorders. The interactions of mindfulness and psychotherapy will be relevant, in three subfields of neuroscience: emotion regulation, learning and resting state connectivity, which each poses different questions: (1) what are the neural correlates of FA and OM meditation and their effects on emotional and attentional processing? (2) How do neural processes between mindfulness meditation and learning interact? (3) What are the effects of mindfulness on functional connectivity, particularly between key cognitive networks? The present dissertation aims at answering parts of these questions with three experiments that are reported next in manuscript form. After that I report a study on the inter iFC of key cognitive networks in BPD, which will serve as an example on how resting state networks that are involved in mindfulness overlap with those, which are affected in psychiatric disorders.

6. PAPER ONE: MINDFUL ATTENTION TO BREATH REGULATES EMOTIONS VIA INCREASED AMYGDALA-PREFRONTAL CORTEX CONNECTIVITY

This paper comprises the report of an experiment that investigated the neural correlates of mindful breathing effects on visual-emotional stimulation. The paper was written as a manuscript meant for publication in a brain imaging journal and has been submitted to “NeuroImage” at the time of thesis submission. The following authors were involved in the creation of this manuscript: Anselm Doll, Britta K. Hölzel, Satja Mulej Bratec, Christine C. Boucard, Xiyao Xie, Afra Wohlschläger and Christian Sorg. The author of this thesis contributed to the idea of the experiment (together with C. Sorg and A. Wohlschläger) and performed both data acquisition (together with C. C. Boucard) and –analysis (together with S. Mulej Bratec). Writing all parts of the manuscript was also performed by the author of the thesis, while co-authors were involved in the editing of introduction, methods, results and discussion.

Title:

MINDFUL ATTENTION TO BREATH REGULATES EMOTIONS VIA INCREASED AMYGDALA-PREFRONTAL CORTEX CONNECTIVITY

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ABSTRACT

Mindfulness practice is beneficial for emotion regulation; however, the neural mechanisms underlying this effect are poorly understood. The current study focuses on effects of attention-to-breath (ATB) as a basic mindfulness practice on aversive emotions at behavioral and brain levels. A key finding across different emotion regulation-strategies is the modulation of amygdala and prefrontal activity. It is unclear how ATB relevant brain areas in the prefrontal cortex integrate with amygdala activation during emotional stimulation. Given this background, we investigated how ATB-induced brain activation patterns in amygdala and prefrontal areas change when emotional stimulation is applied. We proposed that, during emotional stimulation, ATB down-regulates activation in the amygdala and increases its integration with prefrontal regions. To address this hypothesis, 26 healthy controls were trained in mindfulness-based attention-to-breath meditation for two weeks and then stimulated with aversive pictures during both attention-to-breath and passive viewing while undergoing fMRI. Data were controlled for breathing frequency. Results indicate that (1) ATB was effective in regulating aversive emotions. (2) Left dorso-medial prefrontal cortex was associated with ATB in general. (3) A fronto-parietal network was additionally recruited during emotional stimulation. (4) ATB down regulated amygdala activity and increased amygdala-prefrontal integration, with such increased integration being associated with mindfulness ability. Results suggest amygdala-dorsal prefrontal cortex integration as a potential neural pathway of emotion regulation by mindfulness practice.

INTRODUCTION

Mindfulness practice is beneficial for the ability to regulate emotions (Goldin and Gross, 2010; Hölzel et al., 2013; Taylor et al., 2011). For example, only 15 minutes of focused attention-to-breath (ATB) practice reduces negative emotions of subsequently shown aversive pictures (Arch and Craske, 2006). Mindfulness refers to attending to present moment experience and allowing emotions and thoughts without judgment (Bishop et al., 2004). Mindfulness practice is associated with a reduction in psychiatric symptoms particularly in disorders of emotion regulation such as major depressive or anxiety disorders (Aldao et al., 2010; Baer, 2003; Hofmann et al., 2010). Emotion regulation describes a variety of strategies that can influence which emotions arise, when and how long they occur, and how these emotions are experienced and expressed (Gross and Thompson, 2007). Imaging experiments have revealed aberrant brain mechanisms underlying deficiencies in emotion regulation, e.g., in depression (Heller et al., 2009; Johnstone et al., 2007), anxiety (Etkin and Wager, 2007), and bipolar disorder (Phillips et al., 2008). Due to the relevance of mindfulness practice for emotion regulation, particularly in neuropsychiatric disorders of impaired emotion regulation (Goldin and Gross, 2010; Hayes and Feldman, 2004; Way et al., 2010), it is important to understand the neural mechanisms of the effects of mindfulness practice on emotion regulation. The current study focuses on the effects of mindfulness practice on aversive emotions at the level of behavior and brain activation by using ATB as a paradigm for mindfulness practice. ATB is a basic technique of focused attention meditation practice often used first to teach novices in mindfulness practice, and is also typically applied by trained mindfulness practitioners in order to regulate their emotions in stressful situations even years after training (Kabat-Zinn et al., 1987). Therefore, the analysis of neural correlates of ATB effects on emotions appears a relevant paradigm to elucidate brain mechanisms important for the link between mindfulness practice and emotion regulation.

Several studies have investigated the neural correlates of focused attention meditation in general, and ATB in particular (Brefczynski-Lewis et al., 2007; Dickenson et al., 2013; Hasenkamp and Barsalou, 2012; Hölzel et al., 2007). These studies reported the involvement of brain regions related to attentional control, such as activation of a fronto-parietal network in novice meditators (Dickenson et al., 2013), greater activation of anterior cingulate regions in experienced meditators compared to non-meditators (Hölzel et al., 2007), and an inverted u-shaped curve of brain activity in areas involved in sustained attention as a function of meditation expertise (Brefczynski-Lewis et al., 2007). Few studies investigated neural correlates of focused attention mediation and ATB directly in the context of emotion regulation. During different emotional contexts, these studies showed relatively increased activation of temporo-parietal junction, pre- and postcentral gyri, right insula, medial and lateral dorsal PFC (Farb et al., 2007; Taylor et al., 2011) and – in most cases - down regulation of amygdala activity (Farb et al., 2007; Taylor et al., 2011; Zeidan et al., 2011). However, while these studies indicate the involvement of prefrontal areas and the amygdala in emotion regulation effects of ATB, some points remain unclear. First, it is incompletely understood how brain states of ATB such as increased prefrontal and decreased amygdala activations interact with emotional stimulation. ATB is a typical state of mindfulness practice, which might be modulated by emotional stimulation on the one hand and act on stimulation processes on the other. So far, no study has directly compared activations during stimulation with those of no stimulation. Second, it is unclear how, during emotional stimulation, ATB relevant fronto-parietal areas integrate with amygdala activation. Amygdala activity is involved in negative emotions and, during emotion regulation, this activity is directly or indirectly controlled by prefrontal cortex activity (Davidson, 2002; Sotres-Bayon et al., 2004). Since ATB has potential effects on breathing frequency, which might itself exert an influence on emotion regulation, we controlled all data for breathing frequency. Previously, only one study controlled for breathing frequency during meditation (Zeidan et al., 2011).

In the current study, we focused on these questions about neural mechanisms of ATB in the context of emotion regulation. We hypothesized first that brain activation effects of ATB and visual-emotional stimulation interact in prefrontal areas and amygdala. Secondly, we propose that, during emotional stimulation, ATB down-regulates activation in the amygdala and increases its integration with prefrontal regions, independently of effects on breathing frequency. To test these two hypotheses, healthy participants were stimulated with aversive pictures during functional MRI and instructed to either mindfully attend to their breath or to passively view the images. To ensure that participants were able to focus their attention on the breath, this technique was trained for two weeks before the experiment. Neural outcome measures were both blood-oxygenation-level-dependent (BOLD) signals for brain activation and emotion-related BOLD functional connectivity for amygdala integration during visual-emotional processing (i.e., psycho-physiological interaction analysis, PPI). The relationship of brain activation with both regulation success on emotional valence ratings and dispositional mindfulness scores was assessed via correlation analysis. ATB effects on breathing frequency were controlled via linear regression.

MATERIALS AND METHODS

Participants. 29 right handed healthy volunteers with no previous experience in meditation or yoga participated in the study. Three participants had to be excluded from the study (two stopped the training, one fell ill during training) leaving us with a total sample of 26 subjects (10 males, mean age (± SD) = 26.9 ± 4.6). The study was approved by the ethical committee of the Technische Universität München. All participants provided written informed consent prior to the experiment and received a monetary compensation of expenses for participation. All participants had normal or corrected-to-normal vision, no history of neurological or psychiatric disorders, and reported no intake of psychotropic medication.

Experimental Procedure.

Overview. For the two weeks prior to the scanning session, all subjects performed 20 minutes of daily audio-guided training of ATB. The ATB training was supervised by an experienced meditation teacher (CB). Once a week, participants were invited to the Klinikum rechts der Isar to ensure compliance and provide the opportunity to ask questions. At the end of the two-week training period, participants were scanned in an fMRI scanner while performing a task involving the presentation of negative emotional pictures with and without ATB. Prior to scanning, subjects were introduced to the experimental task to make sure they understood instructions correctly.

Instruction for attention-to-breath (ATB). Mindfulness instructions were presented during two meetings. In the first meeting two weeks before the experiment, the experiment and the instructions for focused attention-to-breath were explained. Instructions were taken from a published instructional mindfulness audio program (Hölzel, 2012). Of this program, we only used the first meditation technique, ATB. Instructions included becoming aware of body posture, focus on the sensations of breathing (i.e., in the belly or underneath the nose), accepting the sensations of breathing as they are in the present moment and returning the focus of attention back to the sensations after digression of thoughts. After one week, participants were invited for a second meeting to ask questions and give feedback. During the two presence-training sessions, the coach provided further instructions or advice to those participants who struggled with the training. After the second meeting, the recording of the instructions included the sound of the fMRI scanner in the background in order for the participants to get accustomed to the noise during the experiment.

Experimental task. During fMRI, participants performed an aversive emotion paradigm, in which they expected and perceived cued aversive pictures under two conditions. The two conditions were ATB and passive viewing (PV) with instructions for ATB being “Please focus your attention on your breath as you have learned during the training” and for PV “Please watch the pictures without changing anything about your feelings”. Each trial started with a fixation cross for 1s, followed by one of two cues, i.e., a blue square (‘cue 1’, 50% of trials) or a yellow pentagon (‘cue 2’, 50% of trials), presented for 6s, accompanied by the prompt to press a button in order to indicate whether they expected to see an aversive picture or not. After that, an aversive picture (6s duration) was shown in 50% of the trials (‘aversive-picture’, ‘no-picture’), and after that subjects had 3s to indicate the valence (‘valence scale’) of their current affect. No-picture trials were included in the paradigm to examine potential interactions between regulatory conditions (ATB and PV) and emotional stimulation (picture and no-picture). The inter-trial interval lasted for 3 ± 2 s. Aversive pictures were taken from the international affective picture system (IAPS, Lang et al., 1999). In order to reliably elicit aversive feelings, we only included the 160 pictures with both highest arousal and most negative valence ratings and balanced this over the two conditions.

In total, 80 trials were presented for each emotion regulatory condition. Conditions were presented in two separate runs. The order of the two conditions was randomized and counterbalanced. After the experiment, participants were interviewed about the strategies they had employed. All reported they had adopted a “normal” or “default” stance towards the pictures during the passive condition and had not been aware of any focus on breathing, in contrast to the ATB condition in which they focused explicitly on their breath. Due to the study’s aim of the impact of ATB on aversive emotions, the current analysis investigates ATB effects on visual-emotional processes; ATB effects on expecting aversive stimuli (i.e., the brain response during the presentation of the cue) are analyzed elsewhere. Behavioral valence ratings were analyzed using a mixed model including factors ‘subject‘, ‘regulation’ (conditions: ATB and PV), ‘emotion’ (conditions: picture and no-picture), and breathing rate as covariate in SPSS (IBM Corporation, Version 20).

Measures of mindfulness and breathing.

Mindfulness measure. To link ATB effects with mindfulness practice, dispositional mindfulness was measured before the experiment with the German version of the Mindful Attention and Awareness Scale (MAAS, Michalak et al., 2008). The MAAS focuses on the presence or absence of awareness of what is occurring in the present. The questionnaire has been shown to hold good internal consistency (Cronbach’s α = .82) and validity (Michalak et al., 2008).

Respiration measure. To evaluate effects of ATB on breathing, respiration activity was recorded with a Respiration Belt Transducer (Biopack Systems). The belt was strapped to the participant’s trunk (i.e., border between chest and abdomen) and recorded respiration movements. Data were filtered and processed according to the manufacturer’s guidelines using the AcqKnowledge 4.2 software (Biopack Systems): after down-sampling the signal to 50 samples per second, we bandpass-filtered the data (0.05 – 1 Hz) and extracted the rate of respiration. For comparison between conditions, we used a paired sample t-test.

Functional MRI: data acquisition and analysis.

Acquisition. Magnetic resonance imaging was performed on a 3-T whole body MR scanner (Verio, Siemens, Germany) using a standard head coil. For co-registration of functional data, T1-weighted anatomical data were obtained from each subject by using a magnetization-prepared rapid acquisition gradient echo sequence (MP-RAGE, time to echo (TE) = 4 ms, repetition time (TR) = 9 ms, time for inversion (TI) = 100 ms, flip angle = 5°, field of view (FoV) = 240 mm × 240 mm, matrix = 240 × 240, 170 slices, voxel size = 1mm × 1mm × 1 mm). Functional data were collected using a contrast-gradient echo planar imaging (EPI) sequence (TE = 35 ms, TR = 2000 ms, flip angle = 90°, 35 slices, voxel size = 3mm × 3mm × 3.6mm, no interslice gap).

fMRI data preprocessing. Preprocessing and analysis of imaging data was carried out with SPM8 (Wellcome Department of Cognitive Neurology, London, UK). After coregistration and segmentation, T1-weighted structural images were normalized to a standard T1 template in Montreal Neurological Institute (MNI) space with a 1 x 1 x 1 mm resolution. After discarding the first three volumes, preprocessing of T2*-weighted functional images included slice timing, spatial realignment to the first image of the run, normalization to SPM8’s EPI template in the MNI space, resampling to 3 x 3 x 3 mm and smoothing with an 8 mm full width at half maximum (FWHM) Gaussian filter.

fMRI data analysis. To analyze each subject's fMRI data (i.e., first level analysis), a general linear model (GLM) approach with the following regressors of event types was carried out: a) a hemodynamic response function (HRF)-convolved with onsets of the fixation cross, cue 1, cue 2, picture, no-picture, and valence scale and b) 6 movement regressors derived from realignment as regressors of no interest. The analysis of the current study focused on ATB effects on aversive emotions (i.e., regressors for picture and no-picture). Therefore, at group-level (i.e., second level analysis), a flexible factorial model with factors for subjects, 'regulation' (ATB and PV), 'emotion' (picture and no-picture), and breathing rate as covariate was carried out. Statistical threshold for all activation analyses was set to $p<0.05$ corrected for multiple comparisons (family wise error (FWE) at cluster level) and height threshold 0.001. For the contrast [ATB < PV], we restricted the analysis to amygdala according to our initial hypothesis ($p<0.05$ FWE voxelwise corrected for small volume). The amygdala region-of-interest was defined by an amygdala mask derived from WFU-Pick atlas (http://fmri.wfubmc.edu/software/pickatlas) overlaid with the liberal threshold ($p<0.05$) activation cluster of the contrast picture > no-picture during PV in order to exclude all voxels that were not activated at baseline.

Amygdala task-functional connectivity – PPI analysis. In order to study amygdala integration with prefrontal areas, psycho-physiological interaction (PPI) analysis was carried out, based on the activation results. Specifically, a generalized form of PPI (McLaren et al., 2012) was used, with the amygdala cluster from the main effect contrast ATB < PV (i.e., regions suppressed by ATB) as seed. Amygdala activity was used as physiological variable in the PPI analysis, while the factor 'emotion' (i.e., picture versus no picture) served as psychological factor. We then contrasted the results during ATB and PV using t-tests ($p<0.05$, FWE cluster-corrected).

Analysis of brain-behavior relationship. In order to confirm that brain activation during ATB was related to emotion regulation, we extracted ß-values from the significant clusters and performed a Pearson's correlation analysis with measures of regulation success across subjects ($p<0.05$). Regulation success reflects the difference between valence ratings during ATB and PV. In order to test whether increased amygdala connectivity with the PFC during ATB was specifically related to mindfulness ability, we extracted ß-values from the PPI-cluster of the contrast ATB > PV, and performed a Pearson's correlation analysis with MAAS scores across subjects ($p<0.05$).

RESULTS

EFFECTS OF ATB ON BREATHING FREQUENCY AND EMOTIONAL VALENCE RATINGS.

To test whether ATB affects breathing frequency, we performed a paired t-test between mean breathing frequency during ATB and PV. Breathing frequency was significantly decreased during ATB (13.7 cycles per minute) compared to PV (17.3 cycles per minute; $p < 0.001$, $t = -4.91$). We subsequently controlled for this effect by including breathing frequency as covariate in further behavioral and brain data analyses.

To test whether ATB would down-regulate negative emotion, we performed an analysis of valence ratings using a mixed model with factors regulation and emotion including the co-variate breathing frequency. We found significant main effects for both regulation (ATB vs. PV, F= 5.14, p < 0.027) and emotion (picture vs. no-picture, F= 157.48, p< 0.001) and no interaction between regulation and emotion (F = 0.19, p> 0.892), breathing rate did not explain a significant amount of variance. Post-hoc t-tests revealed that participants felt significantly less negative with ATB than during PV. In addition, valance ratings were more negative when a picture was presented compared to a black background, as would be expected.

INTERACTION OF ATB AND VISUAL-EMOTIONAL STIMULATION ON BRAIN ACTIVATION.

Regarding brain mechanisms involved in ATB during visual-emotional processing, we hypothesized first that brain activation during ATB interacts with visual-emotional stimulation in prefrontal areas and amygdala. To test this hypothesis, we analyzed the interaction effects between regulation and stimulation by the use of a flexible factorial model for individual ß-maps with factors 'regulation' (ATB and PV) and 'emotion' (picture and no-picture) and co-variate breathing frequency, in parallel to the analysis on valence ratings above. The contrast $[\text{ATB} > \text{PV}]_{\text{picture}} > [\text{PV} > \text{ATB}]_{\text{no-picture}}$ revealed significant interactions between regulation and visual-emotional stimulation in a network of regions including medial and lateral parietal regions, the medial cingulate cortex, and anterior cingulate cortex (blue regions in Fig. 1A, Table 1). To evaluate interaction effects in relation to main effects of regulation, we investigated the main effect of ATB-based regulation on brain activation and compared it with interaction analysis results. The contrast [ATB > PV] revealed increased activation in a left lateralized frontotemporal network including left middle and superior temporal gyri and left superior and middle frontal gyri, which was – particularly in the prefrontal cortex - largely non-overlapping with the activations of the interaction analysis (regions depicted in red in Fig. 1A, Table 1).

To complement the analysis of interaction between regulation and stimulation, we tested whether ATB and aversive emotion also interact within the amygdala. Therefore, we re-analyzed the interaction but now restricted to the amygdala. The contrast [PV > ATB] $_{\text{picture}}$ > [ATB > PV] $_{\text{no-picture}}$ revealed a trend towards significance in the right amygdala (MNI coordinates: 24,-7,-14, T=2.1, p<0.103, Fig. 1 B). We next investigated the main effects of regulation (contrast: [ATB < PV]). Again restricting the analysis to the amygdala, we found increased activation in the right amygdala, which overlapped with the results of the interaction analysis (Fig. 1B, Table 1).

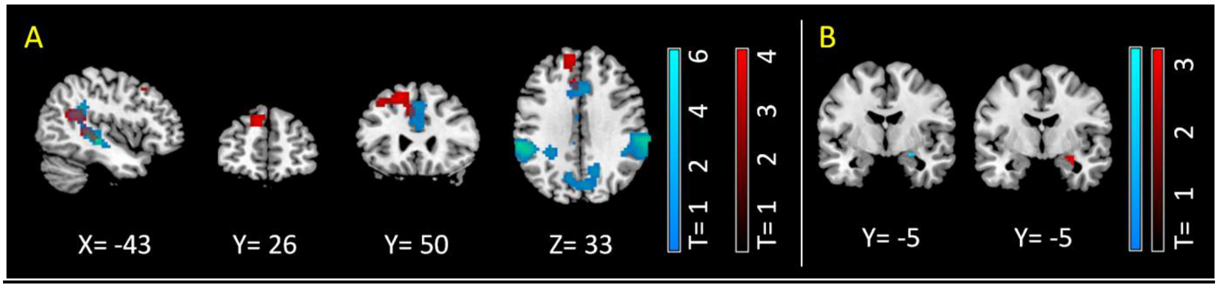

Figure 1. Interaction of ATB and visual-emotional stimulation on brain activation in cingulate and parietal areas and the amygdale.

Shown are the statistical parametric maps of t-tests evaluating the interaction of regulation and emotion, and main effect of regulation of a mixed model with the factors subject, regulation (passive view and ATB), and emotion (picture and no-picture, p<0.05 FWE cluster corrected). (A) The main effect of regulation (contrast [ATB> PV]) is depicted in red and the interaction of regulation and emotion ([ATB > PV] $_{\textit{picture}}$ *> [PV > ATB]* $_{\textit{no-picture}}$*) in blue. While the left middle frontal, inferior frontal and superior temporal gyri were generally more active during attention to breath (red), a network of parietal, superior temporal and anterior cingulate cortex was additionally activated during visual-emotional stimulation. The overlap (in dark grey) was biggest in left superior temporal gyrus. (B) The main effect of regulation (contrast [ATB < PV]) is depicted in red and the interaction of regulation and emotion ([PV > ATB]* $_{\textit{picture}}$ *> [ATB > PV]* $_{\textit{no-picture}}$ *) in blue (p<0.05 FWE corrected for small volume). The analysis was restricted to the amygdala. During ATB, the right amygdala showed reduced activation, which was overlapping with the at trend-interaction [PV > ATB]* $_{\textit{picture}}$ *> [ATB > PV]* $_{\textit{no-picture}}$*. Coordinates are reported according to Montreal*

Neurological Institute standard space. The left hemisphere is depicted in the left side (neurological convention). Abbreviations: ATB attention-to-breath, PV passive viewing.

DURING VISUAL-EMOTIONAL STIMULATION: DECREASED AMYGDALA AND INCREASED PREFRONTAL ACTIVATION.

To test our second hypothesis of breathing-independent ATB effects on amygdala and prefrontal activations during emotional stimulation, we investigated the effects of ATB and PV during the picture condition. Driven by our hypothesis of decreased amygdala activation during ATB, we focused on the contrast [PV > ATB] $_{\text{picture}}$. We found – during visual-emotional stimulation - significantly reduced amygdala activation during ATB compared to PV independent of effects of breathing frequency (Fig. 2A). To test whether this effect of ATB was specific for the amygdala, we repeated this analysis for the whole brain without any spatial restrictions; at a liberal threshold, we found – beyond the amygdala – reduced activation only in few voxels of the cerebellum and thalamus, indicating a largely specific decreasing effect of ATB on the amygdala. Further, to test whether observed amygdala activation decrease was linked with effects on emotional feelings, we investigated the association between the amygdala activation and emotion regulation success. Right amygdala activation decrease was significantly correlated with the behavioral measure of regulation success (r= -0.36, p<0.03, R^2= 0.14, Fig. 2B), suggesting that those participants who showed a stronger reduction in the right amygdala activation reported greater reduction of aversive feelings during ATB.

Next, we investigated the simple effects contrast [ATB > PV] $_{\text{picture}}$. According to our hypothesis, we expected increased activation in prefrontal cortices, independent of breathing effects. The contrast [ATB > PV] $_{\text{picture}}$ showed stronger activation in a network of regions that ranged from medial and lateral parietal regions into superior temporal cortices, bilateral cingulate cortices, and prefrontal cortices (Fig. 2C, Table 1), which, except in prefrontal regions, largely overlapped with the activations seen in the interaction effect (Fig. 1A). In detail, the prefrontal regions included left middle and superior frontal gyrus, left inferior frontal gyrus, right supplementary motor area and right superior frontal gyrus. To test whether these activations in prefrontal cortices were linked with emotion regulation, we calculated the correlation between regulation success and the activation averaged over the prefrontal cortex cluster around the left inferior frontal gyrus of increased activation during ATB compared to PV (Fig. 2C). We found a significant correlation (r= 0.35, p< 0.045, R^2= 0.12, Fig. 2D), indicating that participants with increased left prefrontal cortex activation during ATB, when pictures were shown, reported less negative emotion.

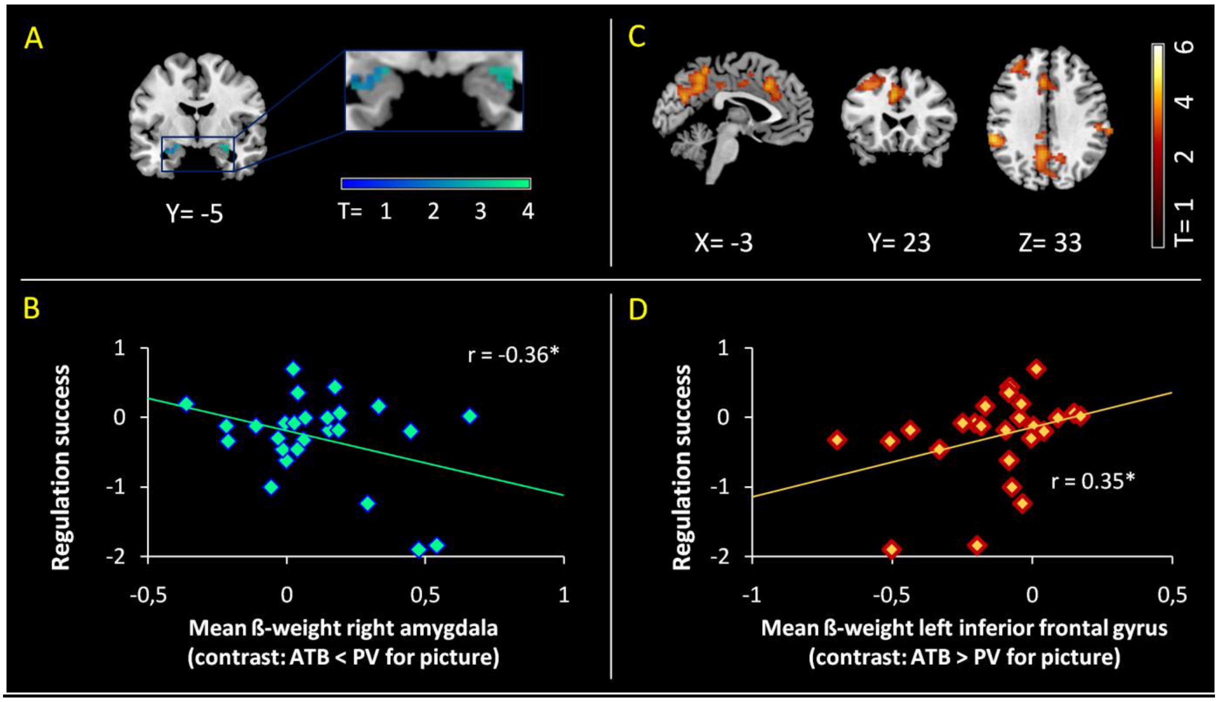

Figure 2. Decreased amygdala and increased fronto-parietal activation during attention-to-breath (ATB) and emotional stimulation.

(A) Amygdala activation was lowered during ATB during picture viewing. The test was restricted to bilateral amygdala ROI (t-test, contrast [ATB < PV] $_{picture}$*, p<0.05 FWE corrected for small volume). (B) The more amygdala activation was reduced during ATB the less negative emotional feelings were induced by aversive pictures (Pearson's correlation, p<0.05). (C) A network of fronto-parietal regions showed increased activation during ATB for picture viewing (t-test, contrast [ATB > PV]* $_{picture}$*, p<0.05 FWE cluster corrected). (D) The more activation was increased in left prefrontal cortex during ATB the less negative emotional feelings were induced by aversive pictures (Pearson's correlation, p<0.05). Regulation success: mean valence rating PV – ATB. Abbreviations: ATB attention-to-breath, ROI region-of-interest, PV passive viewing. Coordinates are reported according to MNI standard space.*

EMOTION-RELATED FUNCTIONAL CONNECTIVITY BETWEEN AMYGDALA AND PREFRONTAL CORTEX IS INCREASED DURING ATB.

We suggested that ATB modifies amygdala integration with prefrontal brain areas relevant for emotion regulation. To test this hypothesis, we used PPI analysis to identify areas of modulated emotion-relevant functional connectivity with the amygdala during ATB compared to PV. For the PPI analysis we extracted and averaged the time-courses of significant voxels from the above mentioned activation-analysis of the amygdala as the physiological variable. Picture presentation vs. no picture served as the psychological (i.e., emotion-related) factor. We then contrasted the results during ATB and PV using paired t-tests. While no voxels showed stronger emotion-related connectivity with the amygdala during PV, a big cluster in left prefrontal cortex spanning the left inferior frontal, precentral, middle frontal, superior medial gyrus and left insula, showed increased connectivity during ATB (Fig. 3A, Table 2). To test whether such ATB-relevant amygdala-prefrontal cortex connectivity was specifically linked to dispositional mindfulness, we investigated the association between the connectivity ß-values within the significant cluster and the individual scores on the MAAS, taken immediately before the experiment. This revealed a significant correlation ($r = 0.33$, $R^2 = 0.11$, $p < 0.05$), suggesting that individuals with greater trait mindfulness showed increased amygdala-left prefrontal cortex connectivity during ATB (Fig. 3B). The cluster of increased amygdala connectivity during ATB was overlapping with areas of increased activation during ATB (Fig. 2C) in the left middle frontal gyrus (Table 2).

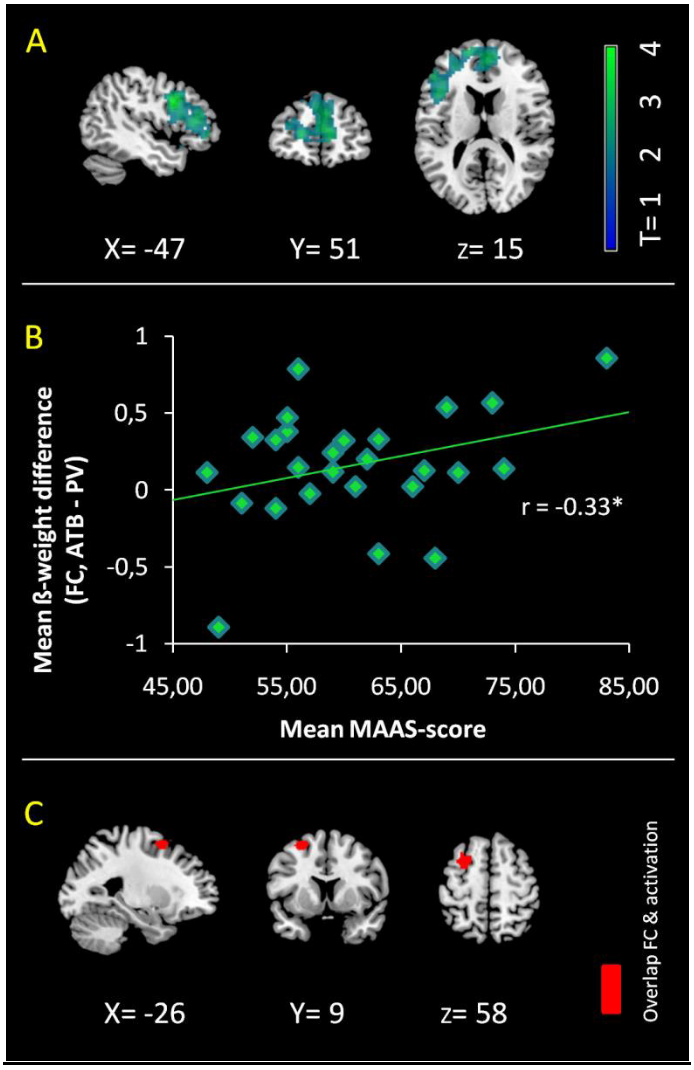

Figure 3. Altered amygdala integration with the dorsal prefrontal cortex during attention-to-breath (ATB).

*(A) During ATB, emotion-related functional connectivity of the amygdala was increased for the dorsal left prefrontal cortex (general psycho-physiological interaction analysis, physiological factor amygdala activity, psychological factor emotion (picture vs. no-picture), paired t-test for contrast ATB > PV, p<0.05 FWE cluster corrected). (B) Scores on the Mindful Attention and Awareness Scale were associated with emotion-related functional connectivity increase between prefrontal cortex and the amygdala during ATB and pictures viewing (Pearson correlation, p<0.05). (C) The brain activation during the simple effect of [ATB > PV] picture overlapped with the amygdala functional connectivity cluster (contrast: ATB > PV) within left middle frontal gyrus. Abbreviations: ATB attention-to-breath, PV passive viewing * sig. at p<0.05.*

DISCUSSION

Functional MRI and visual-emotional stimulation with and without ATB was used to investigate brain mechanisms that underlie emotion regulatory effects of ATB. The specific hypotheses we tested were: (i) brain activation effects of ATB and visual-emotional stimulation interact in amygdala and prefrontal areas; (ii) during visual emotional stimulation, ATB lowers amygdala activation and changes its integration with prefrontal brain areas relevant for emotion regulation, independently from effects on breathing. Independence from breathing effects was tested by including breathing frequency as a co-variate of no interest into the analysis. First, we found significant interaction effects of ATB and emotional stimulation on a broad parieto-cingular network, which was largely not overlapping with the main effect of ATB. While the main effect of ATB indicated that dorsomedial prefrontal activations were associated with ATB in general, the interaction effect indicated that additional medial and lateral parietal regions and the ACC were recruited during visual-emotional stimulation. Second, amygdala activation was decreased during ATB, with decreased activation being associated with emotion regulation success, independently from effects on breathing frequency. In addition, emotion-related functional connectivity between amygdala and left dorsal prefrontal cortex was increased during ATB, with increased connectivity being associated with mindfulness scores. Results provide evidence that attention-to-breath both decreases amygdala activation and increases prefrontal integration of the amygdala during aversive emotions, independently from effects on breathing. Data suggest amygdala-dorsal prefrontal cortex integration as potential neural pathway of emotion regulation by mindfulness practice.

INTERACTION OF ATB AND VISUAL-EMOTIONAL STIMULATION ON PARIETAL, ACC AND AMYGDALA ACTIVATION

We found interaction effects between ATB and visual-emotional stimulation on brain activation patterns, which were significant in the ACC and parietal regions for the contrast $[ATB > PV]_{picture} > [PV > ATB]_{no\text{-}picture}$ (Fig. 1A) and at-trend in the amygdala for the contrast $[PV > ATB]_{picture} > [ATB > PV]_{no\text{-}picture}$ (Fig. 1B). Interaction effects were independent from ATB effects on breathing frequency, since we controlled for these effects.

Concerning the amygdala, we found beyond at-trend interaction effects, a significant main effect of ATB of regulation (Fig. 1B). This finding indicates that ATB down-regulates amygdala activation, while the overlapping at-trend interaction effect suggests that during visual-emotional stimulation, additional down-regulation of amygdala activity might appear during ATB. However, to get definitive and robust evidence for such interpretation, further studies have to be performed.

Concerning and beyond prefronto-parietal interaction effects, we found a significant main effect of ATB-based regulation on brain activation in a left lateralized fronto-temporal network including left superior and middle frontal gyri by using the contrast [ATB > PV] (regions depicted in red in Fig. 1A, Table 1). Increased activations of this main effect were – particularly in prefrontal areas - largely non-overlapping with the activations of the interaction analysis. ACC and parietal interaction effects suggest that stronger activations in these areas during ATB in comparison with PV depend on visual-emotional stimulation i.e., they increase with additional emotional stimulation. Thus, regulatory activation of ATB during emotional stimulation seems to have two components. One comprises an extended network including lateral and medial parietal, superior temporal and medial and anterior cingulate cortices, which is additionally recruited during emotional stimulation, and is known for its critical role in both cognitive emotion regulation (Kohn et al., 2013) and mindfulness practice (Dickenson et al., 2013). The other covers a prefrontal-temporal network centered in the superior and middle frontal gyrus, which both are strongly involved in attentional and cognitive control in general and in focused attention tasks and meditation in particular (Brefczynski-Lewis et al., 2007; Hasenkamp and Barsalou, 2012; Hölzel et al., 2007; Manna et al., 2010; Tomasino et al., 2012). For example, the left superior frontal gyrus/middle frontal gyrus area showed consistently increased activation in expert meditators during focused attention meditation (Brefczynski-Lewis et al., 2007) and was associated with anxiety relief during breathing meditation (Zeidan et al., 2014).

DURING VISUAL-EMOTIONAL STIMULATION, ATTENTION TO BREATH DOWN-REGULATES THE AMYGDALA AND INCREASES FRONTO-PARIETAL ACTIVATION

In line with our second hypothesis we found, during emotional stimulation and independent from breathing effects, reduced amygdala activation and increased lateral and medial prefrontal-parietal cortex activation during ATB in contrast to PV (Fig. 2 A, C). Furthermore, ATB effects on amygdala and fronto-parietal activations were associated with emotion regulation success, i.e., the stronger amygdala decrease and fronto-parietal increase during ATB, the better negative feelings induced by emotional pictures were down-regulated (Fig. 2 B, D). These findings indicate that ATB effects on amygdala and fronto-parietal cortices are relevant for emotion regulation. The observed down-regulation of the amygdala by ATB is a consistent finding in mindfulness studies that involve aversive stimuli (Creswell et al., 2007; Farb et al., 2007; Goldin and Gross, 2010; Hölzel et al., 2013; Lutz et al., 2013; Modinos et al., 2010; Taylor et al., 2011). The present data also fit with findings from cognitive emotion regulation, which indicate amygdala decrease via dorso-medial and ventro-medial PFC/ACC during emotion regulation as consistent finding (Kohn et al., 2013). Our finding demonstrate that – independent from effects on breathing – focused attention to breath has an emotion regulatory effect that is related with decreased amygdala and increased prefrontal-parietal cortex activation.

INCREASED AMYGDALA-FRONTAL CORTEX INTEGRATION DURING EMOTION REGULATION BY ATTENTION TO BREATH AND ITS LINK WITH TRAIT MINDFULNESS

Focusing on the amygdala's integration with prefrontal cortices, we found increased emotion-related functional connectivity between the right amygdala and left prefrontal and cingulate areas during ATB (Fig. 3A). This means that BOLD synchrony between amygdala and prefrontal areas during emotion processing increases with ATB in contrast to PV. The pattern of prefrontal regions involved in such increase of synchronicity with the amygdala was partly overlapping with the pattern of prefrontal areas involved in ATB (e.g., demonstrated by the contrast [ATB > PV], Fig. 2C). This overlap in the middle frontal gyrus suggests that these regions are potential sources of emotion regulation by ATB. While it is well known that medial prefrontal regions exert direct influence on the amygdala during emotion regulation via direct structural pathways (Wager et al., 2008), lateral prefrontal cortices are assumed to realize their effects on amygdala during emotion regulation indirectly via the medial prefrontal and orbitofrontal system (Ray and Zald, 2012). According to this model, our data suggest that during ATB, lateral prefrontal areas might influence amygdala activity indirectly to down regulate negative emotions.

In addition, we found that individuals' trait mindfulness was linked with ATB-based amygdala integration into the prefrontal cortex during emotional processing (Fig. 3 B). Trait mindfulness was measured by the Mindful Attention and Awareness Scale, which focuses on the presence or absence of awareness of what is occurring in the present. The link between MAAS and amygdala integration indicates that one's disposition to be aware of the present moment is associated with amygdala-frontal cortex integration during ATB and emotional processing. Since ATB is a key element in mindfulness practice and therefore intimately linked with mindfulness trait, the link between ATB-related amygdala integration during emotions and trait mindfulness suggests that amygdala integration with prefrontal cortices is relevant for the effects of mindfulness practice on emotion regulation.

POTENTIAL IMPLICATIONS FOR TREATMENT MODELS

Mindfulness training has been shown to reduce ruminating thoughts (Chambers et al., 2008; Deyo et al., 2009; Jain et al., 2007). Further, sustained amygdala activation has been linked to increased rumination tendency during emotional processing (Siegle et al., 2002). The present experimental data suggest a potential pathway of this anti-ruminating effect of mindfulness training via down-regulation of the amygdala through the prefrontal cortex. According to our data it might be possible that through repeated practice the controlling effect of the prefrontal cortex over the amygdala might be increased, thereby facilitating the engagement of control in situations that require regulation. To test this hypothesis future studies are needed that focus on the change in connectivity between portions of the prefrontal cortex and the amygdala over time and relate this to rumination tendency.

LIMITATIONS

Findings of the present study suffer from a number of limitations. First, we cannot rule out that the observed activations are due to changes in low level processing of visual stimuli as our control condition did not include neutral images. However, we did not find any activation differences in primary visual cortices, which would be expected for modulation of perceptual visual processing. In addition, effects in amygdala and PFC are present in both the picture and the no-picture condition (Fig. 1), indicating a general effect of ATB on emotions rather than on perceptual processing. Also, the activations seen in the present study are very similar to experiments that have used a neutral picture condition (Lutz et al., 2013). Second, the instructions during the PV condition (i.e., watching the pictures without changing anything about feelings) could be interpreted as a more mindful condition than the one for ATB. However, a reduced breathing rate during the ATB condition indicates that participants' attention was focused on the breath during ATB as it would be expected during mindful breathing especially in novices (Farb et al., 2013). Also, participants had only been trained in mindful breathing and not in any other type of mindfulness practice (e.g. mindfulness to emotions), thus the instruction during PV was not associated with mindfulness for our participants. Third, the regulation effect could be explained by participants simply looking away from the negative pictures, since we did not control for eye movements. While we did train participants to spend an equal amount of time looking at the pictures during both condition, this should be controlled in future studies, if possible.

CONCLUSION

We provide evidence that attention-to-breath both decreases amygdala activation and increases prefrontal integration of the amygdala during aversive emotions independently from breathing effects. Data suggest amygdala-dorsal prefrontal cortex integration as a potential neural pathway of emotion regulation by mindfulness practice

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TABLES

Table 1: Task activation during emotion processing with and without attention-to-breath (ATB)

Contrast	Region	Voxel: T-value	P-value	Cluster size	Peak MNI-coordinates		
					x	y	z
Interaction of regulation and emotion: [ATB > PV] $_{\text{picture}}$ > [PV > ATB] $_{\text{no-picture}}$	Left Supramarginal Gyrus	5.57	<0.001	2074	-60	-40	25
	Left Superior Temporal Gyrus	5.38			-60	-40	16
	Left Middle Temporal Gyrus	5.37			-57	-55	7
	Left Precuneus	4.37			0	-46	52
	Right Supra Marginal Gyrus	5.53	<0.001	760	66	-34	28
	Right Superior Temporal Gyrus	4.58			60	-46	13
	Right Inferior Parietal Lobule	3.54			63	-40	46
	Right Middle Cingulate Cortex	3.55	0.013	303	6	23	40
	Left Anterior Cingulate Cortex	3.05			-6	32	25
Main effect of regulation: [ATB > PV]	Supramarginal Gyrus	4.23	0.033	245	-36	-49	16
	Left Middle Temporal Gyrus	4.00			-48	-28	-2
	Left Superior Temporal Gyurs	3.11			-63	-46	22
	Left Superior Medial Frontal Gyrus	3.82	0.016	292	-9	50	37
	Left Superior Frontal Gyrus	3.75			-15	26	52
	Left Middle Cingulate Cortex	3.4			-6	23	37
	Left Anterior Cingulate Cortex	3.37			-12	35	28
	Left Middle Frontal Gyrus	3.27			-36	23	46
Interaction of regulation and emotion: [PV > ATB] $_{\text{picture}}$ > [ATB > PV] $_{\text{no-picture}}$	Amygdala right	2.10	0.103	3	24	-7	-14
Main effect of regulation: ATB < PV	SVA: Amygdala right	2.96	0.031	20	30	-7	-14
Simple effect of regulation during picture presentation: [ATB < PV] $_{\text{picture}}$	SVA: Amygdala right	3.19	0.012	20	30	-4	-17
	SVA: Amygdala left	2.77	0.049	14	-18	-4	-14
	Left Superior Temporal Gyrus	6.02	<0.001	888	-45	-31	-2
	Left Superior Temporal Gyrus	5.4			-45	-49	22

	Left Supramarginal Gyruss	5.16			-60	-37	37
	Left Middle Temporal Gyrus	5.08			-57	-46	16
Simple effect of regulation during picture presentation: [ATB > PV] $_{\text{picture}}$	Left Precuneus	5.03	<0.001	896	-9	-49	43
	Left Cuneus	4.52			0	-70	28
	Right Middle Cingulat Coretex	4.47			9	-34	43
	Left Middle Cingulate Cortex	4.47			0	-46	55
	Left Middle Frontal Gyrus	4.46	<0.001	361	-24	14	55
	Left Superior Frontal Gyrus	3.9			-15	8	64
	Right SMA	4.29	0.003	181	12	-7	67
	Right Superior Frontal Gyrus	4.1			18	2	67
	Left Middle Cingulate Gyrus	3.85			0	-1	40
	Right Middle Cingulate Gyrus	3.72			3	2	49
	Left Middle Cingulate Gyrus	4.63	0.004	167	-6	23	37
	Left Anterior Cingulate Gyrus	4.24			-6	32	25
	Left Inferior Frontal Gyrus	4.57	0.022	113	-51	5	10
	Left Temporal Pole	3.57			-48	11	-5
	Right Superior Temporal Gyrus	4.38	0.033	100	51	-40	22
	Right Supramarginal Gyrus	4.37			69	-28	31

Table 1: Task activation during emotion processing with and without attention-to-breath (ATB).

Activation analysis: flexible factorial model with factors subjects, ‘regulation’ (ATB and PV), and ‘emotion’ (picture and no-picture), and co-variate breathing frequency; height threshold p<0.001 uncorrected, p<0.05 FWE cluster corrected). Due to the study´s hypothesis, the amygdala was investigated using a small volume analysis (SVA, p<0.05 FWE voxelwise corrected). Task-functional Abbreviations: ATB attention-to-breath, PV passive viewing, SMA supplementary motor area, MNI Montreal neurological institute.

Table 2: Functional connectivity during emotion processing with and without attention-to-breath (ATB)

Contrast	**Region**	**Voxel: T-value**	**P-value**	**Cluster size**	**Peak MNI-coordinates x**	**y**	**z**
Emotion- related functional connectivity of right Amygdala (PPI): ATB > PV	Left Inferior Frontal Gyrus	4.07	0.004	2318	-45	11	28
	Left Precentral Gyrus	3.84			-54	14	34
	Left Middel Frontal Gyrus	3.75			-24	26	37
	Left Insula	3.36			-30	26	1
	Left Superior Medial Gyrus	3.32			-6	56	40
Overlap Activation (simple effect of $[ATB> PV]_{picture}$) **and emotion-related functional connectivity of amygdala**	Left Middle Frontal Gyrus	-	-	49	-26	9	58

Table 2: Functional connectivity during emotion processing with and without attention-to-breath (ATB).

Emotion-related functional connectivity analysis: general PPI with physiological factor amygdala activity, psychological factor emotion (picture, no-picture), and paired t-test for contrast ATB > PV (p<0.05 FWE cluster corrected). Overlap: shows the overlapping voxels between the activation and connectivity analyses. Abbreviations: ATB attention-to-breath, PV passive viewing, PPI psycho-physiological interaction, MNI Montreal neurological institute.

7. PAPER TWO: THE EFFECTS OF MINDFUL ATTENTION TO BREATH ON AVERSIVE PREDICTION ERROR-BASED LEARNING IN THE STRIATUM

This paper comprises the report of an experiment that investigated the neural correlates of prediction error modulation by mindful breathing in the striatum. The paper was in preparation for submission at the time of thesis submission. The following authors were involved in the creation of this manuscript: Anselm Doll, Satja Mulej Bratec, Afra Wohlschläger and Christian Sorg. The author of this thesis performed both data acquisition (together with C. C. Boucard) and – analysis (together with S. Mulej Bratec). Writing of all parts of the manuscript was also performed by the author of the thesis, while co-authors were involved in the editing of introduction, methods, results and discussion.

Title:

THE EFFECTS OF MINDFUL ATTENTION TO BREATH ON AVERSIVE PREDICTION ERROR-BASED LEARNING IN THE STRIATUM

Short Title:

Mindfulness modulates aversive prediction errors

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ABSTRACT

Mindfulness based emotion regulation strategies are used widely in the therapy of affective and anxiety disorders. It has been proposed that these strategies not only affect emotion regulation but also learning (Tang, Hölzel, & Posner, 2015; Treanor, 2011). However, no evidence exists that mindfulness based emotion regulation can modulate prediction errors related to aversive stimuli. Neural data on aversive learning indicate the striatum as one of the main sites of aversive prediction error computations. The present experiment tested first, the hypothesis that attentional regulation of emotion using a basic mindfulness strategy modulates aversive prediction error (aPE)-related activation in the striatum, and second, which areas in the frontal cortex might provide the regulating input. **Methods:** 26 healthy individuals predicted and watched negative pictures during both attention to breath (ATB) and passive viewing. Using the Rescorla-Wagner model, we simulated aPE computation to identify aPE-related brain areas. A psychophysiological interaction (PPI) analysis was used to find changes in connectivity. All data were corrected for respiration frequency. **Results.** Region of interest (ROI) analysis revealed an aPE-related deactivation in the right putamen during ATB. Connectivity analysis further revealed a fronto-limbic network that showed increased connectivity with the right putamen during ATB. Mindfulness, as measured by the mindful attention and awareness scale (MAAS), predicted the strength of this connection. **Conclusion:** The presented data show for the first time that attention to breath as a regulation strategy not only modulates emotional responses but also learning related aPEs in the striatum.

INTRODUCTION

Mindfulness refers to a meta-cognitive skill that monitors and controls attention towards the present with a curious, non-judgmental attitude towards all experiences (Bishop, Lau, & Shapiro, 2004). It has been shown to improve general well-being (Carmody, 2009), and is associated with improved emotion regulation (Hill & Updegraff, 2012). The most prevalent strategy for learning mindfulness is focused breathing or attention to breath (ATB), whereby one focuses on the sensations and perceptions of respiration (Kabat-Zinn, 1990; Teasdale et al., 2000). ATB has been shown to modulate emotional responses (Arch & Craske, 2006) and to effectively reduce emotional reactions to negative stimuli in novices by down-regulating amygdala activations and increasing dorsomedial prefrontal cortex (DMPFC) activation (Taylor et al., 2011). The beneficial effects of ATB on emotion regulation have motivated the integration of mindfulness-based interventions in numerous treatments of psychopathology (Chiesa & Serretti, 2011; Goldin & Gross, 2010; S. C. Hayes, Strosahl, & Wilson, 1999; Linehan, 1993a; Miklowitz et al., 2009; Segal, Williams, & Teasdale, 2012; Stange & Eisner, 2011; Weber et al., 2010). More specifically, mindfulness-based interventions are used to improve and support the effects of extinction learning in anxiety disorders and addiction (Chiesa & Serretti, 2011; Goldin & Gross, 2010; S. C. Hayes et al., 1999; Linehan, 1993a; Miklowitz et al., 2009; Segal et al., 2012; Stange & Eisner, 2011; Weber et al., 2010) and share neuronal activations with extinction processes (Tang et al., 2015). Mindfulness has been hypothesized to impact extinction learning by two possible mechanisms: increased salience of the conditioned stimulus (CS), and the mindfulness mode as a retrieval cue for extinction (Treanor, 2011). Even though the mechanisms by which mindfulness might impact extinction have not been investigated, the existing evidence supports the idea that mindfulness might affect learning, potentially by modulating prediction error (PE)-related signaling (Kirk, Montague, Mascaro, & Montague, 2015).

Avoiding aversive events and actively seeking rewards are basic and adaptive behaviors that rely on PE-based learning (Schultz, Dayan, & Montague, 1997). This type of learning is usually studied in the context of classical and operant conditioning. Learning during a classical conditioning task critically relies on brain circuits processing emotional information such as the amygdala, insula and anterior cingulate cortex (Büchel, Morris, Dolan, & Friston, 1998; Sehlmeyer et al., 2009). In order to better understand the processes underlying associative learning, computational models have been proposed that model learning-related computations in the brain, such as the Rescorla-Wagner model (Rescorla & Wagner, 1972). The Rescorla-Wagner model predicts probabilities for future events (prediction, P) based on previously made errors in prediction (prediction errors, PE). Neuroimaging studies have begun to shed light on the neural correlates of PE signaling: The existing data indicate the striatum, receiving dopamine projections from the ventral tegmental area (VTA), as one of the main sites of aversive prediction error (aPE) computations (Corlett et al., 2004; M. R. Delgado, Li, Schiller, & Phelps, 2008; Gläscher & Büchel, 2005; Jensen et al., 2007; McClure, Berns, & Montague, 2003; O'Doherty et al., 2004; O'Doherty, Dayan, Friston, Critchley, & Dolan, 2003; Palminteri et al., 2012; Pessiglione, Seymour, Flandin, Dolan, & Frith, 2006; Robinson, Frank, Sahakian, & Cools, 2010; Seymour et al., 2004; Shohamy, 2011).

To date, it is not clear whether in humans, reward and aPE signaling stem from different sources. There is evidence supporting distinct mechanisms and specific populations of neurons involved in reward and aPE signals. A number of animal studies have now confirmed the existence of distinct populations of dopamine neurons in the VTA, showing different activation patterns and projection paths to the striatum, and most importantly, are sensitive to either rewarding, aversive or salient (i.e., both rewarding and aversive) stimuli (Bromberg-Martin, Matsumoto, & Hikosaka, 2010; Lammel et al., 2012; Lammel, Ion, Roeper, & Malenka, 2011; Lammel, Lim, & Malenka, 2014; Matsumoto & Hikosaka, 2009; Volman et al., 2013). Furthermore, corresponding fMRI experiments have found similar activations in humans (M. R. Delgado, Li, et al., 2008; Garrison, Erdeniz, & Done, 2013; Jensen et al., 2007; Metereau & Dreher, 2013). In addition, a selective impairment of reward but not punishment learning in depression provides further evidence for separate signaling of the corresponding error signals (Robinson, Cools, Carlisi, Sahakian, & Drevets, 2012). Together, the above studies indicate that reward and aPEs are based on distinct neural processes that should be studied separately.

The notion that humans can modify learning by regulating emotions is a necessary assumption in psychotherapy. In computational terms, it implies that the regulation of emotions should impact PEs. While a few studies have demonstrated this relationship for reward-related PE signaling (M. R. Delgado, Gillis, & Phelps, 2008; Kirk et al., 2015; Staudinger, Erk, Abler, & Walter, 2009; Staudinger, Erk, & Walter, 2011), evidence for aPE being affected by emotion regulation is insufficient. Emotion regulation has, however, been shown to modulate an aspect of aversive conditioning, namely neural responses of conditioned stimuli predicting shocks within the striatum (M. R. Delgado, Gillis, et al., 2008), or painful stimuli within the anterior cingulate cortex (Kalisch et al., 2005). Together, these data provide evidence that emotion regulation can impact learning-related processes and that these processes are consistently located within the striatum. However, the detailed mechanism by which aversive learning could be affected by a mindfulness-based emotion regulation strategy is unclear. We hypothesized that a mindfulness-based emotion regulation strategy affects aPE-related brain activity in the striatum. The present experiment investigated the impact of attention to breath (ATB) on aPE-related neural activity. Furthermore, we used connectivity analysis to investigate which areas in the frontal cortex are involved in the regulation of aPE-related activity in the striatum. Since the used emotion regulation strategy is based on breath awareness, it might change respiration frequency. Consequently, all analyses were controlled for this by including breathing frequency as a covariate. We modeled participants' learning by the Rescorla-Wagner model (Rescorla & Wagner, 1972) and investigated aPE-related brain activations and connectivity specifically within the striatum.

METHODS

Participants. 29 healthy right-handed controls with normal or corrected-to-normal vision predicted and watched negative pictures during both ATB and passive viewing. Three participants had to be excluded from the study, leaving us with a total sample of 26 subjects (10 males, mean age (± SD) = 26.9 ± 4.6). Participants were recruited through an online portal and gave informed consent to participate in the experiment. The study was approved by the ethical committee of the Technische Universität München (Munich, Germany).

Procedure. For 2 weeks before scanning, participants daily practiced ATB through an auditory instruction CD (further description below; Hölzel, 2012). During the scanning session, participants were asked to predict and emotionally evaluate negative pictures. The experiment was designed in two counterbalanced runs with 80 trails each: participants were asked to either view the pictures as they would normally (passive viewing) or focus on the sensations of breathing while watching and predicting the pictures (ATB-condition). Valence and arousal levels of the pictures in the two runs were balanced. On each trial, participants were presented with one of two symbols (conditioned stimulus, CS) that were either followed by a negative picture (unconditioned stimulus, US+) or a blank screen (US-). Pictures were taken from the international affective picture system (IAPS; Lang, Bradley, & Cuthbert, 1999).

The contingency between CS and US systematically varied over each run. The probability of a US occurrence varied from 0 to 100% and followed a sine function with the effect that participants had to constantly adapt their predictions (Gläscher & Büchel, 2005). Participants were asked to respond with their right (dominant) hand. Prior to the scanning session, participants were trained to ensure they understood the experimental task. Using the Rescorla-

Wagner model (Rescorla & Wagner, 1972), we simulated aPE computations to identify aPE-related brain areas using functional magnetic resonance imaging.

Focused breathing task. Mindfulness instructions were given in two meetings by an experienced meditation teacher (Christine C. Boucard). The teacher supervised and observed the practice to provide further instructions and advice if necessary. For standardization purposes, the instructions were provided on a CD. ATB instructions included becoming aware of body posture, relaxed sitting, focusing on the sensations of breathing in the belly or around the nostrils, accepting the sensations of breathing as they are in the present moment and returning back to the sensations after digression of thoughts. Each participant received a copy of the instruction CD and was asked to perform the training once a day. In addition, participants were asked to note down any sensations, experiences and questions that came up during the practice. After the second meeting, the sound of the scanner was played in the background of the instructions in order to minimize distraction due to scanner noise during the scanning session.

Behavioral measures. We measured trait mindfulness using the German version of the Mindful Attention and Awareness Scale (MAAS), which focuses on the attentional ability to focus on the present moment (Michalak, Heidenreich, Ströhle, & Nachtigall, 2008). The questionnaire was administered twice, once during the first ATB training meeting and once right before the experiment in the scanner. Behavioral measures during the experiment in the scanner were valence ratings, reaction times, and accuracy. All behavioral measures were analyzed using paired t-tests.

Respiration measure. To evaluate effects of ATB on breathing, respiration activity was recorded with a Respiration Belt Transducer (Biopack Systems). The belt was strapped to the participant's trunk (i.e., border between chest and abdomen) and recorded respiration movements. Data were filtered and processed according to the manufacturer's guidelines using the AcqKnowledge 4.2 software (Biopack Systems): after down-sampling the signal to 50 samples per second, we bandpass-filtered the data (0.05 – 1 Hz) and extracted the rate of respiration. For comparison between conditions, we used a paired sample t-test.

fMRI data acquisition. All measurements were performed on a 3 Tesla Siemens Verio scanner at the Klinikum rechts der Isar, Technische Universität München (Munich, Germany). Visual stimuli, presented with Presentation software (Neurobehavioral Systems), were rear-projected on a screen at the head of the scanner and could be seen by the participant through an adjustable mirror mounted to a standard head coil. Presentation software also received trigger pulses signaling the beginning of each volume acquisition from the scanner.

Anatomical images were acquired with the magnetization-prepared rapid acquisition gradient echo (MP-RAGE) T1-weighted sequence (1 x 1 x 1 mm resolution), and functional scans with the contrast-gradient echo-planar T2*-weighted sequence with a repetition time of 2s, echo time of 30 ms, flip angle of 90°, acquisition matrix of 64 × 64, 35 slices, voxel size of 3mm × 3mm × 3.6mm and no interslice gap.

fMRI data preprocessing. For each participant, the first two functional scans of each fMRI-session were discarded to remove magnetization effects. SPM8 (Welcome Department of Cognitive Neurology, London) was used for slice time and motion correction, spatial normalization into stereo-tactic space of the Montreal Neurological Institute (MNI), spatial smoothing by applying an 8 mm full width at half maximum Gaussian kernel and temporal high-pass filtering. Realignment parameters were calculated for later use in the statistical model. None of the participants had to be excluded due to excessive head motion (linear shift < 3 mm across run and on a frame-to-frame basis, rotation < 3°).

Statistical analysis of imaging data

Prediction error-related activations. In a first-level analysis, reference vectors for each condition were convolved with the canonical hemodynamic-response function provided by SPM8 to account for the delay in BOLD-response peak. In addition, we included head motion regressors for each participant into the model. By means of the Rescorla-Wagner model (Rescorla & Wagner, 1972) we simulated the prediction task. The model was fit to the individual performance of each participant by adapting the learning rate. This resulted in a regressor representing the size of the aPE for each trial. Using this regressor as a parametric modulation, we analyzed the aPEs at the time-point of US presentation. We used an optimized subject- and run-specific learning rate λ, derived from behavioral prediction scores. In detail, for each subject, separately for each CS and each run, subject's prediction responses were compared with the modeled prediction values from the Rescorla-Wagner equation. Root-mean-square deviation (RMSD) was calculated for a range of λ from .001 to 1, in increments of .001. Best-fit learning rate λ for a specific CS, run and subject was determined by the associated global RMSD minimum. A 2x2 ANOVA with factors Regulation Strategy (ATB, Passive viewing) and CS (CS1, CS2) was used to compare mean λ.

At the second level, we used a paired sample t-test to analyze activations related to aPE and the difference between passive viewing and ATB conditions while pictures were presented. Previous studies indicate differential roles for putamen and caudate in reward and punishment prediction and PE signaling (M. Delgado, Nystrom, Fissel, Noll, & Fiez, 2000; Haruno & Kawato, 2006; Mattfeld, Gluck, & Stark, 2011). We therefore restricted our analysis to the individual parts of the striatum (caudate and putamen) and performed a region-of-interest (ROI) analysis separately. The resulting contrasts were voxel-level FWE small-volume corrected with $p < .05$, and additionally masked with the activation map of all aPE-related voxels (based on the contrast aPE-passive viewing vs. baseline, liberal threshold, $p < .05$, uncorrected).

Striatum connectivity. Following the activation analysis, we planned to investigate striatum connectivity using a general form of psychophysiological interaction analysis (gPPI; McLaren, Ries, Xu, & Johnson, 2012). The physiological factor included a mean time course of significantly activated striatum voxels, while the psychological factor reflected the two conditions of passive viewing and ATB when pictures were presented. Whole-brain differences between conditions were analyzed using paired sample t-tests, and FWE cluster-corrected, based on a height threshold of $p < .05$, masked by a combination of the anatomical regions of the frontal and limbic lobes from the WFU Pick Atlas (http://fmri.wfubmc.edu/software/pickatlas).

Brain-behavior correlations. In order to relate imaging results with behavioral scores, we performed Pearson's correlation analyses between beta values and questionnaire scores. To this end, we extracted mean-corrected average beta values from a 12-mm sphere centered on the peak of the connectivity-analysis.

RESULTS

NEURAL ACTIVATIONS

To examine modulations of aPE activity during ATB, we performed a region of interest (ROI) analysis, based on anatomical masks of individual striatal parts, putamen and caudate separate. Of these areas, the right putamen showed a decrease in aPE-related activity during the ATB condition (Fig. 1, Table 1).

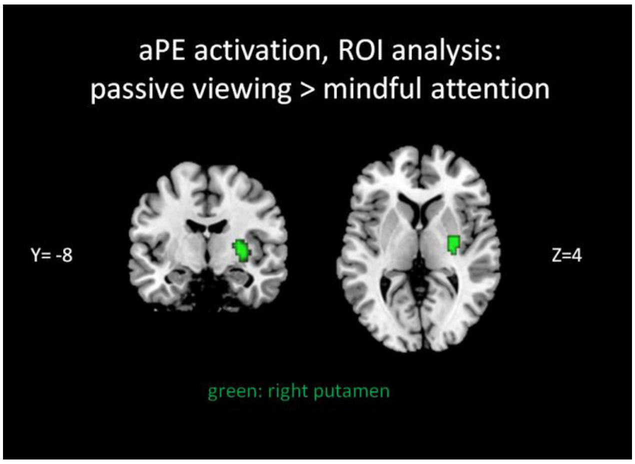

Figure 1. Decreased activation of aPE signaling during attention to breath in right putamen.

Shown are spatial maps of a paired t-test restricted to the putamen when aversive pictures were presented, contrast ATB < PV (p < .05 FWE voxelwise corrected for small volume). Abbreviations: aPE aversive prediction error, ROI regions of interest, ATB attention to breath, PV passive viewing, FWE family wise error.

CONNECTIVITY ANALYSIS

To investigate which areas might be related to the modulation of aPE signals during ATB, we performed a PPI analysis using the mean time course of significant voxels in the right posterior putamen (Fig. 1) as the physiological, and the conditions passive viewing and ATB as the psychological component. This analysis revealed an increase in connectivity during ATB in bilateral medial and lateral frontal cortices, with the peak in right medial PFC and right superior parietal, superior temporal, and precentral cortex (Fig. 2, Table 1). Furthermore, extracted connectivity ß-values from the peak-centered 12mm-sphere (coordinates: 15, 32, 16) revealed a significant correlation of the difference in connectivity between passive viewing and ATB conditions with the MAAS-score (r=.34, p<.05, Fig. 3). Higher mindfulness scores were associated with increased connectivity during ATB.

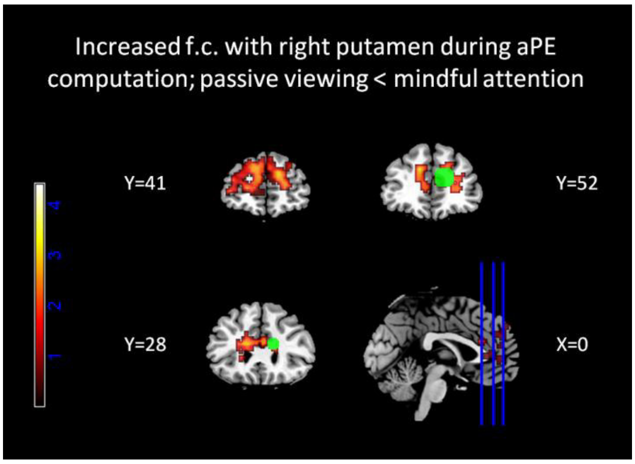

Figure 2. Increased functional connectivity with right putamen during aPE computation.

Shown are spatial maps representing functional connectivity with the cluster of decreased connectivity during ATB (Fig. 1), paired t-test when pictures were presented, contrast PV < ATB, p < .05 FWE cluster corrected. The green sphere (12mm radius) is located around the peak of the cluster (coordinates: 15, 32, 16). Abbreviations: FC functional connectivity, aPE aversive prediction error, ATB attention to breath, PV passive viewing, FWE family wise error.

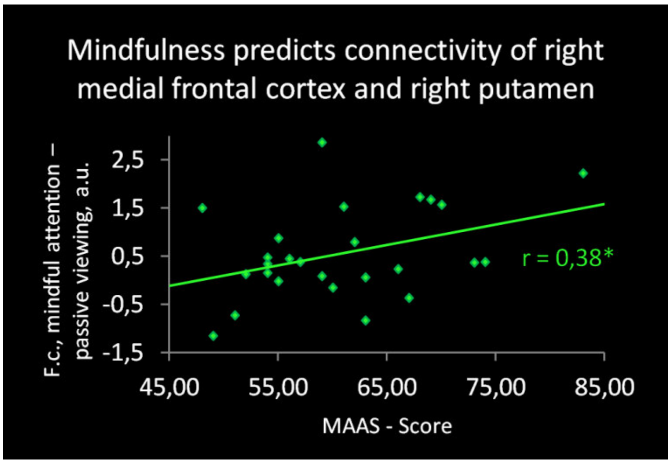

Figure 3. Association between Mindfulness and functional connectivity of right putamen.

*Shown is a Pearson correlation between mindfulness scores and difference scores of functional connectivity between right putamen and dorsomedial prefrontal cortex for ATB-PV. Connectivity beta values were extracted from the 12mm sphere placed around the peak of the connectivity analysis (Fig. 2, sphere shown in green). Abbreviations: FC functional connectivity, MAAS mindful attention and awareness scale, ATB attention to breath, PV passive viewing. *p < .05*

BEHAVIORAL RESULTS

Participants evaluated negative pictures to be significantly less negative during the ATB condition (paired t-test, $p < .05$), showing the emotion-regulation effect of ATB. This did not change, when including breathing frequency as a covariate. As participants were trained on both the mindful breathing and the prediction task, we did not expect any differences in accuracy or RTs between conditions. Confirming this, paired sample t-tests revealed no significant difference between ATB and passive viewing for accuracy or RTs (all $p > .27$, Supp. Fig. 1), also corrected for breathing frequency. The mean best-fit λ across participants and conditions was .044 (SEM: .002), which is consistent with previous studies (den Ouden, Friston, Daw, McIntosh, & Stephan, 2009; Gläscher & Büchel, 2005; Mulej Bratec et al., under review). The 2x2 ANOVA revealed no significant differences for λ between conditions (for both main effects and interaction, $F < .22$, $p > .64$).

DISCUSSION

The present fMRI-study investigated the effect of emotion regulation by ATB on aPE-related activity and connectivity within the striatum. Embedded in a classical conditioning paradigm, aPEs were calculated by means of the Rescorla-Wagner model (Rescorla & Wagner, 1972). By determining the individual optimal learning rate, we obtained an aPE regressor, which was used in a ROI-based analysis to identify aPE-activations within the striatum at the time of US presentation. PPI analysis was used to find whole-brain changes in striatum connectivity related to the conditions of ATB and passive viewing. Results indicate a reduction in aPE-related activity in the right posterior putamen that was accompanied by an increased connectivity of this area with the right DMPFC. The present data are in line with previous results indicating the putamen as a main site of aPE computations (M. R. Delgado, Li, et al., 2008; Garrison et al., 2013; O'Doherty et al., 2003; Robinson et al., 2010), which seems to be regulated by a fronto-limbic network during mindfulness-based emotion regulation. Interestingly, trait mindfulness was related to the increase in striatum connectivity with the DMPFC. Data provide evidence for a modulation of aPE-related activity within the striatum by emotion regulation using a basic mindfulness strategy.

DEACTIVATION OF THE POSTERIOR PUTAMEN

We found an aPE-related deactivation during ATB within the right posterior putamen. A similar cluster, located in the left hemisphere, including both ventral and dorsal putamen, was found in an activation likelihood estimation meta-analysis on aPEs (Garrison et al., 2013), supporting the finding that both dorsal and ventral putamen are involved in aPE computations. In addition, our results overlap with a study investigating reward PE modulation by mindfulness (Kirk et al., 2015). The present data are also in line with the hypothesis that the anterior portion of the striatum is targeted in reward PE signaling, while the posterior portion is related to punishment PEs (Mattfeld et al., 2011; Seymour, Daw, Dayan, Singer, & Dolan, 2007). However, to date, it is not clear what behavioral impact a reduction in aPE-related activation could have. Intuitively, a reduction in aPE-related activation might suggest an impairment of learning. This would suggest that strategies, which are designed to divert attention away from the stimuli and towards e.g., the breath like in the present study, would reduce the person's learning ability, while strategies, designed to focus cognition towards the stimulus like e.g., reappraisal would improve learning performance. This is in accordance with research, which suggests that reappraisal-based strategies of emotion regulation induce an increase in memory of the negative stimuli (Dillon, Ritchey, Johnson, & LaBar, 2007; J. P. Hayes et al., 2010). Unfortunately, the present experiment was not designed to be sensitive enough to behavioral changes in learning, and can therefore not provide any evidence as to the behavioral consequences of a reduction in aPE-related activity. Additional studies investigating the behavioral relevance of PE modulation are warranted to further address the issue.

INCREASED CONNECTIVITY OF THE RIGHT PUTAMEN WITH DORSOMEDIAL PREFRONTAL CORTEX

The reduction in aPE-related signal during ATB was accompanied by an increase in connectivity of the right putamen and bilateral PFC. The DMPFC has previously been shown to control activations within the striatum in response to negative stimuli during cognitive emotion regulation (e.g., M. R. Delgado, Nearing, Ledoux, & Phelps, 2008). In addition, the connectivity strength of the DMPFC and the ventral striatum was found to predict the ability in changing predictions based on feedback (Bos, Cohen, Kahnt, & Crone, 2012). Together, these data support a regulatory role of DMPFC in both emotional and PE processing. The increased synchrony of aPE-related activation in DMPFC and striatum is also supported by a correlation of this connectivity with a behavioral measure of mindfulness. Connectivity changes between DMPFC and the right striatum were correlated with individual MAAS scores. Higher trait mindfulness was related to a stronger increase in connectivity between the regulatory region and the striatum. The MAAS questionnaire is designed to measure attentional capacities to stay focused on the present during everyday life experiences. With a stronger focus on the present moment, one´s ability to sustain attention on the perception of breathing might be increased. This, in turn, might lead to a stronger regulation of PE-related activation gain. It has been suggested that attentional processes are used to optimize PE precision estimates that might modulate the synaptic gain of PEs (den Ouden, Kok, & de Lange, 2012). According to this hypothesis, it is possible that the conscious control of attention towards the breath could reduce the synaptic gain of aPE-related activity associated with negative stimuli in visual cortex, which could account for a reduction in the aPE signal in striatum. However, the hypothetical nature of these considerations calls for further studies that investigate the relationship between attentional control and modulation of PE signaling. For instance, studies involving patients with attentional difficulties (e.g., attention deficit disorder patients) might be able to elucidate the relationship of attention and PE signals.

IMPLICATIONS

PE computations have been associated with numerous functions in perception, cognitive control, motivation and memory (for a review, see den Ouden et al., 2012). Specifically, it has been suggested that the modulation of synaptic associations (e.g., long-term potentiation) relies on PE computations. A modulation of PE signaling by emotion regulation could explain its beneficial effects on distressing memories. Mindfulness has been integrated into dialectic behavioral therapy (Linehan, 1993b) and has been theorized to support habituation during exposure to traumatic life events (van der Kolk, 2006). Correspondingly, PE modulation could result in a relearning of emotional salience of the elicited emotions of a traumatic event. Further studies including patients previously exposed to traumatic life-events (e.g., those with post-traumatic stress disorder), are needed to investigate the relationship between emotion regulation, PE and memory.

CONCLUSION

The presented data show for the first time that attention to the breath as a regulation strategy not only modulates emotional responses but also aversive learning-related prediction errors.

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TABLES

Table 1: Activation and Connectivity Clusters

Contrast	Region	Voxel: T-value	P-value (FWE-cluster corrected)	Cluster size	MNI-coordinates		
					x	y	z
Activation: Mindful attention < Passive Viewing	Putamen , right (FWE-voxel corrected, ROI analysis)	4.03	0.035	56	30	-10	1
Connectivity, Putamen cluster: Mindful attention > Passive Viewing	Right Anterior Cingulate Cortex	4.75	< 0.001	2231	15	32	16
	Left Caudate Nucleus	4.43			-15	11	13
	Left Putamen	4.06			-21	23	4
	Right Superior Frontal Gyrus	3.96			12	59	25
	Left Middle Frontal Gyrus	3.7			-24	38	25
	Left Superior Frontal Gyrus	3.63			-22	42	23
	Rigth inferior Frontal Gyrus	3.51			39	26	16
	Left Superior Medial Gyrus	3.5			-15	38	16
	Left Anterior Cingulate Cortex	3.34			-15	32	25
	Right Putamen	2.96			24	14	1
	Right Precentral Gyrus	4.29	0.009	1163	33	-19	43
	Right Rolandic Operculum	4.07			48	-19	22
	Right Heschl's Gyrus	3.90			45	-19	4
	Right Superior Temporal Gyrus	3.89			45	-25	7
	Right Superior Parietal Lobule	3.27			39	-52	61
	Right Angular Gyrus	3.25			48	-52	40
	Right Insula	3.01			44	-13	12
	Right Cuneus	1.92			24	-58	64

Table 1: Activation and Connectivity Clusters.

Shown are the results of t-tests for activation and connectivity analyses during aPE computations while pictures were presented.

8. PAPER THREE: MINDFULNESS IS ASSOCIATED WITH INTRINSIC FUNCTIONAL CONNECTIVITY BETWEEN DEFAULT MODE AND SALIENCE NETWORKS

This paper comprises the report of an experiment that investigated the relationship between trait mindfulness and the functional connectivity between key cognitive intrinsic brain networks. At the time of thesis submission, the paper was under review in the journal “Frontiers in Human Neuroscience”. The following authors were involved in the creation of this manuscript: Anselm Doll, Britta K. Hölzel, Christine C. Boucard, Afra Wohlschläger and Christian Sorg. The author of this thesis was involved in the idea of the study (together with C. Sorg), performed both data acquisition (together with C. C. Boucard) and –analysis. Writing of all parts of the manuscript was performed by the author of the thesis, while co-authors were involved in the editing of introduction, methods, results and discussion.

Title

MINDFULNESS IS ASSOCIATED WITH INTRINSIC FUNCTIONAL CONNECTIVITY BETWEEN DEFAULT MODE AND SALIENCE NETWORKS

Running title:

Mindfulness is linked with resting-state connectivity between default mode and salience networks

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Key Words:

Resting state, connectivity, mindfulness, fmri, salience network, central executive network, default network

ABSTRACT

Mindfulness is attention to present moment experience without judgment. Mindfulness practice is associated with brain activity in areas overlapping with the default mode, salience, and central executive networks (DMN, SN, CEN). We hypothesized that intrinsic functional connectivity (i.e. synchronized ongoing activity) across these networks is associated with mindfulness scores. After two weeks of daily 20-minutes attention to breath training, healthy participants were assessed by mindfulness questionnaires and resting-state functional MRI. Independent component analysis of imaging data revealed networks of interest, whose activity time series defined inter-network intrinsic functional connectivity (inter-iFC) by temporal correlation. Inter-iFC between subnetworks of the DMN and SN - and inter-iFC between subnetworks of the SN and left CEN at trend - was correlated with mindfulness scores. Additional control analyses about visual networks' inter-iFC support the specificity of our findings. Results provide evidence that mindfulness is associated with intrinsic functional connectivity between default mode and salience networks. Data suggest that ongoing interactions among central intrinsic brain networks link with the ability to attend to current experience without judgment.

INTRODUCTION

Mindfulness refers to attending to present moment experience without judging occurring feelings or thoughts (Bishop et al., 2004). Mindfulness practice such as meditation has proved beneficial for well-being (Carmody, 2009), and is an efficient element of treatments for mental disorders (Hofmann et al., 2010). Mindfulness practice typically recruits a number of brain regions, mainly prefrontal, parietal and subcortical brain areas (Creswell et al., 2007; Dickenson et al., 2013; Frewen et al., 2010; Hasenkamp et al., 2012). For example, Dickenson et al. (2013) found activations in dorso-medial prefrontal cortex (DMPFC), anterior cingulate cortex (ACC), insula, and temporo-parietal junction during a controlled focused breathing task – the most prominent first technique in teaching mindfulness to novices. Due to its widespread activation pattern, distributed functional brain networks have been suggested as critical neural correlates of mindfulness practice. For example, Hasenkamp and Barsalou (2012) recently identified four different mental states during meditation with each state being preferentially related to activity in different intrinsic brain networks: focus on the present experience was most strongly related to dorso-lateral prefrontal cortex activation of the central executive network (CEN), mind wandering was associated with the default mode network (DMN), awareness of mind wandering was linked with activation in the salience network (SN), and a shift of attention back towards focus on the present experience was again linked with the right DLPFC and right posterior parietal cortex with both regions being part of the CEN.

Intrinsic brain networks such as the DMN, SN, and CEN are characterized by coherent ongoing activity at infra-slow frequencies and are often studied during resting state. These networks are believed to subserve specific cognitive functions like attentional control or core affect (Fox and Raichle, 2007) as their patterns of coherent ongoing activity overlap and reflect the activation patterns observed during goal directed behavior. (Berkes et al., 2011; Lewis et al., 2009; Riedl et al., 2011; Smith et al., 2009). Multiple experiments have shown that correlated resting-state activity (i.e. intrinsic functional connectivity - iFC) within the DMN, SN, CEN, respectively, is associated with mindfulness (Berkovich-Ohana et al., 2013; Hasenkamp and Barsalou, 2012; Kilpatrick et al., 2011; Shaurya Prakash et al., 2013; Taylor et al., 2013). However, previous studies focused mainly on within-network functional connectivity, ignoring that additional networks are involved in mindfulness and particularly that these networks interact with each other (see Froeliger et al., 2012; Kilpatrick et al., 2011). Based on Hasenkamp and Barsalou’s model, we hypothesized that the ability of mindfulness is coded in ongoing inter-network interactions between DMN, SN, and CEN. To test this hypothesis we investigated the inter-network functional connectivity during resting state (inter-iFC) of the SN, DMN, and CEN in 26 healthy controls that were trained in breath awareness for two weeks prior to scanning, and correlated these values with participants' mindfulness scores of psychometric assessment.

METHODS

Participants. 26 right-handed meditation naïve volunteers that were free from past and present neurological and psychiatric disorders participated in the study (10 males, mean age (± SD) = 26.9 ± 4.6). The study was approved by the ethical committee of the Technische Universität München. All participants provided written informed consent prior to the experiment and received a monetary compensation of expenses for participation.

Mindfulness ability. To ensure mindfulness ability, participants received 20 minutes of audio-guided training in attention to breath, based on a meditation as taught in a mindfulness based stress reduction (MBSR) program (Hölzel, 2012) daily for two weeks. Mindfulness ability was measured with the Mindful Attention and Awareness Scale (MAAS; Brown & Ryan, 2003) and the Freiburg Mindfulness Inventory (FMI; Walach, Buchheld, Buttenmüller, Kleinknecht, & Schmidt, 2006). While the MAAS focuses on the presence or absence of awareness of what is occurring in the present, the FMI assesses the accepting and curious attitude towards this experience that is inherent to mindfulness. Both questionnaires have been shown to hold good internal consistency (Cronbach's $\alpha = .82$ and .86, respectively) and validity.

Functional MRI: data acquisition and analysis. For imaging, participants were instructed to remain still with eyes closed and to not fall asleep during acquisition. All participants reported to not have fallen asleep during the scanning session.

Imaging acquisition. Magnetic resonance imaging was performed on a 3-T whole body MR scanner (Verio, Siemens, Germany) using a standard head coil. For co-registration of functional data, T1-weighted anatomical data were obtained from each subject by using a magnetization-prepared rapid acquisition gradient echo sequence (MP-RAGE, time to echo (TE) = 4 ms, repetition time (TR) = 9 ms, time for inversion (TI) = 100 ms, flip angle = 5°, field of view (FoV) = 240 mm × 240 mm, matrix = 240 × 240, 170 slices, voxel size = 1mm × 1mm × 1 mm). Functional data were collected using a contrast-gradient echo planar imaging (EPI) sequence (TE = 35 ms, TR = 2000 ms, flip angle = 90°, 35 slices, slice thickness = 3 mm, and 0 mm interslice gap).

fMRI data analysis. Preprocessing and analysis of imaging data was carried out with SPM8 (Wellcome Department of Cognitive Neurology, London, UK). After coregistration and segmentation, T1-weighted structural images were normalized to a standard T1 template in MNI space with a 1 x 1 x 1 mm resolution. After discarding the first three volumes, preprocessing of T2*-weighted functional images included slice timing, spatial realignment to the first image of the run, normalization to SPM8's EPI template in the Montreal Neurological Institute (MNI) space, resampling to 3 x 3 x 3 mm and smoothing with an 8 mm full width at half maximum (FWHM) Gaussian filter.

To define intrinsic networks, we applied high-model-order independent component analysis (ICA) to the preprocessed data by using the GIFT-toolbox (http://icatb.sourceforge.net) with the infomax algorithm implemented in Matlab (Calhoun et al., 2001). Data were decomposed into 75 spatial independent components (IC), correspondent with a framework for high-model-order decomposition (Abou Elseoud et al., 2011; Allen et al., 2011). High-model-order ICA approaches of about 70 components yield independent components, which are in optimal accordance with known anatomical and functional segmentations (Damoiseaux et al., 2006; Kiviniemi et al., 2009; Smith et al., 2009). Data were concatenated and reduced by two-step principal component analysis (PCA), followed by independent component estimation with the infomax-algorithm. We subsequently ran 40 ICAs (ICASSO) to ensure stability of the estimated components (Himberg et al., 2004). This results in a set of average group components which are then back reconstructed into single subject space, each represented by a spatial map of z-scores reflecting the within-network intrinsic functional connectivity and one associated time course of BOLD-signal fluctuations representative for this IC.

To select the independent components reflecting networks of interest in an automated and objective way, we conducted multiple spatial regressions of 75 independent components' spatial maps on T-maps of intrinsic connectivity networks (ICNs) as described in Allen et al. (2011). These T-maps were generated by the identical ICA approach as performed in the current study based on 603 healthy adolescents and adults and were made available online by the Medical Image Analysis Lab (MIALAB) (http://mialab.mrn.org/data/hcp/RSN_HC_unthresholded_tmaps.nii.). For each ICN, the independent component with the largest correlation coefficient was chosen. According to our hypothesis, we restricted our selection to ICNs, which were characterized as part of either SN, DMN, or CEN (ICs 25, 34, 50, 53, 55, 60, 68 in Allen et al., 2011), resulting in a total of 7 ICNs for further analysis.

To define outcome measures of inter-network iFC, we performed Pearson correlation analyses for all of these networks resulting in 21 correlations per participant. Pearson correlation coefficients were transformed into z-values via Fisher r-to-z transformation. Subsequently, we correlated these z-values with the two measures of mindfulness ability across participants, respectively, and evaluated statistical significance of results via t-tests ($p<0.05$, Bonferroni corrected for 21 tests with corrected p-value $p<0.0024$).

In order to test the specificity of the link between inter-iFC and mindfulness for neuro-cognitive key networks, we additionally selected three visual occipital networks from Allen et al. 2010: IC 46, 64 and 67 and performed the identical analysis, including computation of inter-iFC between these visual networks and associations with mindfulness scores. We chose occipital visual networks, since a previous study demonstrated intra-network connectivity changes in such a visual network after 8 week mindfulness training (Kilpatrick et al., 2011), suggesting that its inter-network connectivity might be linked with trait mindfulness, too. Furthermore, we performed a similar analysis for the inter-iFC between the visual and neuro-cognitive networks, respectively. I.e. we computed inter-iFC and its association with mindfulness scores.

RESULTS

PSYCHOMETRIC ASSESSMENT OF MINDFULNESS

Mindfulness was assessed using the MAAS and the FMI. Mean scores were 60.9 (SD =8.5) for the MAAS and 37.5 (SD=3.1) for the FMI. The FMI contained two outliers (based on the outlier labeling rule, Hoaglin & Iglewicz, 1987) that were excluded from all analyses pertaining to FMI scores. The correlation between the questionnaires was significant ($r = 0.45$, $p < 0.02$).

INTRINSIC NETWORKS AND INTER-NETWORK CONNECTIVITY

Automated component selection revealed seven components of interest for each individual. Selected components matched previous results of SN, DMN, and CEN (Allen et al., 2011; Fig. 1 and Table 1; $p<0.05$, FWE-corrected). The SN was represented in two components, comprising ACC (accSN) and bilateral anterior insula (insSN). DMN was represented in three components (anterior DMN (aDMN; medial prefrontal cortex), posterior-ventral DMN (pvDMN; posterior cingulate cortex) and posterior-dorsal DMN (pdDMN; precuneus). CEN was represented in two components, comprising two lateralized fronto-parietal networks corresponding to left (lCEN; left middle and superior frontal cortex, and inferior parietal lobule), and right CEN (rCEN; right middle and superior frontal gyri, right angular gyrus, and right inferior parietal lobule). The three visual control networks were located in medial and lateral occipital cortex and matched well with the templates in Allen et al. (2010; Fig. 2).

From the seven intrinsic networks of interest and the three control networks, we extracted the network time courses and defined inter-iFC via Pearson's correlation (see Table 2 for mean correlation coefficients of networks of interest and Table 4 for visual control networks).

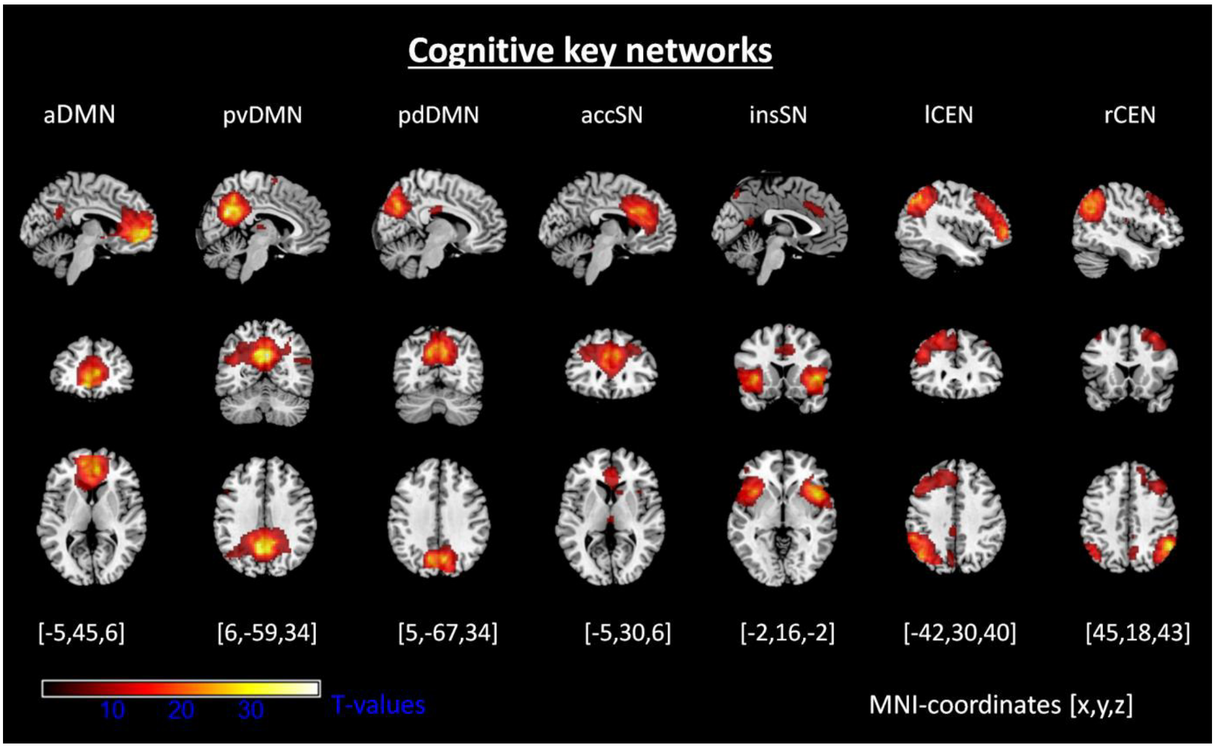

Figure 1. Intrinsic networks of interest.

Shown are spatial maps of one-sample t-tests (voxel wise family wise error corrected, p < 0.05). Abbreviations: aDMN anterior default mode network, pvDMN posterior ventral default mode network, pdDMN posterior dorsal default mode network, accSN cingular salience network, insSN insula salience network, lCEN left central executive network, rCEN right central executive network.

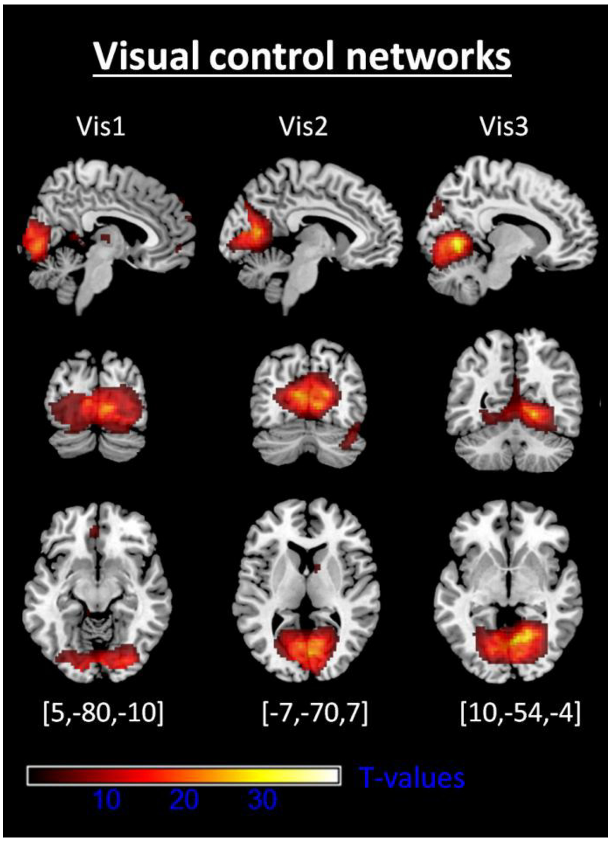

Figure 2. Intrinsic visual control networks.

Shown are spatial maps of one-sample t-tests (voxel wise family wise error corrected, p < 0.05). Abbreviations: Vis1 visual network 1, Vis2 visual network 2, Vis3 visual network 3, coordinates are given with respect to Montreal Neurological Institute standard space.

ASSOCIATION BETWEEN INTER-IFC AND MINDFULNESS SCORES

After Fisher r-to-z transformation, we correlated z-scores of inter-iFC with the mindfulness scores of both FMI and MAAS (Pearson correlation, p<0.05, Bonferroni corrected for 21 comparisons, corrected threshold p < 0.0024; Figure 3 & 4, Table 3). We found significant negative correlations between FMI and inter-iFC of insSN and pvDMN (*r* = -0.60, *p* < 0.002). In addition, inter-iFC between the aDMN and the pdDMN was significantly negatively correlated with the MAAS scores (r= -0.65, p < 0.001). At border significance (i.e. p<0.05, but not surviving correction for multiple testing), we found negative associations between MAAS and inter-iFC of aDMN and lCEN (r= -0.40, p< 0.045), FMI and inter-iFC of insSN and aDMN (*r* = -.53, sig. *p* < .008), as well as FMI and inter-iFC between accSN and lCEN (r = -0.45, p < 0.03).

To evaluate the influence of sex on the association between mindfulness and inter-network connectivity, we re-analyzed the dependence between inter-iFC and MAAS and FMI, respectively, by the use of partial correlation analysis with sex as additional control variable. In partial correlation analysis, the dependence between two variables (i.e. inter-iFC and mindfulness score) is evaluated while controlling for the influence of further variables (i.e. sex) on both variables of interest, respectively. While almost all results concerning the link between inter-iFC and mindfulness scores changed only marginally, merely the association between MAAS and inter-iFC of aDMN and lCEN, which was at-trend ($p=0.05$) in the analysis without control for sex, lost its trend to significance. This finding indicates that the observed link between mindfulness and inter-iFC between salience and default mode network is largely independent from sex differences.

For the association between mindfulness scores and inter-iFC among visual control networks, we found no significant correlation (Table 4). The analysis of the association between mindfulness scores and inter-iFC between visual and neuro-cognitive networks of interest yielded one at trend result (Tab. 5). The correlation between FMI and the connectivity between the anterior DMN and a secondary visual network (reflecting IC 67 component of Allen et al. (2010) and covering mainly the lingual gyrus) had a Pearson's coefficient of $r = -0.53$ with a p-value of 0.01. This p-value did not survive correction for multiple testing via Bonferroni for corrected threshold of $p<0.0024$.

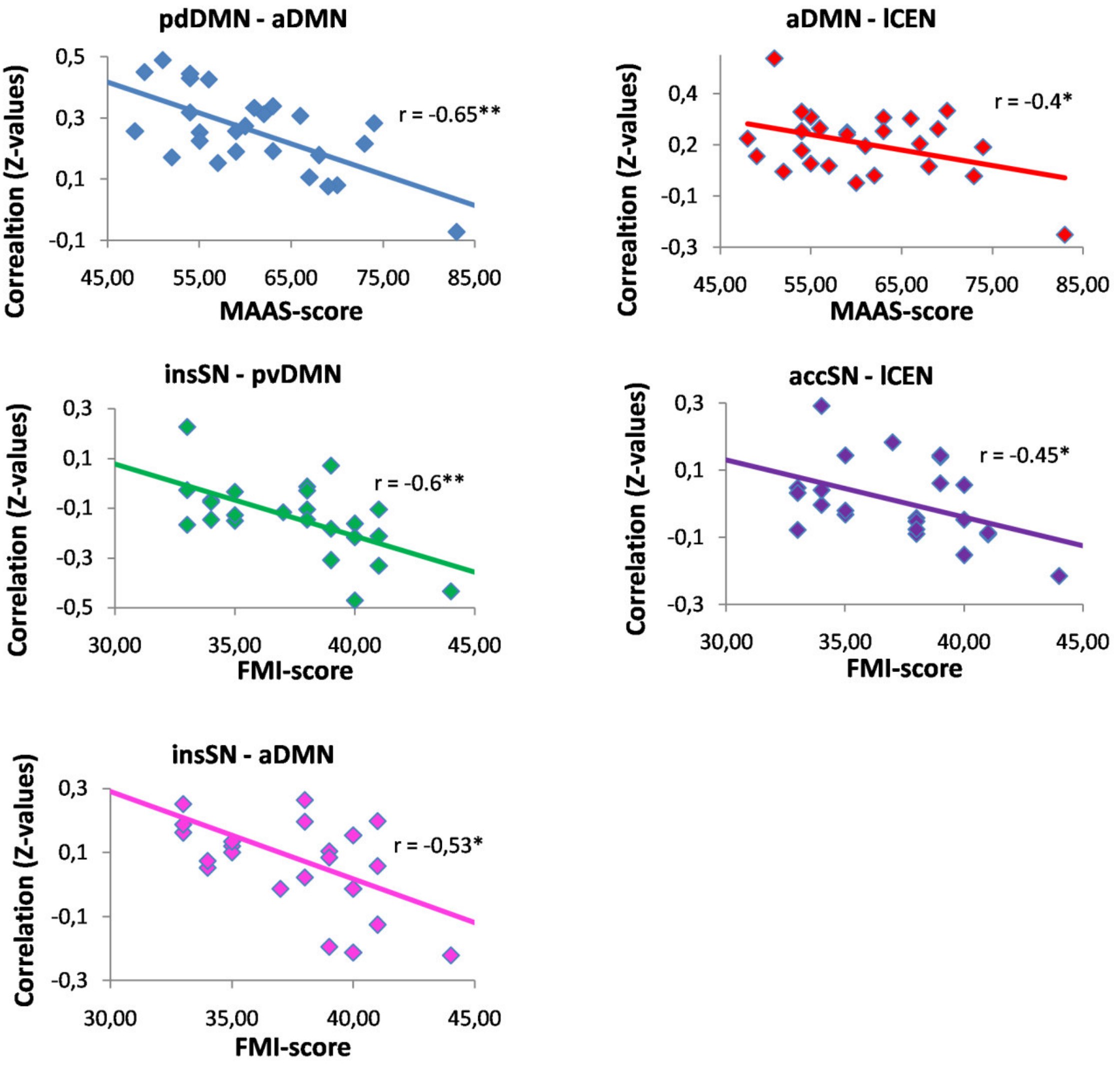

Figure 3. Correlations between mindfulness ability and inter-network functional connectivity.

*Abbreviations: MAAS Mindful Attention and Awareness Scale, FMI Freiburg Mindfulness Inventory, aDMN anterior default mode network, pvDMN posterior ventral default mode network, pdDMN posterior dorsal default mode network, accSN cingular salience network, insSN insula salience network, lCEN left central executive network, rCEN right central executive network. * sig at $p < 0.05$ **sig with Bonferroni correction for multiple comparisons.*

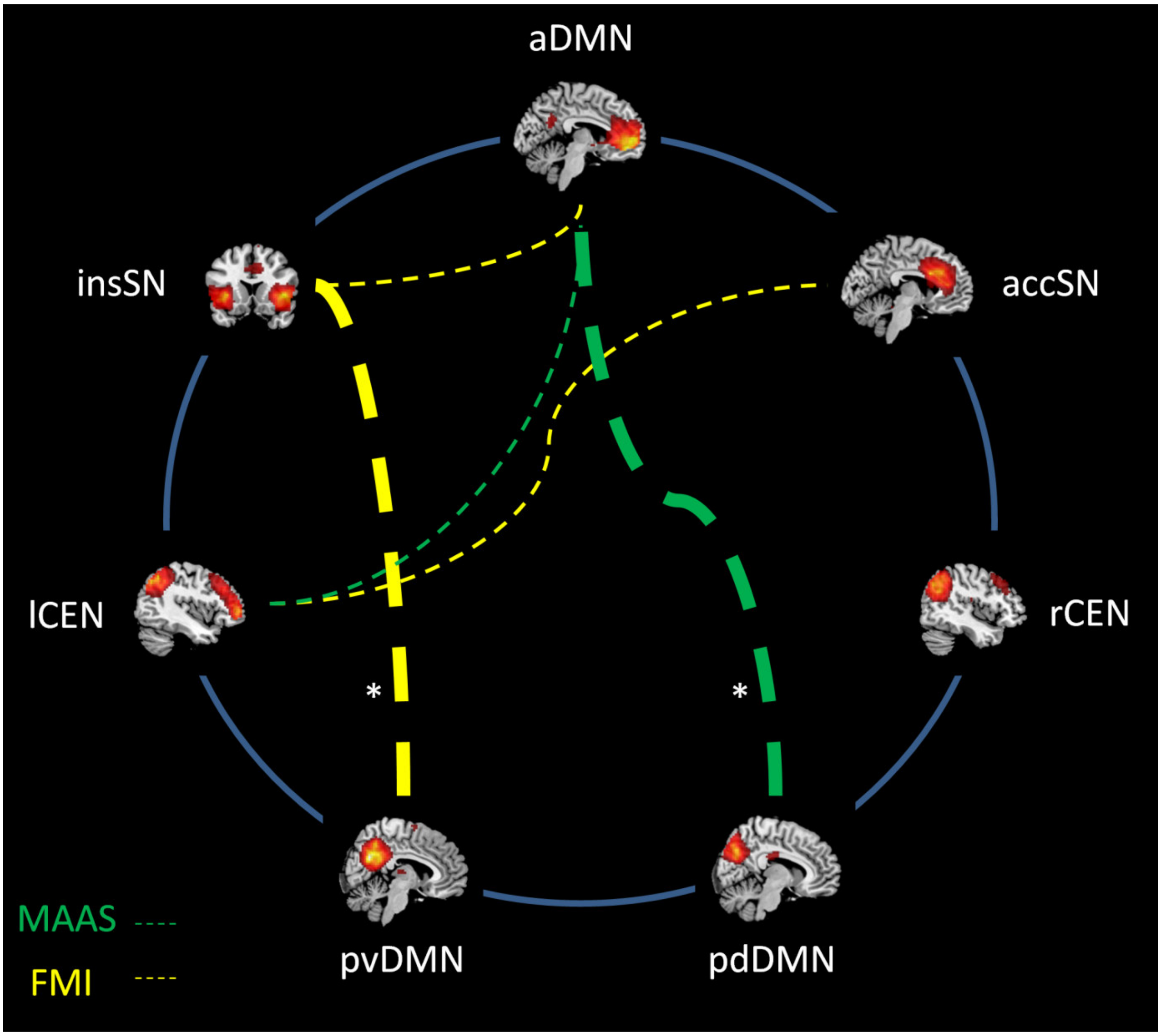

Figure 4. Association between mindfulness ability and inter-network intrinsic functional connectivity.

*Networks are represented by spatial maps of one-sample t-tests (voxel wise family wise error corrected, p < 0.05). Dashed lines indicate negative correlations between mindfulness and connectivity strength. Abbreviations: MAAS Mindful Attention and Awareness Scale, FMI Freiburg Mindfulness Inventory, aDMN anterior default mode network, pvDMN posterior ventral default mode network, pdDMN posterior dorsal default mode network, accSN cingular salience network, insSN insula salience network, lCEN left central executive network, rCEN right central executive network. * sig with Bonferroni correction for multiple comparisons.*

DISCUSSION

The present study investigated the association between mindfulness and functional connectivity of intrinsic brain activity among three central neurocognitive networks (inter-iFC): the salience, default mode, and central executive networks. Inter-iFC between DMN and SN - and inter-iFC between SN and CEN at trend - was correlated with mindfulness scores. Results suggest that mindfulness is significantly associated with ongoing network interactions of central neurocognitive networks.

RELATIONSHIP BETWEEN MINDFULNESS AND INTER-NETWORK CONNECTIVITY

We found negative correlations of mindfulness ability and inter-iFC among SN, DMN and CEN (Fig. 3&4, Tab. 3). These correlations were significant for the negative inter-iFC between insSN and pvDMN. This result was specific for neuro-cognitive key networks, since control analysis for visual networks inter-network connectivity did not yield significant results (Tab. 5). Furthermore it was independent from sex differences, for which we controlled in additional control analyses. The increase in anti-correlation between the insSN and pvDMN for more mindful individuals replicates previous findings (Kilpatrick et al., 2011). Kilpatrick and colleagues (2011) compared intrinsic brain networks in participants of an eight week course of mindfulness stress reduction (MBSR) to waitlist controls during a mindful resting state. After training in MBSR, participants showed increased anti-correlation between a region within the cuneus (part of the pvDMN) and their equivalent of the salience network (Kilpatrick et al., 2011). In another study, Hasenkamp and Barsalou (2012) performed a whole brain resting state FC analysis of a network comprising bilateral posterior cingulate cortex (PCC) and ventro-medial prefrontal cortex (VMPFC) regions of interest, representing the DMN, and compared this between high and low practice meditators. Supporting the present study, they found a decrease in correlation between the hubs of the DMN and the insSN, in high practiced meditators (Hasenkamp and Barsalou, 2012). The SN has been hypothesized to be involved in the detection and evaluation of motivationally salient stimuli, i. e. stimuli with relevance for the organism (Seeley et al., 2007) and in controlling interactions between the DMN and CEN (Sridharan et al., 2008), while the DMN is involved in memory, self-related, and social processing (for a review, see Buckner et al., 2008). Furthermore, the DMN has been shown to be activated during mind wandering (Hasenkamp et al., 2012; Mason et al., 2007). Anti-correlation could be interpreted as a clearer distinction between the networks which might result in better effective connectivity (Lewis et al., 2009; Deco et al., 2009;

Clare Kelly et al., 2008*)*. Following this line of thought, an increased anti-correlation between insSN and the pvDMN might indicate improved sensitivity to mind wandering in more mindful individuals. This anti-correlation-based connectivity between the insSN and pvDMN was particularly related to the FMI, which is focused on measuring the accepting stance towards all experience that is inherent to mindfulness (Walach et al., 2006). The pvDMN included the PCC, which is active during personal evaluations (Whitfield-Gabrieli et al., 2011) and emotional processing (Kober et al., 2008), which has been hypothesized to be related to the meditative experience (Brewer and Garrison, 2013). Together with the insSN's involvement in directing attention to salient stimuli (Seeley et al., 2007), stronger negative correlation between pvDMN and insSN might indicate a less evaluative stance during rest towards experience, which would fit well with the topic of the FMI measuring acceptance (Walach et al., 2006).

Interestingly, participants of the studies cited above (Hasenkamp and Barsalou, 2012; Kilpatrick et al., 2011) had considerable more experience with meditation than the participants of the present study, but show a comparable pattern of changes in connectivity. It seems thus, that changes in connectivity between the SN and the DMN are among the first to become apparent during mindfulness training that could be extended by changes in connectivity of e.g. task positive or attentional networks.

In addition to the above mentioned results, we found several results that were significant only at trend level. The connection of the aDMN and the lCEN being sensitive to mindfulness may confirm results found previously for experienced meditators (Hasenkamp and Barsalou, 2012; Taylor et al., 2013) although these studies found an increase in connectivity rather than a reduction for experienced meditators. The CEN is thought to be involved in the redirection of attention (Corbetta and Shulman, 2002), while the aDMN, specifically the ventromedial PFC is involved in self-related processing (e.g. Andrews-Hanna et al., 2010). The present data might suggest that more mindful individuals may have a lower correlation between these networks, which could indicate an increased switching of attention away from self-related towards e.g. more sensory focused processing.

Moreover, we found a relationship of mindfulness scores and connectivity of the lCEN and the accSN, which had not been investigated previously. The accSN has been associated with processing of emotions, cognition and action inhibition (Smith et al., 2009). Speculating towards a reduced connectivity between the lCEN and accSN in more mindful individuals, it might be possible that this emphasizes conscious attentional processing over emotional value based evaluation of stimuli. Together, the present data show that connectivity in resting state networks may be sensitive for mindfulness effects. Concerning the direction of mindfulness effect (i.e. more or less inter-iFC), there are a number of inconsistencies about certain connections and the directionality in the literature and consequently when comparing our findings with those of previous studies. Possible explanations for these irregularities could be factors related to study design that can influence resting state connectivity. Activations during tasks performed immediately before a resting sate scan have been shown to carry over into resting state connectivity (Tambini et al., 2010). This might e.g. occur if meditation is performed or trained immediately before the resting state scan. Researchers should consider an appropriate break between task or training and rest scans. Similarly, we cannot control for what participants actually do during the resting state scan. Especially in meditation research this aspect is critical as meditation itself is performed under conditions very similar to resting and some individuals might by default engage in focused attention or other meditation during rest. This aspect is seldom discussed and should receive additional attention. Future studies should carefully instruct participants before performing a resting state scan making sure participants do not enter a meditation state.

CONNECTIVITY BETWEEN THE ANTERIOR AND POSTERIOR DMN

The present study showed that the connectivity of the anterior and the posterior parts of the DMN was sensitive to mindfulness ability (Figure 3). The DMN has most strongly been in the focus of mindfulness research and a number of studies have reported connectivity changes related to mindfulness (Brewer et al., 2011; Hasenkamp and Barsalou, 2012; Jang et al., 2011; Kilpatrick et al., 2011; Shaurya Prakash et al., 2013; Taylor et al., 2013). The present study showed decreased connectivity in individuals with higher mindfulness ability between the aDMN and pdDMN. This result is in accordance with the results by Hasenkamp and Barsalou (2012) who found that a region in mPFC/ACC showed decreased connectivity with the PCC, the main hub of the pDMN, in mindfulness experts compared to novices. However, this result seems to contradict two previous results, which showed increased connectivity in more mindful individuals (Shaurya Prakash et al., 2013) and in experienced meditators (Jang et al., 2011). Yet, while one of these studies focused on elderly participants (Shaurya Prakash et al., 2013) the other used a region of interest approach to identify the DMN, which does not differentiate between posterior and anterior DMNs (Jang et al., 2011). These differences in study design might explain the difference in the results. In addition, other studies did not find any relationship for the connection of the anterior and posterior parts of the DMN with mindfulness (Kilpatrick et al., 2011; Taylor et al., 2013). The main hubs of the DMN are the precuneus/PCC (posterior

DMN) and the VMPFC/ACC region (anterior DMN). The precuneus, is involved in the affective relevance of a given stimulus and is a critical structure for conscious processing (for a review, see Vogt and Laureys, 2005) while the VMPFC is involved in self-referential processing (Andrews-Hanna et al., 2010). A decreased connectivity of the aDMN and pDMN might indicate that more mindful individuals interpret the affective relevance of a given stimulus as less self-related. This is also supported by the association of the MAAS questionnaire with this connectivity. The MAAS focuses on measuring the ability to consciously perceive the present moment (Brown and Ryan, 2003). This present moment experience has been associated with a deactivation of the PCC/Precuneus (Garrison et al., 2013) area and with activations in dorso medial (Hölzel et al., 2007; Dickenson et al., 2013) and lateral prefrontal regions (Brefczynski-Lewis et al., 2007). Thus, this would speak for a reduced synchrony of the antDMN and the pDMN regions during this experience, which could transition into a stronger decoupling of these parts of the DMN network in more mindful individuals during rest. Instead, these regions may be coupled more strongly to either lateral parietal or DLPFC in expert meditators. E.g. Brewer et al. (2011) found increased connectivity between the PCC, dorsal ACC and dlPFC in participants with more meditation experience both during rest and during different kinds of meditation. The authors interpreted these results as an at baseline increased connectivity and activity of task positive control regions together with reduced activation of the DMN in experienced meditators regardless of condition. Other authors have argued for a coactivation of the aDMN together with inferior parietal regions during rest, which might reduce distractibility by mind wandering in experienced meditators (Hasenkamp and Barsalou, 2012). Our data are more in accordance with the model by Hasenkamp & Barsalou (2012), which suggests a critical interplay between medial DMN and lateral CEN for engaging attention on present experience. Instead of being engaged in mind-wandering which results in activation of the anterior and posterior DMN (Mason et al., 2007), regions in the DMPFC might be responsible for focusing attention back to present experience likely reflected by stronger anti-correlated coupling between CEN and DMN. Future studies will have to further clarify the directionality of connectivity between the anterior DMN, posterior DMN, and attention-relevant regions of frontal and parietal CEN and how this is related to meditation experience and mindfulness disposition.

LIMITATIONS

To evaluate the key findings of our study, some limitations have to be considered. Firstly, our approach to study the relevance of inter-iFC in neuro-cognitive key networks for mindfulness is a correlation-based approach (i.e. we linked mindfulness scores with inter-iFC via linear correlation). Whether increased negative iFC between SN and DMN, which we demonstrated to correlate with mindfulness ability, is causal for the variability in mindfulness ability is not addressable by a correlation-based approach. To address such causal link between inter-iFC and mindfulness, controlled longitudinal training studies of mindfulness practice are necessary. In such studies, a controlled change in mindfulness ability can be linked with changes in inter-iFC of neuro-cognitive key networks. Secondly, given the wide range of functional domains, in which SN, CEN, and DMN are involved, it is hard to specify the behavioral implications of inter-iFC variability for mindfulness (i.e. which functional aspect of neuro-cognitive networks is relevant for mindfulness). Future studies combining resting-state and task fMRI with mindfulness might be helpful, if tasks are included that are part of mindfulness practice such as e.g. focused attention to breathing."

MINDFULNESS AS A COUNTERWEIGHT OF PSYCHOPATHOLOGY.

It is striking that mindfulness impacts the connectivity of three resting state networks (DMN, CEN, and SN) that have been shown to play a critical role in various psychopathologies (Menon, 2011). In detail, it has been hypothesized that the SN acts to control switching between DMN and CEN: depending on the demands of the task at hand the SN is hypothesized to balance activation in the other two networks (Menon and Uddin, 2010; Sridharan et al., 2008). Given that mindfulness has been shown to reduce psychopathological symptoms (Aldao et al., 2010; Baer, 2003; Hofmann et al., 2010), affecting the inter-iFC might be one possible pathway for beneficial effects of mindfulness in psychotherapy.

CONCLUSION

Mindfulness is correlated with the inter-iFC of subnetworks of the default mode and salience networks. Specifically, more mindful individuals show a decreased correlation between the aDMN and pdDMN and stronger negative correlation between the insSN and pvDMN.

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TABLES

Table 1: Default mode (DMN), salience (SN), and central executive (CEN) network.

Network	Region	Voxel: T-value	P-value	Cluster size	Peak MNI-coordinates		
					x	y	z
aDMN	Left Anterior Cingulate Cortex	30.7	<0.01	2047	-6	53	1
	Left Middle Orbital Gyrus	30.6	<0.01		-6	47	-8
	Right Anterior Cingulate Cortex	29	<0.01		6	47	7
	Left Posterior Cingulate Cortex	11.6	<0.01	87	0	-52	28
pvDMN	Right precuneus	39.98	<0.01	2632	6	61	28
	Left Posterior Cingulate Cortex	28.34	<0.01		-6	-52	28
	Left Precuneus	34.4	<0.01		-6	-61	34
	Right Middle Cingulate Cortex	28.7	<0.01		12	-49	34
pdDMN	Left Precuneus	27.3	<0.01	1275	-12	-67	34
	Right Precuneus	26.3	<0.01		9	-70	37
	Left Cuneus	24.8	<0.01		-6	-76	34
accSN	Right middle Cingulate Cortex	27.1	<0.01	2714	9	26	31
	Left Anterior Cingulate Cortex	26.7	<0.01		-6	14	28
insSN	Right Insular Lobe	34.2	<0.01	891	45	14	1
	Left Insular Lobe	25.8	<0.01	813	-36	17	1
	Left Inferior Frontal Gyrus	18.8	<0.01		-39	14	-5
	Right Middle Cingulate Cortex	11.5	<0.01	280	9	11	40
	Left Middle Cingulate Cortex	9.7	<0.01		0	26	34
lCEN	Left Middle Frontal Gyrus	26.2	<0.01	1808	-36	56	7
	Left Superior Frontal Gyrus	19.9	<0.01		-24	13	63
	Left Inferior Parietal Lobule	18.9	<0.01		-54	-49	43
	Left Angular Gyrus	26.9	<0.01	1342	-42	-58	46
	Left Inferior Temporal Gyrus	19.5	<0.01	104	-54	-49	-8
	Left Middle Cingulate Cortex	10.0	<0.01		-3	-34	43
rCEN	Right Inferior Parietal Lobule	34	<0.01	1027	54	-58	40
	Right Angular Gyrus	32.9	<0.01		51	-58	31
	Right Middle Frontal Gyrus	16.8	<0.01	603	33	17	52
	Right Superior Frontal Gyrus	13.5	<0.01		21	26	55
	Left Angular Gyrus	17.2	<0.01	338	-42	-58	34
	Left Inferior Parietal Lobule	14.5	<0.01		-48	-55	46
	Right Precuneus	13.5	<0.01	216	6	-58	37
	Right Middle Cingulate Cortex	13.5	<0.01		6	-46	34

Table 1: Intrinsic brain networks of interest.

Shown are results of one-sample t-tests of resting state brain intrinsic brain networks after independent component analysis with 75 components (voxel wise family wise error correction for multiple comparisons, $p < 0.05$). Abbreviations: aDMN anterior default mode network, pvDMN posterior ventral default mode network, pdDMN posterior dorsal default mode network, accSN cingular salience network, insSN insula salience network, lCEN left central executive network, rCEN right central executive network.

Table 2: Inter-network functional connectivity.

Network	insSN	pdDMN	pvDMN	aDMN	accSN	rCEN	lCEN
insSN	1,00	0,08	-0,14	0,08	0,14	-0,09	-0,05
pdDMN	0,08	1,00	0,29	0,25	0,06	0,23	0,24
pvDMN	-0,14	0,29	1,00	0,33	-0,17	0,37	0,24
aDMN	0,08	0,25	0,33	1,00	0,17	0,29	0,15
accSN	0,14	0,06	-0,17	0,17	1,00	0,08	0,01
rCEN	-0,09	0,23	0,37	0,29	0,08	1,00	0,25
lCEN	-0,05	0,24	0,24	0,15	0,01	0,25	1,00

Table 2: Functional connectivity between intrinsic networks.

Shown are mean Pearson-correlation coefficients for each pair of networks of interest. Abbreviations: aDMN anterior default mode network, pvDMN posterior ventral default mode network, pdDMN posterior dorsal default mode network, accSN cingular salience network, insSN insula salience network, lCEN left central executive network, rCEN right central executive network.

Table 3: Pearson's correlation coefficients of inter-network connectivity and mindfulness ability.

	rCEN / lCEN	aDMN / lCEN	aDMN /rCEN	aDMN /accSN	pvDMN / lCEN
r-value FMI	0,05	0,29	-0,06	0,02	0,13
P-value	0,82	0,16	0,79	0,94	0,54
r-value MAAS	-0,12	-0,40	-0,18	0,02	-0,33
P-value	0,55	0,05*	0,39	0,92	0,10

	pdDMN / lCEN	pdDMN / rCEN	pdDMN / aDMN	pdDMN / pvDMN	pdDMN / accSN
r-value FMI	0,13	0,01	-0,36	-0,16	0,14
P-value	0,53	0,98	0,09	0,45	0,50
r-value MAAS	0,24	-0,13	-0,65	-0,10	0,03
P-value	0,24	0,51	< 0,01**	0,63	0,87

	pvDMN / rCEN	pvDMN / aDMN	pvDMN / accSN	accSN / lCEN	accSN / rCEN
r-value FMI	-0,05	-0,09	0,11	-0,45	-0,14
P-value	0,80	0,69	0,61	0,03*	0,53
r-value MAAS	-0,09	-0,30	0,04	0,06	-0,11
P-value	0,66	0,14	0,83	0,79	0,59

	insSN / lCEN	insSN / rCEN	insSN / aDMN	insSN / pvDMN	insSN / accSN
r-value FMI	-0,04	-0,34	-0,53	-0,60	-0,02
P-value	0,86	0,10	0,01*	< 0,01**	0,94
r-value MAAS	0,33	0,08	-0,13	-0,14	0,02
P-value	0,09	0,69	0,53	0,49	0,93

	insSN / pdDMN
r-value FMI	-0,09
P-value	0,67
r-value MAAS	0,30
P-value	0,14

Table 3: Pearson's correlation coefficients between inter-network intrinsic functional connectivity and mindfulness ability.

*Abbreviations: MAAS Mindful Attention and Awareness Scale, FMI Freiburg Mindfulness Inventory, aDMN anterior default mode network, pvDMN posterior ventral default mode network, pdDMN posterior dorsal default mode network, accSN cingular salience network, insSN insula salience network, lCEN left central executive network, rCEN right central executive network. * sig at $p < 0.05$ **sig with Bonferroni correction for multiple comparisons for 21 multiple comparisons (corrected threshold $p = 0.0024$).*

Table 4: Control analysis: Inter-network connectivity and associations with mindfulness.

Network	Vis1 / Vis2	Vis1 / Vis 3	Vis2 / Vis3
Inter-iFC	0.27	0.43	0.38
Correlation with FMI	-0.34	-0.33	-0.38
p-value	0.1	0.11	0.07
Correlation with MAAS	-0.18	-0.12	-0.09
p-value	0.38	0.57	0.67

Table 4: Control analysis: Inter-network connectivity and associations with mindfulness of visual networks.

Shown are mean Pearson-correlation coefficients for each pair of visual control networks and below corresponding correlations of inter-iFC and mindfulness scores. Abbreviations: Vis1 visual network 1, Vis2 visual network 2, Vis3 visual network 3, FMI Freiburg Mindfulness Inventory, MAAS Mindful Attention and Awareness Scale.

Table 5: Control analysis: inter-network connectivity between visual networks and neuro-cognitive key networks and associations with mindfulness ability.

Network	insSN	pdDMN	pvDMN	aDMN	accSN	lCEN	rCEN
Visual 1	0.04	0.30	0.17	0.13	-0.08	0.15	-0.05
Correlation with FMI	-0.07	-0.12	0.02	-0.36	0.35	0.31	0.31
p-value	0.75	0.57	0.93	0.08	0.09	0.14	0.14
Correlation with MAAS	0.21	0.00	-0.22	-0.09	0.28	0.10	0.10
p-value	0.31	0.99	0.27	0.66	0.16	0.64	0.64
Visual 2	0.05	0.29	0.23	0.09	-0.18	0.11	> -0.01
Correlation with FMI	-0.24	-0.11	-0.27	0.02	0.04	0.28	0.35
p-value	0.25	0.61	0.20	0.94	0.84	0.18	0.09
Correlation with MAAS	0.14	0.00	-0.23	-0.27	-0.22	0.15	0.02
p-value	0.51	0.99	0.26	0.17	0.28	0.47	0.92
Visual 3	0.10	0.23	0.12	< 0.01	-0.21	-0.07	0.04
Correlation with FMI	-0.17	-0.09	-0.14	-0.53	0.28	0.28	0.28
p-value	0.43	0.69	0.52	0.01	0.18	0.18	0.18
Correlation with MAAS	0.13	0.08	-0.18	-0.16	0.09	0.15	0.15
p-value	0.53	0.69	0.37	0.43	0.65	0.47	0.47

Table 5: Control analysis: inter-network connectivity between visual networks and neuro-cognitive key networks and associations with mindfulness ability.

*Shown are mean Pearson-correlation coefficients for each pair of networks of interest and three control networks. In addition, correlations and p-values of the respective inter network connectivity and mindfulness scores are shown. Abbreviations: aDMN anterior default mode network, pvDMN posterior ventral default mode network, pdDMN posterior dorsal default mode network, accSN cingular salience network, insSN insula salience network, lCEN left central executive network, rCEN right central executive network. Vis1 visual network, Vis 2 visual network 2, Vis3 visual network 3, * p-value significant without bonferroni correction (cutoff p = 0.0024).*

9. PAPER FOUR: SHIFTED INTRINSIC CONNECTIVITY OF CENTRAL EXECUTIVE AND SALIENCE NETWORK IN BORDERLINE PERSONALITY DISORDER

This paper comprises the report of an experiment that investigated the changes in functional connectivity between three key cognitive networks: the DMN, SN and CEN in borderline personality disorder. The paper has been published in the journal “Frontiers in Human Neuroscience” in 2013. The article is reprinted here with permission of Frontiers in Human Neuroscience. The following authors were involved in the creation of this manuscript: Anselm Doll, Christian Sorg, Andrei Manoliu, Andreas Wöller, Chun Meng, Hans Förstl, Claus Zimmer, Afra M. Wohlschläger, Valentin Riedl. The author of this thesis performed the data analysis. Writing of all parts of the manuscript was performed by the author of the thesis together with C. Sorg, thus sharing first authorship. The co-authors were involved in the editing of introduction, methods, results and discussion.

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Shifted intrinsic connectivity of central executive and salience network in borderline personality disorder

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Borderline personality disorder (BPD) is characterized by "stable instability" of emotions and behavior and their regulation. This emotional and behavioral instability corresponds with a neurocognitive triple network model of psychopathology, which suggests that aberrant emotional saliency and cognitive control is associated with aberrant interaction across three intrinsic connectivity networks [i.e., the salience network (SN), default mode network (DMN), and central executive network (CEN)]. The objective of the current study was to investigate whether and how such triple network intrinsic functional connectivity (iFC) is changed in patients with BPD. We acquired resting-state functional magnetic resonance imaging (rs-fMRI) data from 14 patients with BPD and 16 healthy controls. High-model order independent component analysis was used to extract spatiotemporal patterns of ongoing, coherent blood-oxygen-level-dependent signal fluctuations from rs-fMRI data. Main outcome measures were iFC within networks (intra-iFC) and between networks (i.e., network time course correlation inter-iFC). Aberrant intra-iFC was found in patients' DMN, SN, and CEN, consistent with previous findings. While patients' inter-iFC of the CEN was decreased, inter-iFC of the SN was increased. In particular, a balance index reflecting the relationship of CEN- and SN-inter-iFC across networks was strongly shifted from CEN to SN connectivity in patients. Results provide first preliminary evidence for aberrant triple network iFC in BPD. Our data suggest a shift of inter-network iFC from networks involved in cognitive control to those of emotion-related activity in BPD, potentially reflecting the persistent instability of emotion regulation in patients.

Keywords: resting-state functional connectivity, brain networks, central executive network, default mode network, salience network, brain connectivity, large-scale networks, triple network hypothesis

INTRODUCTION

Borderline personality disorder (BPD) is characterized by "stable instability" (Schmideberg, 1959) of emotions, impulsivity, social relationships, and self-image. Additionally most patients suffer from chronic feelings of emptiness, complex dissociations, self-injury, and suicidal tendencies with a suicide rate of 10% (Oldham, 2006). BPD, which often co-occurs with other psychiatric disorders (about 85% of patients with BPD fulfill criteria for having at least one Axis I disorder; Lenzenweger et al., 2007), is common with a prevalence of more than 20% for psychiatric inpatients (Torgersen, 2005). Behavioral and emotional dysregulation is suggested as critical factors underlying this variety of symptoms (Leichsenring et al., 2011). We suggest that the stability of fluctuating symptoms across time and different situations might be related to consistent and profound functional alterations in the patient's brain intrinsic functional architecture, particularly in brain regions involved in behavior/emotion regulation.

Previous functional neuroimaging studies revealed context specific patterns of altered brain activity in BPD patients during emotion- or self-related tasks. For example, negative emotional pictures or fearful/angry faces evoke stronger activity in the extrastriate, posterior cingulate, and frontal cortices, as well as weaker activity in the amygdala (Minzenberg et al., 2007; Koenigsberg et al., 2009a; Niedtfeld et al., 2010; Hazlett et al., 2012). In healthy subjects, self-distancing of negative pictures activates parietal regions overlapping with the so-called default mode network (DMN) including the medial prefrontal, medial and lateral parietal cortex (Koenigsberg et al., 2009b). Patients with BPD, however, fail to activate the DMN but show increased activity in the amygdala. On the contrary, memories of unresolved life events activate regions of the DMN in addition to amygdala, insula, and occipital cortices in patients (Beblo et al., 2006). Overall, emotional and self-related context increasingly activates an aberrant distributed pattern of brain regions including the DMN, insula, amygdala, and occipital cortices in BPD patients.

The measure of intrinsic functional connectivity (iFC), i.e., coherence of ongoing blood-oxygenation-level-dependent (BOLD) signal fluctuations in resting-state functional magnetic resonance imaging (rs-fMRI) data, is a surrogate for organized intrinsic brain activity (Fox and Raichle, 2007). At a large-scale level, coherent BOLD activity across remote brain areas forms consistent intrinsic connectivity networks (ICNs) in humans (Damoiseaux et al., 2006). Importantly, ICNs show strong spatial correspondence in independent analyses of resting-state and task-related activity patterns (Smith et al., 2009; Laird et al., 2011), suggesting that certain intrinsically coupled functional networks are also systematically engaged during cognition and behavior. Moreover, direct evidence exists that ongoing activity in ICNs serves as a scaffold for patterns of evoked neuronal activity (Keller et al., 2011), supporting the idea that the intrinsic architecture maintains and updates the brain's repertoire of functional responses.

A recently proposed neurocognitive framework identified ICNs related to self-, emotion-, and cognitive control processing as neurocognitive "core" networks to study higher cognitive function and dysfunction (Menon and Uddin, 2010; Menon, 2011). In more detail, the anterior and posterior DMN (a/pDMN) covering the medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC), and precuneus consistently activate during self-related and social cognitive functions (Buckner et al., 2008; Andrews-Hanna et al., 2010). The salience network (SN) covers anterior and posterior parts of the insula (AI, PI) and the anterior cingulate cortex (ACC) is critically involved in emotions, pain, and interoception (Seeley et al., 2007; Taylor et al., 2009; Legrain et al., 2011). Finally, left and right lateralized fronto-parietal networks (central executive network, CEN) are robustly associated with cognitive and executive control processes during goal-directed behavior (Seeley et al., 2007; Dosenbach et al., 2008; Habas et al., 2009). The consistent involvement of these three networks does not exclude other areas or networks to be also relevant for these functions particularly in specific contexts. However, it seems that these networks critically contribute (like a "core") to self-, emotion-, and cognitive control-related processes (Menon, 2011), which are impaired in patients with BPD.

Several studies reported aberrant iFC within and across these ICNs in various neuropsychiatric diseases such as major depression (MD) or schizophrenia (Greicius, 2008; Hamilton et al., 2011; Uddin et al., 2011; Manoliu et al., 2013a,b) indicating the large-scale brain impact of these diseases on basic intrinsic functional network architecture and associated functions (for review, see also Menon, 2011; Palaniyappan and Liddle, 2012; Hamilton et al., 2013). Due to both the persistent nature of BPD and its "stable instability" in emotion-, self-, and control-related functions, we suggest altered iFC among DMN, SN, and CEN in BPD. In the so far only previous study focusing on iFC in BPD, Wolf et al. (2011) found aberrant (i.e., increased and decreased) iFC within the DMN and CEN of patients with BPD; but this did not yield information about the SN and the intrinsic connectivity across networks. To test our hypothesis about aberrant iFC within and across SN, DMN, and CEN in BPD, we acquired rs-fMRI data from patients with BPD and matched healthy controls (HC). We applied data-driven, high-model-order independent component analysis (ICA) to the rs-fMRI data to extract ICNs of coherent ongoing BOLD activity (Calhoun et al., 2001; Allen et al., 2011). We then examined the relationship, i.e., iFC, within (intra-iFC) and between (inter-iFC) ICNs-of-interest and provide a new measure capturing the balance across these neurocognitive networks.

MATERIALS AND METHODS

SUBJECTS

Fourteen right-handed patients and 16 age-, sex-, and handedness-matched HC participated in the study after signing the informed consent form in accordance with the Human Research Committee guidelines of the Klinikum Rechts der Isar, Technische Universität München (**Table 1**). Patients were recruited from the Department of Psychiatry, Klinikum rechts der Isar, Technische Universität München. Controls were recruited by word-of-mouth advertising from the larger Munich area. Participants' examination included medical history, psychometric assessments [i.e., Beck Depression Inventory (BDI; Beck et al., 1961), Hamilton Depression Scale (HDS; Hamilton, 1960), short version of the Borderline Symptom List (BSL; Bohus et al., 2001), and Global Assessment of Functioning (GAF) Scale (Endicott et al., 1976)] and a structured psychiatric interview for patients only [Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I; First et al., 1996b) and Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II; First et al., 1996a), German version]. All participants were examined by their psychiatrists (Andreas Wöller, Christian Sorg), professionally trained for SCID-based interviews with an inter-rater reliability of more than 95%. Psychiatric diagnoses were based on Diagnostic and Statistical Manual of Mental Disorders-IV (DSM IV).

Patients with BPD constitute a heterogeneous group of patients, who vary in diagnostic subcategories (e.g., with/without feeling of emptiness or stress-related paranoid ideation), comorbidity (e.g., with/without MD or post-traumatic stress disorder, PTSD), and degree of medication (e.g., with/without neuroleptica; Skodol et al., 2002). We adopted selection criteria for a representative group of patients recommended by Skodol et al. (1999) based on a longitudinal examination of 240 patients with BPD. BPD was the primary diagnosis for all patients. We excluded patients with current psychosis, intoxication, or confusional states, with a

Table 1 | Demographics and psychometric scores.

Parameter	Patients with BPD	HC
n	14	16
Age (year)	30.4	34.0
Sex, male/female	1/13	1/15
GAF	43.7 ± 9.1*	100 ± 0
HDS	17.1 ± 7.4*	0.5 ± 0.8
BDI	18.1 ± 15.4*	1.8 ± 2.7
BSL	51.0 ± 17.4*	10.9 ± 3.9

*Data are presented as mean ± SD. HC, healthy controls; BPD, borderline personality disorder; GAF, Global Assessment of Functioning, HDS, Hamilton Depression Scale; BDI, Beck Depression Inventory; BSL, Borderline Symptom List; *$p < 0.05$ (two-sample t-tests).*

history of schizophrenia, schizoaffective disorder or bipolar disorder but we allowed co-occurrence of Axis I disorders MD or PTSD and psychotropic medication (Skodol et al., 1999). Additional exclusion criteria were an age below 18 or above 60 years, pregnancy, neurological or internal systemic diseases, and general contraindications for MRI assessment. A detailed description of each patient's current comorbidity and medication can be found in **Table 2**. All control subjects were free of any current or past neurological or psychiatric disorder or psychotropic medication.

All participants in this study underwent 10 min of rs-fMRI with the instruction to keep their eyes closed and not to fall asleep. We verified that subjects stayed awake by interrogating via intercom immediately after the rs-fMRI scan. Before and after scanning, a medical examination of patients validated their stable condition and investigated whether they had feelings of odd situations during the scanning. No patient dropped out during the scanning session.

MRI DATA ACQUISITION

Magnetic resonance imaging was performed on a 3-T whole body MR scanner (Achieva, Philips, Netherlands) using an eight-channel phased-array head coil. For co-registration of functional data, T1-weighted anatomical data were obtained from each subject by using a magnetization-prepared rapid acquisition gradient echo sequence [time to echo (TE) = 4 ms, repetition time (TR) = 9 ms, time for inversion (TI) = 100 ms, flip angle = 5°, field of view (FoV) = 240 mm × 240 mm, matrix = 240 × 240, 170 slices, voxel size = 1 mm × 1 mm × 1 mm]. fMRI data were collected using a gradient echo planar imaging (EPI) sequence (TE = 35 ms, TR = 2000 ms, flip angle = 82°, FoV = 220 mm × 220 mm, matrix = 80 × 80, 32 slices, slice thickness = 4 mm, and 0 mm interslice gap; an fMRI run of 10 min results in 300 volumes).

fMRI DATA ANALYSIS

Preprocessing

For each participant the first three functional scans of each fMRI-session were discarded due to magnetization effects. SPM5[1] (Wellcome Department of Cognitive Neurology, London) was used for motion correction, spatial normalization into the stereotactic space of the Montreal Neurological Institute (MNI) with resampling of voxel size to 3 mm × 3 mm × 3 mm, and spatial smoothing by applying an 8 mm × 8 mm × 8 mm Gaussian kernel. None of the participants had to be excluded due to excessive head motion (linear shift <3 mm across run and on a frame-to-frame basis, rotation <1.5°). Two-sample t-tests between groups yielded no significant results regarding translational and rotational movements of any direction as well as voxel-wise signal-to-noise ratio of fMRI data calculated with DPARSFA toolbox[2] ($p < 0.05$).

Independent component analysis of fMRI data

Following a recent approach (Manoliu et al., 2013b), we applied high-model-order ICA to the preprocessed data by using the

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[1] http://www.fil.ion.ucl.ac.uk/spm/

[2] http://www.restfmri.net

Table 2 | Detailed clinical characteristics of patients with BPD.

Patients	Medication	Current comorbidity	History of comorbidity
1	Quetiapine 50 mg, Fluoxetine 20 mg	PTSD	Substance abuse
2	Olanzapine 5 mg, Quetiapine 600 mg (prolong), Escitalopram 20 mg	Alcohol abuse	MDD
3	Escitalopram 20 mg, Zopiclone 7.5 mg	Bulimia nervosa	Recurrent MDD
4	Quetiapine 100 mg, Lamotrigine 12.5 mg	Substance abuse, Cannabis dependence	Recurrent MDD
5	Quetiapine 300 mg (prolong), Sertraline 150 mg, Aripiprazole 10 mg	Multiple personality disorders	None
6	None	None	None
7	Atomoxetine 50 mg, Fluoxetine 20 mg, Paliperidone 3 mg	MDD, ADHD, alcohol abuse	Anorexia nervosa, recurrent MDD
8	Fluoxetine 40 mg	MDD	Substance abuse
9	Fluoxetine 30 mg, Quetiapine 12.5 mg, Pregabalin 225 mg	Undifferentiated somatoform disorder, alcohol abuse	Alcohol abuse
10	Aripiprazole 20 mg, Venlafaxine 150 mg	Alcohol abuse	Alcohol abuse
11	Pregabalin 300 mg, Quetiapine 60 mg, Venlafaxine 225 mg	PTSD, undifferentiated somatoform disorder, alcohol dependence	Recurrent MDD
12	None	None	None
13	Sertraline 75 mg	PTSD, substance abuse	Recurrent MDD
14	Sertraline 50 mg	Cannabis abuse	Recurrent MDD

BPD, borderline personality disorder; PTSD, post-traumatic stress disorder; MDD, major depressive disorder.

Group ICA of fMRI Toolbox (GIFT)-toolbox[3] (version 1.3h) with the infomax algorithm implemented in Matlab (Calhoun et al., 2001). Data were decomposed into 70 spatial independent components (ICs), correspondent with a recently suggested framework for high-model-order decomposition (Abou Elseoud et al., 2011; Allen et al., 2011). High-model-order ICA approaches yield ICs, which are in accordance with large-scale functional networks from low-order approaches but offer a more detailed and particularly robust decomposition of sub-networks (Damoiseaux et al., 2006; Kiviniemi et al., 2009; Smith et al., 2009). Before volumes were entered into ICA analysis, voxel-wise z-transformation on time course data $y_{ijk}(t)$ was applied by subtracting the mean $\langle y_{ijk}\rangle$ and dividing by the standard deviation σ_{ijk} $\{\hat{y}_{ijk}(t) = [y_{ijk}(t) - \langle \mathrm{y}_{ijk}\rangle]/\sigma_{ijk}\}$, t time, i,j,k directions in space; Sorg et al., 2007). The sensitivity of the multivariate ICA algorithm for correlation of variance between voxels, i.e., functional connectivity, was thereby rendered independent of the original BOLD signal magnitude across subjects. Data were concatenated and reduced by two-step principal component analysis (PCA), followed by IC estimation with the infomax algorithm. We subsequently ran 40 ICAs (ICASSO) to ensure stability of the estimated components (Himberg et al., 2004). This results in a set of average group components, which are then back reconstructed into single subject space employing a dual regression analysis (group ICA (GICA) back-reconstruction approach (GICA-3) in GIFT; Erhardt et al., 2011). Each thus reconstructed IC results in a spatial map of z-scores reflecting the within-network iFC (intra-iFC) of a voxel within this component and an associated time course of BOLD signal fluctuations representative for this IC. We then reintegrated the initially calculated scaling factor σ_{ijk} into the data by voxel-wise multiplication in order to preserve each individual's profile of variance magnitude while leaving the normalized time course component unchanged.

Network selection

As previously described (Manoliu et al., 2013b), we ran a multiple spatial regression with a previously established baseline set of functionally relevant ICNs as regressors of interest (Allen et al., 2011) to automatically identify DMN, SN, and CEN in our dataset. From this publication, we selected the posterior (IC 53) and anterior (IC 25) DMN (a/pDMN), left and right lateralized fronto-parietal networks (ICs 34 and 60) reflecting left and right CEN, and an insular network (IC 55) reflecting the SN. The template for the insular network revealed a second component covering PI and bilateral amygdala and hippocampus [which we called posterior SN (pSN) in contrast to the anterior SN (aSN); see also Seeley et al., 2007; Taylor et al., 2009; Legrain et al., 2011]. Due to the importance of insular structures in BPD we also selected this component for further analyses.

Statistical analysis

To evaluate the spatial consistency of ICNs (intra-iFC), we calculated voxel-wise one-sample t-tests on participants' reconstructed spatial maps using SPM5 for each ICN and group ($p < 0.05$, corrected for false discovery rate, FDR). We then examined group differences of intra-iFC. The individual z-maps were entered into voxel-wise two-sample t-tests and a conjunction map of the one-sample t-test image ($p < 0.001$ uncorrected) was applied as a mask to the analysis. In order to control for antipsychotic medication we added chlorpromazine (CPZ)-equivalent doses (Woods, 2003) as covariate-of-no-interest in all imaging analyses. The resulting SPMs were thresholded at $p < 0.001$ (voxel level) and $p < 0.05$ [corrected for family wise error (FWE) at cluster level].

In order to investigate group effects of inter-iFC *between* ICNs, we extracted each subject's IC-timecourse of a/pDMN, l/r CEN, and a/pSN, calculated pairwise Pearson's correlation coefficients between the time course of all ICNs for each subject, transformed the correlation matrix into z-values via Fisher r-to-z-transformation and tested differences between the two groups (two-sample t-tests with CPZ as covariate-of-no-interest, $p < 0.05$, Bonferroni-corrected for 15 pairwise correlations).

CEN/SN-inter-iFC index

Finally, we calculated the ratio (r) of overall inter-iFC for SN and CEN within the intrinsic functional architecture of DMN, SN, and CEN for each group controlling for effects of antipsychotic medication (two-sample t-test, $p < 0.05$): $r = \text{inter-iFC}_{\text{sum}}(\text{CEN})/\text{inter-iFC}_{\text{sum}}(\text{SN})$. Here, the inter-iFC$_{\text{sum}}$ reflects the inter-network connectivity of CEN and SN, and is calculated as the summarized absolute z-values of each network from the between ICN analysis. This integrated score is motivated by the idea that both SN and CEN interact with the DMN and among each other during emotion regulation, and that they are involved in cognitive control processes (task-positive networks; Seeley et al., 2007) with stronger representation of motivational/emotional aspects by the SN and of attention-related aspects by the CEN (Dosenbach et al., 2008; Menon, 2011; Hamilton et al., 2013).

RESULTS

Psychometric assessment revealed significant differences between patients and controls for GAF (two-sample t-test, $t = 17.3$, $p < 0.05$), HDS ($t = -7.1$, $p < 0.05$), BDI ($t = -3.1$, $p < 0.05$), and BSL ($t = -5.8$, $p < 0.05$) between the two groups (**Table 1**).

INTRA-iFC

Automated component selection, which was based on spatial templates representing subsystems of the DMN, SN, and CEN (see Figure 4 in Allen et al., 2011 for spatial templates), revealed six IC of interest from high-model-order analysis of fMRI data for each individual. The SN was represented in an anterior and posterior insular network (a/pSN), the DMN in an a/pDMN, and the CEN in left and right (l/r) CEN. Selected components were spatially consistent across groups and matched previous results of SN, DMN, and CEN (Allen et al., 2011; see **Figure 1** and **Table 3** for detailed description of intra-iFC within selected ICNs, $p < 0.05$, FDR-corrected).

Group comparisons of networks' intra-iFC revealed regionally increased intra-iFC in each ICN of patients and decreased intra-iFC in only two ICNs (i.e., pSN, lCEN; $p < 0.05$ FWE-corrected cluster level and Bonferroni-corrected for six ICNs; **Figure 2**;

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[3] http://icatb.sourceforge.net

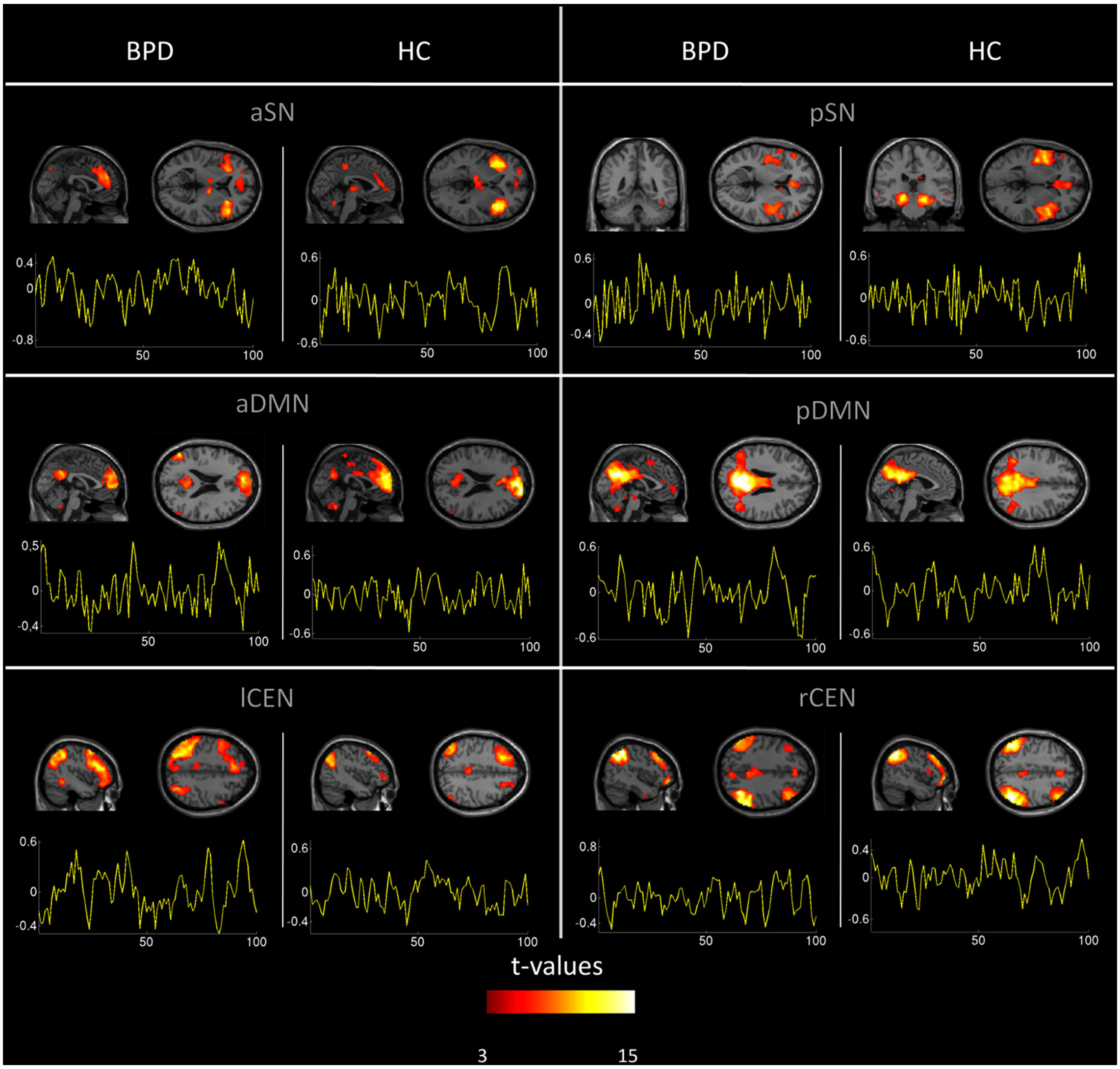

FIGURE 1 | Spatial maps and time courses of default mode, salience, and central executive network (DMN, SN, CEN) in healthy controls and patients. Spatial statistical parametric maps (SPM, one-sample *t*-tests controlled for medication) and associated time courses of intrinsic networks in healthy controls (HC) and patients with borderline personality disorder (BPD). Maps and time courses are derived from independent component analysis of resting-state fMRI of subjects. SPMs are thresholded at $p < 0.05$ FDR-corrected and superimposed on a single subject high resolution T1 image. Color coding (red > yellow) represents *t*-values ranging from 3 to 25. The *x*-axis of signal time courses reflects number of fMRI scans; the *y*-axis represents normalized signal amplitude. First to third row: anterior and posterior (a/p) DMN, anterior and posterior SN, left and right (l/r) CEN.

Table 4). Increased intra-iFC in the BPD group covered various brain regions (*midline structures*: ACC, PCC, medial frontal gyrus; *parietal lobe*: bilateral SPL; *insula*: posterior part), decreased intra-iFC occurred in right hippocampus and left superior frontal gyrus.

INTER-iFC

To explore inter-iFC across DMN, SN, and CEN, we calculated the pairwise correlation between network time courses and tested significance of correlations and their potential group differences by using one- and two-sample *t*-tests controlling for effects of medication (CPZ covariate-of-no-interest). In HC, we found significant inter-iFC for 9 of 15 network pairs, while only four significant correlations occurred in BPD ($p < 0.05$, Bonferroni-corrected, black lines in **Figure 3A**; **Table 5**). The analysis of group differences revealed specific changes in the intrinsic functional architecture of patients ($p < 0.05$, Bonferroni-corrected for 15 connections; **Table 5**). More specifically, absent inter-network connectivity was found mainly for interactions concerning the CEN where four of six connections significantly decreased. Contrary to this overall decrease of iFC in patients, two additional intrinsic inter-network connections occurred in the patients group for the SN (red lines in **Figure 3A**).

Interestingly, in our correlation analysis of ICA-derived network time courses we found increased connectivity between the r/lCEN and a/pDMN in HC. This finding might be

Table 3 | Spatial intra-iFC maps of DMN, SN, and CEN in controls and patients.

Networks and brain regions	HC					BPD				
	Cluster size	$t_{\max}$	MNI			Cluster size	$t_{\max}$	MNI		
			x	*y*	*z*			*x*	*y*	*z*
aDMN										
Superior frontal gyrus	2506	18.39	15	63	21	1460	14.39	−6	54	15
Anterior cingulate cortex		17.68	6	48	21		12.18	−3	60	30
Inferior frontal gyrus						63	6.24	−45	33	−12
Middle cingulate cortex	56	4.8	0	−3	30					
Posterior cingulate cortex, precuneus	195	6.78	0	−60	27	330	12.9	−3	−51	33
Angular gyrus						266	10.91	−51	−66	30
Precentral sulcus	54	6.5	−6	−36	66					
Cerebellum	155	10.11	12	−54	−42	43	5.12	6	−54	−42
Putamen						25	5.41	−21	6	12
Middle occipital gyrus						74	5.08	57	−63	24
pDMN										
Posterior cingulate cortex	2749	17.13	3	−48	21	4122	26.56	12	−48	30
Precuneus							22.45	−9	−57	33
Angular gyrus	247	15.48	45	−51	27					
Anterior cingulate cortex						39	3.87	6	39	21
Middle temporal gyrus	34	5.69	60	0	−21	79	4.87	−57	3	−24
Hippocampus						40	6.71	24	−36	−3
Cerebellum						47	4.12	−3	−24	−21
Fusiform gyrus						42	3.62	36	−75	−3
aSN										
Right anterior insula	882	18.58	39	18	−3	723	18.88	48	24	−3
Left anterior insula	696	12.84	−33	9	−6	631	12.78	−30	27	−6
Orbitofrontal gyrus						53	4.94	−30	51	−3
Anterior cingulate cortex	275	6.41	9	39	15	868	8.19	−9	48	18
Superior medial gyrus										
Middle cingulate cortex	81	6.39	−6	−36	45		9.32	9	24	33
Thalamus	138	7.46	−9	−21	6	14	4.86	−9	−9	9
Cerebellar vermis	53	6.33	9	−57	−30					
Middle frontal gyrus	37	5.02	33	51	12		12.78	−39	27	−6
Angular gyrus	150	6.31	48	−45	30					
pSN										
Right posterior insula	1239	11.6	48	9	0	679	14.82	51	−3	−12
Left posterior insula	892	11.03	−45	−12	3	487	11.96	−51	0	−6
Hippocampus	989	13.07	−15	−30	−6					
Anterior cingulate cortex	298	7.03	0	36	9	111	8.32	0	36	9
Inferior frontal gyrus	85	5.37	−48	30	15	50	5.91	−54	33	3
Right Amygdala	31	4.02	24	−3	−15					
lCEN										
Middle frontal gyrus	1229	13.95	−24	23	59	2580	14.51	−45	36	18
Superior frontal gyrus		10.09	−15	36	51					

(Continued)

Table 3 | Continued

Networks and brain regions	HC					BPD				
	Cluster size	$t_{\max}$	MNI			Cluster size	$t_{\max}$	MNI		
			x	y	z			x	y	z
Inferior frontal gyrus						277	10.05	48	36	21
Superior medial gyrus	181	7.25	0	63	0					
Middle orbital gyrus	47	5.44	−42	48	−3					
Middle cingulate cortex	388	8.86	0	−36	36					
Thalamus						62	5.95	−6	−15	12
Inferior parietal lobe	128	6.52	48	−60	27	2071	14.46	−27	−66	39
							13.49	−48	−42	48
Superior temporal gyrus						45	4.86	66	−15	6
Insula						66	4.27	42	0	6
Hippocampus						44	6.5	−15	−3	−21
Cerebellum	298	7.78	39	−75	−30	293	8.35	30	−66	−33
Superior occipital gyrus						255	8.13	33	−72	45
rCEN										
Middle frontal gyrus	1271	11.93	39	18	54	757	10.64	39	21	42
Middle orbital gyrus	54	4.92	−39	48	−9	220	8.54	36	51	−12
Middle cingulate cortex	85	7.68	3	−39	39	155	7.51	6	−45	33
Middle temporal gyrus	46	5.91	69	−42	0					
Inferior parietal lobule	641	19.16	−51	−54	45	665	10.65	−48	−54	48
Angular gyrus	1047	19.2	42	−60	39	967	20.56	42	−63	42
Precuneus						133	7.65	6	−78	42
Cerebellum	210	9.39	−36	−66	−42	124	7	−30	−66	−36
Fusiform gyrus						83	4.57	30	−66	−9

One-sample t-test (corrected for medication), $p < 0.05$ corrected for false discovery rate. HC, healthy controls; BPD, borderline personality disorder; aDMN, pDMN, anterior and posterior default mode network; aSN, pSN, anterior and posterior salience network; lCEN, rCEN, left and right central executive network. Coordinates are presented in MNI standard space.

counterintuitive, since CEN and DMN are usually found anti-correlated (e.g., Fox et al., 2005). However, our findings for CEN and DMN sub-networks are perfectly in line with those of Allen et al. (2011), suggesting that such sub-networks are positively related among each other. This result might be explained by recent findings of Smith et al. (2012) based on a combination of high-model order spatial and temporal ICA; these authors demonstrated that the DMN can be subdivided into several functionally distinct sub-networks, each with its own characteristic patterns of correlations and anticorrelations with other intrinsic networks.

Finally, the observed global "shift" of inter-iFC among SN and CEN in patients was reflected by an altered CEN/SN-inter-iFC index r (**Figure 3B**). This ratio reflects the relative intrinsic impact of the CEN in comparison to the SN within the global intrinsic functional architecture of SN, CEN, and DMN. We found a significant difference between r (controls) $= 1.64 \pm 0.80$ and r (BPD) $= 0.99 \pm 0.52$ with $p = 0.015$ (two-sample t-test), potentially indicating a relative shift from cognitive control to emotion processing in patients with BPD (**Figure 3B**).

DISCUSSION

The aim of this study was to investigate iFC among SN, DMN, and CEN in patients with BPD. This aim was motivated by previous findings demonstrating that interactions within and between these three networks contribute critically to behavior and emotion regulation; impaired emotion/behavior regulation, in turn, is suggested as an essential property of BPD. In a sample of 14 patients, we found aberrant intra-iFC in all three networks. While patients' inter-iFC of the CEN was generally decreased, only inter-iFC of the SN was increased. In particular, a "balance" index reflecting the relationship of CEN- and SN-inter-iFC across networks was strongly shifted from CEN to SN connectivity in patients. This result provides first preliminary evidence for aberrant intrinsic connectivity among the DMN, SN, and CEN in BPD. Data suggest that patients' impaired emotion/behavior regulation may rely on

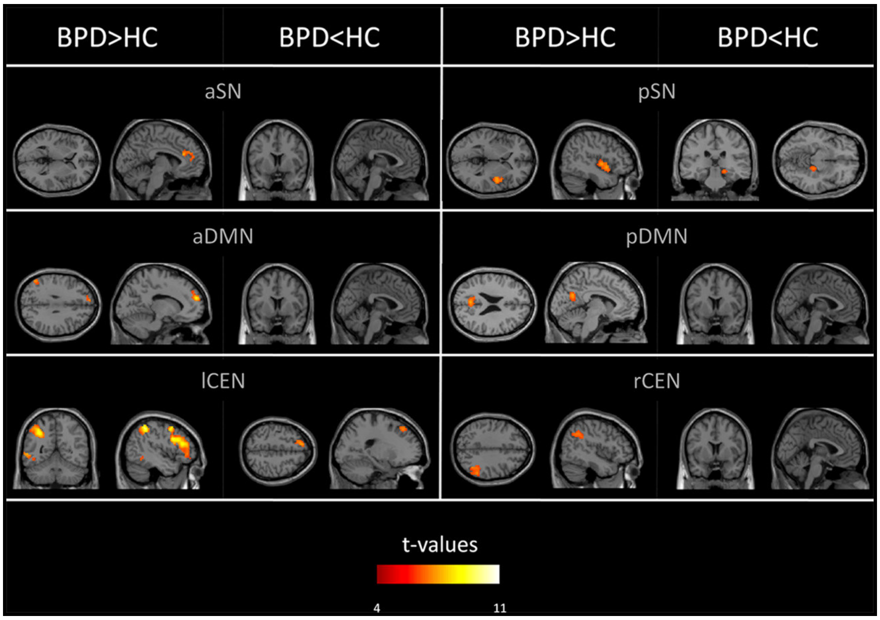

FIGURE 2 | Aberrant intrinsic functional connectivity within DMN, SN, and CEN (intra-iFC) of patients. SPMs of group differences in intra-iFC for the DMN, SN, and CEN (voxel-wise two-sample *t*-tests) controlled for antipsychotic medication. SPMs are thresholded at $p < 0.05$, FWE-corrected at cluster level and superimposed on a single subject high resolution T1 image. Color coding (red > yellow) represents *t*-values ranging from 4 to 11.

anomalous iFC among intrinsic networks that is centered on the SN.

ABERRANT INTRA-iFC IN SALIENCE, DEFAULT MODE, AND CENTRAL EXECUTIVE NETWORK IN BPD

In patients, we found increased intra-iFC in the DMN, SN, and CEN with increases covering midline structures such as frontal and parietal cingulate cortices, prefrontal cortices (PFC), parietal lobes, and insular regions (**Figure 2**; **Table 4**). Decreased intra-iFC was found in right hippocampi and in the left dorsolateral frontal cortex (**Figure 2; Table 4**). Identified group differences were not due to a disintegration of investigated networks in patients, since basic spatial maps of networks were both largely consistent across groups (**Figure 1**; **Table 3**) and in line with previous findings (Damoiseaux et al., 2006; Allen et al., 2011). Patients' counter-intuitively increased and decreased intra-iFC in intrinsic networks particularly in one and the same network (such as lCEN) has been observed also in other neuropsychiatric disorders such as schizophrenia (Manoliu et al., 2013b) or Alzheimer's disease (Zhou et al., 2010) and – in line with our findings – in BPD (for the DMN and CEN; Wolf et al., 2011); however, the functional significance of the direction of intra-iFC changes in brain disorders is still unclear (e.g., iFC decreases are suggested to reflect connectivity disruptions while iFC-increases might reflect compensatory processes; but also a loss of desynchronization and therefore system complexity may play a role; Zhou et al., 2010). Previous imaging studies, which explored the neural correlates of impaired self- or emotion-processing in BPD, revealed aberrant task-related activity in areas similar to those of aberrant intra-iFC we found (Minzenberg et al., 2007; King-Casas et al., 2008; Driessen et al., 2009; Koenigsberg et al., 2009a; Smoski et al., 2011; Holtmann et al., 2013). For example, patients with BPD, who had to engage with emotional stimuli, had aberrant levels of activity in ACC, dorsolateral PFC, and amygdala (Minzenberg et al., 2007; Koenigsberg et al., 2009a; Holtmann et al., 2013); the insula was found to be the key region distinguishing BPD patients from HC in a more complex setting of a gambling task (King-Casas et al., 2008); in healthy subjects, self-distancing of negative pictures activates parietal regions overlapping with DMN (Koenigsberg et al., 2009b), while patients with BPD fail to activate the DMN. Furthermore, so far limited literature of resting-state imaging data in BPD supports the spatially widespread pattern of functional changes in BPD. A study using ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET) found aberrant brain metabolism in prefrontal and cuneal regions (Juengling et al., 2003). Importantly, the only rs-fMRI study in BPD reported altered intra-iFC of prefrontal, cuneal, and insular regions within the DMN and CEN (Wolf et al., 2011), in line with our results. Taken together, our result demonstrates regionally specific iFC changes within DMN, SN, and CEN, which fit spatially previous findings of aberrant activity during tasks involved in emotion- and self-related processing.

ABERRANT INTER-iFC AMONG DMN, SN, AND CEN IN PATIENTS

In addition, we found altered inter-iFC among DMN, SN, and CEN in patients (**Figure 3**; **Table 5**). More specifically, we observed an overall decrease of inter-iFC (with only two significant exceptions); this decrease of inter-iFC concerned mainly the CEN while increases were only found in the SN (**Figure 3A**; **Table 5**). The "shift" from a rather evenly spread inter-iFC pattern among the three networks in HC (**Figure 3A**) to a SN-centered pattern in patients (**Figure 3A**) was further indicated

Table 4 | Group differences of intra-iFC maps for DMN, SN, and CEN.

Network with brain region	HC					BPD				
	Cluster size	$t_{\max}$	MNI			Cluster size	$t_{\max}$	MNI		
			x	*y*	*z*			*x*	*y*	*z*
aDMN										
Left superior medial frontal gyrus						108	7.35	−9	57	24
Left superior frontal gyrus							3.92	−12	51	33
Intraparietal junction						55	3.42	−51	−63	33
pDMN										
Left precuneus						207	6.67	−3	−63	24
aSN										
Left superior medial gyrus						111	5.13	−9	48	18
Left anterior cingulate gyrus							4.15	−3	45	9
Right anterior cingulate gyrus							4.07	6	45	12
pSN										
Right insular lobe						186	5.64	48	6	−6
Right hippocampus	38	4.45	21	−30	−12					
lCEN										
Left precentral gyrus						639	8.12	−45	12	30
Left inferior frontal gyrus (pars triangularis)							7.77	−42	3021	
Left inferior parietal lobule						398	9.06	−45	−45	51
Left middle temporal gyrus						47	5.51	−57	−54	0
Left superior frontal gyrus	85	5.21	−15	36	51					
rCEN										
Right angular gyrus						168	5.49	54	−48	30
Right inferior parietal lobule							4.54	45	−51	39

Two-sample t-test (corrected for medication), $p < 0.05$ corrected for family wise error at cluster level and Bonferroni-corrected for six comparisons; green indicates increased intra-iFC in patients, red reduced intra-iFC. HC, healthy controls; BPD, borderline personality disorder; aDMN, pDMN, anterior and posterior default mode network; aSN, pSN, anterior and posterior salience network; lCEN, rCEN, left and right central executive network. Coordinates are presented in MNI standard space.

by a strongly reduced CEN-/SN-inter-iFC index (**Figure 3B**). The strong impairment of coordinated activity among these networks appears to be in line with a previous EEG study that found strongly impaired gamma-band synchrony in the parietal lobes of BPD patients during a cognitive control task (Williams et al., 2006). The most prominent cognitive model of BPD suggests that patients have deficits in emotion regulation due to impaired interactions between (pre-)frontal and limbic areas (Skodol et al., 2002; Mauchnik and Schmahl, 2010; Malhi et al., 2013). This is supported by several above-mentioned task-fMRI studies of either emotion processing (Minzenberg et al., 2007; Koenigsberg et al., 2009a) or cognitive control (Driessen et al., 2009; Koenigsberg et al., 2009b; Lang et al., 2012). Since these prefrontal–limbic areas largely overlap with the DMN, CEN, and SN, our results suggest an integrative model of altered intrinsic connectivity between emotion- and cognitive control-relevant intrinsic networks in BPD, which may be related to prefrontal–limbic regulatory deficits. This model implicates that neither system nor brain region alone is responsible for the various and stable behavioral symptoms in BPD. Future studies combining rs-fMRI and task-fMRI are necessary to test explicitly the relationship between aberrant iFC and emotion-evoked activity in BPD.

PARALLELS WITH OTHER NEUROPSYCHIATRIC DISORDERS

Our result of aberrant iFC among DMN, SN, and CEN is largely consistent with the more general triple network hypothesis of psychopathology (Menon, 2011). This hypothesis states that psychopathological symptoms are associated with specifically altered coordinated activity across SN, DMN, and CEN; particularly, aberrant SN control function of DMN and CEN might underlie specific mental dysfunctions (Palaniyappan and Liddle, 2012). For example patients with schizophrenia with and without psychotic symptoms demonstrate distinctive changes of intra- and inter-iFC in the insular SN that are associated with impaired DMN/CEN interactions and positive and negative symptoms of patients (Manoliu et al., 2013a,b); in depressive patients, rumination is associated with aberrant coordination of intrinsic SN, DMN, and CEN activity (Hamilton et al., 2011). Concerning BPD, our data suggest that impaired behavior/emotion

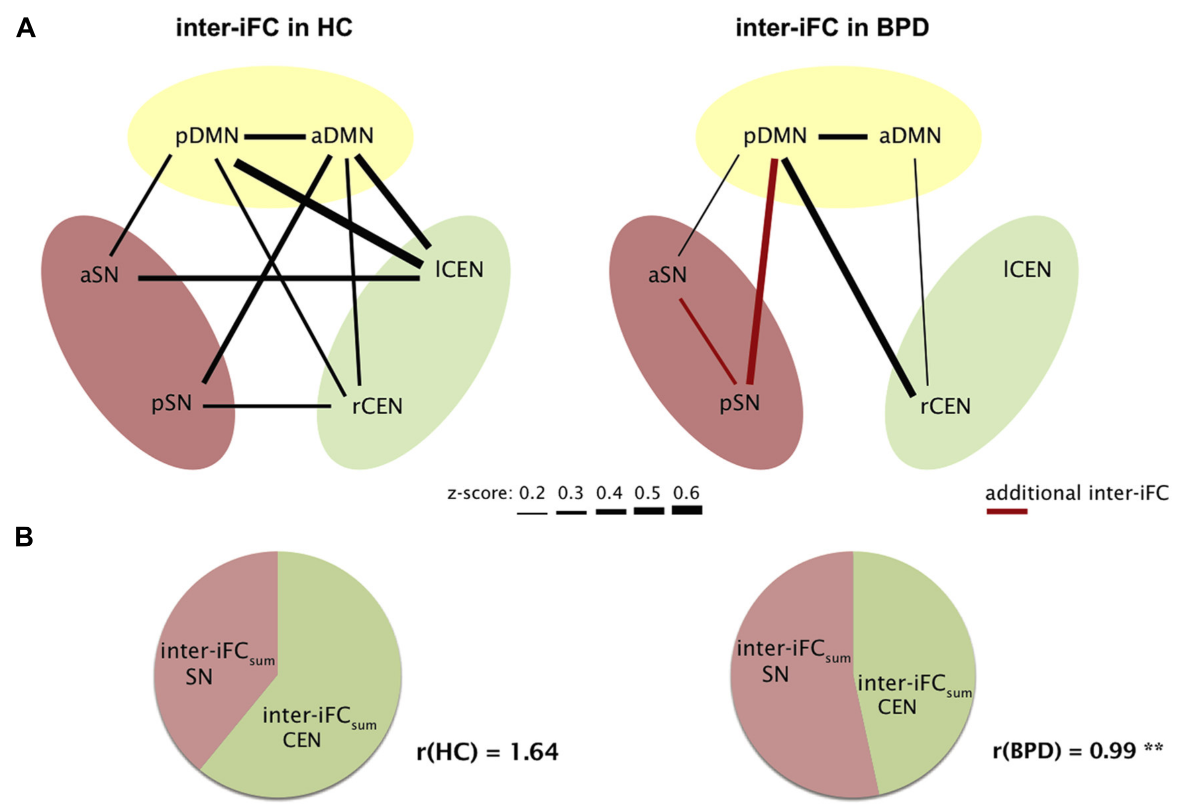

FIGURE 3 | Aberrant intrinsic functional connectivity between DMN, SN, and CEN (inter-iFC) of patients. (A) Inter-iFC between two networks is based on Pearson's correlation between network time courses. In healthy controls (HC), black lines indicate significant inter-iFC (one-sample *t*-tests, $p < 0.05$, Bonferroni-corrected for 15 correlations). Thickness of lines reflects absolute values of Fisher-*z*-normalized correlation coefficients. In patients with BPD, red lines indicate increased inter-iFC compared to healthy controls, while missing lines indicate significantly reduced and absent connections in BPD (two-sample *t*-tests, $p < 0.05$, Bonferroni-corrected). See also **Table 5** for correlation coefficients of significant inter-iFC. Results are controlled for antipsychotic medication. **(B)** For each subject, the ratio (*r*) of overall inter-iFC for CEN and SN within the intrinsic functional architecture of DMN, SN, and CEN was calculated by $r = \text{inter-iFC}_{\text{sum}}(\text{CEN})/\text{inter-iFC}_{\text{sum}}(\text{SN})$, with inter-iFC$_{\text{sum}}$ for CEN and SN, respectively, reflecting summarized absolute *z*-values of inter-iFC. We found significantly reduced *r* in patients (two-sample *t*-test, $^{**}p = 0.007$).

regulation might be associated with SN-centered inter-iFC reorganization of triple network functional architecture; however, more explicit evidence for such specific link between network interaction changes and behavioral deficits in BPD is necessary (for more detailed discussion of this point see below "limitations"). Furthermore, in comparing among different disorders one has to pay attention to potential confounding effects of psychotropic medication, which might be used in both compared disorders, e.g., antipsychotics in BPD and schizophrenia. Based on these findings, three basic questions about the specificity of aberrant triple network iFC in BPD arise: how specific are iFC changes for distinct psychopathological symptoms such as emotional response style or impulsivity in BPD? Beyond symptoms, how specific are iFC changes for comparisons with other neuropsychiatric disorders? Beyond triple network, which further brain changes outside the triple network such as subcortical or neurochemical changes are critical for distinct symptoms or differences with other disorders? To disentangle such questions, future studies, which may include different psychiatric disorders and brain measures beyond iFC, are necessary.

LIMITATIONS

First, although comparable with previous studies in BPD, the sample size of our study is small ($n = 14$; e.g., Koenigsberg et al., 2009a; Wolf et al., 2011; Lang et al., 2012). In general, a small sample size reduces the power of effects, and increases the likelihood of false positive results (Button et al., 2013). Therefore the presented results are preliminary and warrant further replication with higher sample sizes. Second, our patient sample is heterogeneous due to gender, comorbidity, and medication status. This heterogeneity is due to clinically based inclusion criteria, which provided a clinical representative patient sample (Skodol et al., 1999). On the one hand this heterogeneity together with small sample size precluded us to link brain changes with specific behavioral changes; in such groups, the distribution of symptom severity is too heterogeneous to allow for brain–behavior relationship analysis. On the other hand, our results are independent of specific BPD subgroups, suggesting that observed changes of triple network iFC are a general feature of BPD. Nevertheless, studies in more homogeneous sub-groups of BPD might be helpful to specify aberrant network iFC due to BPD sub-groups. Third, patients of the study were therapeutically treated with psychotropic substances

Table 5 | Inter-iFC between DMN, SN, and CEN.

Inter-iFC between ICNs	Healthy controls			BPD patients			Two-sample *t*-test (*p*)
	SEM	Mean	One-sample *t*-test (*p*)	SEM	Mean	One-sample *t*-test (*p*)	
aDMN–aSN	0.083	−0.089	0.300	0.112	0.144	0.220	0.177
aDMN–lCEN	0.059	0.472	0.000**	0.059	−0.036	0.550	0.000**
aDMN–pDMN	0.077	0.391	0.000**	0.086	0.417	0.000**	0.887
aDMN–pSN	0.067	0.361	0.000**	0.073	−0.063	0.406	0.000**
aDMN–rCEN	0.075	0.348	0.000**	0.086	0.262	0.010*	0.574
aSN–lCEN	0.089	−0.392	0.001**	0.079	0.014	0.860	0.003**
aSN–pSN	0.056	0.041	0.472	0.075	0.372	0.000**	0.009**
aSN–rCEN	0.084	−0.150	0.095	0.118	−0.017	0.889	0.323
lCEN–pDMN	0.064	0.563	0.000**	0.062	−0.112	0.095	0.000**
lCEN–pSN	0.090	−0.057	0.534	0.052	−0.035	0.507	0.783
lCEN–rCEN	0.112	0.236	0.053	0.097	0.056	0.574	0.220
pDMN–aSN	0.061	−0.347	0.000**	0.081	−0.236	0.012*	0.461
pDMN–pSN	0.082	−0.019	0.824	0.076	−0.446	0.000**	0.003**
pDMN–rCEN	0.083	0.354	0.001**	0.093	0.437	0.000**	0.672
rCEN–pSN	0.077	0.354	0.000**	0.089	−0.252	0.014*	0.000**

One-sample and two-sample t-tests (*$p < 0.05$ uncorrected, **$p < 0.05$, Bonferroni-corrected for 15 tests) including CPZ-equivalent doses as covariate-of-no-interest, for inter-iFC between intrinsic networks in healthy controls and patients with BPD (mean and standard error of Fisher r-to-z-transformed Pearson's correlation coefficient among network time courses). aDMN, pDMN, anterior and posterior default mode network; aSN, pSN, anterior and posterior salience network; lCEN, rCEN, left and right central executive network.

(**Table 2**). While we did control for antipsychotic medication, we did not control for antidepressant medication because no appropriate numerical procedure (comparable to CPZ conversion) is available for antidepressants. Previously, antidepressant effects on brain activity and functional connectivity have been discussed for the BOLD signal (Miller et al., 2001; Phillips et al., 2008; Heller et al., 2013). Although recent studies suggest that antidepressants normalize brain function (Anand et al., 2005; Fu et al., 2007; Heller et al., 2013), we cannot exclude antidepressant medication effects on our results. Future studies of non-medicated patients are necessary. Forth, some limitations concerning the use of ICA to identify ICNs have to be considered. Our selection of a model order 70 was empirical; although a model order of about 75 components seems to be an optimal choice (Abou-Elseoud et al., 2010), no clear computational or objective criterion for that number is available. Furthermore, the selection of ICNs of interest from ICA-derived components is intricate, particularly due to subjective bias; to account for this problem, we performed maximally controlled spatial regression analysis of all ICs on ICN templates as previously described (Manoliu et al., 2013b), which stem from a previous study using a very similar approach (Allen et al., 2011).

CONCLUSION

The current study provides evidence for aberrant iFC within and across DMN, SN, and CEN in patients with BPD. Data suggest a "shift" of inter-network iFC from networks of cognitive control to those of emotion-related activity, potentially reflecting the persistent instability of emotion regulation in patients.

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10. GENERAL DISCUSSION

Mindfulness has unique effects on well-being, interpersonal, and emotional functioning (Sedlmeier et al., 2012). In addition, it is associated with changes in the structure (Hölzel et al., 2008) and function of the brain (e. g., Slagter et al., 2007; Zeidan et al., 2011). The aim of this dissertation was to provide an investigation of brain processes involved in mindfulness for novices in order to generate predictions and hypotheses pertaining to the efficacy of mindfulness in the treatment of affective disorders. To this end, the study reported in paper one investigated the effects of the basic meditation technique “attention to breath”, a form of focused attention meditation on the neural correlates of *emotion regulation*, *learning*- in form of prediction error modulation - and correlations of *functional connectivity with trait mindfulness*. To investigate these effects we used task activation and connectivity analyses as well as resting state functional connectivity analysis of the BOLD response, measured by fMRI. This discussion comprises first a summary of the research findings presented in papers one to four, and second, a joint discussion of the conclusions beyond each of the individual experiments.

10.1 MINDFUL ATTENTION TO BREATH REGULATES EMOTIONS VIA INCREASED AMYGDALA-PREFRONTAL CORTEX CONNECTIVITY

Mindful attention to breath (ATB) is the most basic form of mindfulness exercise mostly used to teach novices. It has been shown to have good regulatory effects on emotions (e. g., Arch & Craske, 2006). ATB is associated with brain activations of fronto-parietal regions involved in the regulation of attention together with the insula and the ACC in beginners (Farb et al., 2007; Goldin et al., 2012; Haase et al., 2014; Taylor et al., 2011) while experts mainly show a deactivation of the default mode network (Desbordes et al., 2012; Taylor et al., 2011). However, there is considerable disagreement on the neural correlates of ATB in combination with aversive stimuli in novices regarding deactivation of the amygdala and regulatory regions like the insula and the ACC. We investigated the neural correlates of ATB in novices, controlled for breathing frequency, after two weeks of training ATB. Participants were asked to watch negative pictures either during ATB or passive viewing. Valence ratings of aversive pictures were found to be less negative during ATB than during passive viewing. This was accompanied by reduced activation of the right amygdala and increased activation in fronto-parietal, lateral, and medial frontal activations, which were independent of breathing frequency. A connectivity analysis revealed increased connectivity of the left PFC and the right amygdala during ATB, which was associated with trait mindfulness scores of the MAAS. Activation during emotion regulation by ATB and functional connectivity of the amygdala overlapped in left middle frontal gyrus.

The activations seen during ATB in frontal, parietal, temporal and cingulate cortices are replications of earlier studies on mindful emotion regulation. For example, when presented with emotional pictures during a mindful state, novice meditators showed activation of parietal, temporal, DMPFC and ACC (Taylor et al., 2011), while during pain, ATB activated the ACC, insula and orbitorfontal regions (Zeidan et al., 2011). Our findings are largely overlapping with these regions. However, we additionally showed that the pattern of brain activation during ATB critically depends on whether there is additional emotional stimulation or not.

Right amygdala deactivation also is a prominent finding in mindfulness studies that include aversive emotional stimuli (Creswell et al., 2007; Farb et al., 2007; Goldin & Gross, 2010; Hölzel et al., 2013; J. Lutz et al., 2013; Modinos et al., 2010; Taylor et al., 2011). Although some studies did not replicate this finding (Brefczynski-Lewis et al., 2007; Haase et al., 2014; Zeidan et al., 2011). Often, the deactivation of the amygdala is associated with less negative valence ratings of participants as in our experiment, which is the aim of emotion regulation strategies. However, deactivation of the amygdala can be interpreted as supression of emotional experience which would not be in accordance with the philosophy of mindfulness. In a similar line of thought, Engen & Singer (2015) compared the neural activations of compassion based meditation, a tradition that is closely linked with mindfulness and aims at producing a state of compassion (A. Lutz, Brefczynski-Lewis, Johnstone, & Davidson, 2008), with reappraisal. While they, too, found a deactivation of the amygdala during compassion meditation, this was not as strong as during reappraisal. Instead, they showed that compassion based meditation regulated emotion through the induction of increased positive affect, while also feeling the negative affect at the same time. Their data showed that amygdala activation does seem to be directly related to the feeling of negative emotion and stronger deactivation seems to be related to less experience of negative emotion (Engen & Singer, 2015). In addition, these data show that amygdala deactivation seems to be an often replicated finding of mindfulness based meditation techniques, as also shown in our experiment. In sumarry, two conclusions can be drawn from our analyses: (1) ATB leads to a deactivation of the amygdala during stimulation with aversive pictures. (2) The deactivation is associated with an increase in connectivity between DMPFC and the amygdala.

10.2 EFFECTS OF MINDFUL ATTENTION TO BREATH ON AVERSIVE PREDICTION ERROR-BASED LEARNING IN THE STRIATUM

Mindfulness has been shown to reduce anxiety (Zeidan et al., 2014) and has successfully been integrated in therapeutic interventions against anxiety disorders (for a meta-analysis, see Vøllestad, Nielsen, & Nielsen, 2012). Furthermore, relearning of conditioned responses is an essential aspect of anxiety therapy. It has been hypothesized that mindfulness can support relearning and extinction processes as well as serve as a cue for extinction supporting stimuli (Treanor, 2011). A recent review was partly dedicated to the support of mindfulness in re-learning and extinction effects and their potential applications in the therapy of anxiety disorders and concluded that mindfulness shows similarities with extinction processes (Tang et al., 2015). Learning is based on prediction error signals that stem from the ventral tegmental area (VTA) and, especially with aversive stimuli, from the striatum (for a meta analysis, see J. Garrison et al., 2013). However, no evidence exists that mindfulness based emotion regulation can modulate aversive prediction error signaling in human striatum. We used fMRI to record brain activations while participants predicted aversive pictures either during passive viewing or mindful attention to breath. Using the Rescorla-Wagner model (Rescorla & Wagner, 1972), we calculated prediction errors and explored related activations in the striatum. Results support a modulation of aversive prediction error signaling by ATB. During ATB, we found reduced aversive PE signaling in posterior putamen which is in line with the model of an anterior – reward, posterior – punishment prediction errors (Mattfeld, Gluck, & Stark, 2011; Seymour, Daw, Dayan, Singer, & Dolan, 2007). Furthermore, medial PFC showed a stronger functional connectivity with the right putamen during attention to breath. This is in line with evidence showing PE modulation through medial PFC during reappraisal of emotions (Delgado, Nearing, Ledoux, & Phelps, 2008). The medial PFC has been hypothesized to affect PE calculations by modulating synaptic gain (during voluntary attentional control) of visual cortex regions, which could change aPE related processing downstream (Kok, Rahnev, Jehee, Lau, & De Lange, 2012). Finally, mindfulness, as measured by the mindful attention and awareness scale (MAAS) predicted the strength of the DMPFC-putamen connectivity. The DMPFC is part of the anterior DMN that has been shown to have increased connectivity to posterior putamen after an eight week mindfulness training during rest (Kilpatrick et al., 2011), supporting our results. In summary, two conclusions can be drawn for these data: (1) mindfulness interventions can reduce aversive PE related activations in the striatum. (2) The signal for reduction is likely to stem from regions in the medial prefrontal cortex.

10.3 MINDFULNESS IS ASSOCIATED WITH INTRINSIC FUNCTIONAL CONNECTIVITY BETWEEN DEFAULT MODE AND SALIENCE NETWORKS

Attention to breath in novices is associated with activations in a fronto-parietal attention network, regions of the medial PFC, insula and subcortical areas (Dickenson et al., 2013). These regions are located within established resting state networks that are associated with attentional processes: the DMN (e. g., Buckner et al., 2008), central executive (Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008) and salience network (Seeley et al., 2007). In addition, mindfulness has been associated with changes in resting state connectivity of resting state networks (Brewer et al., 2011; Hasenkamp & Barsalou, 2012; Jang et al., 2011; Kilpatrick et al., 2011; Shaurya Prakash et al., 2013; Taylor et al., 2013). However, except for findings within the default mode network, these data are surprisingly variable, hampering clear conclusions. The study reported in paper three investigated the between network connectivity (inter-iFC) of the default mode (DMN), salience (SN) and central executive networks (CEN), involved during focused attention meditation, during rest in a sample of novice meditators that had received two weeks of mindfulness training. The data showed a correlation of mindfulness scores for the connectivity between subnetworks of the DMN and the SN and for the CEN and SN. Overall, trait mindfulness was associated with stronger anti-correlation between named networks. The study shows a link between ongoing intrinsic brain activations and mindfulness. Our data indicate that especially the functional connectivity between the posterior DMN and the SN may be sensitive to mindfulness. This is supported by similar results showing stronger negative correlations between these networks after an eight week course in MBSR (Kilpatrick et al., 2011). Furthermore, Hasenkamp and Barsalou (2012) also found a stronger decoupling of the SN and the hubs of the DMN in expert meditators. The significance of these networks during meditation may lie in the focus on sensory experience and detection of mind-wandering. Mind-wandering is associated with DMN activation (Mason et al., 2007), while the SN is thought to mediate attentional focus to motivationally salient stimuli (Seeley et al., 2007) and mediation between activation in DMN and CEN (Sridharan, Levitin, & Menon, 2008). A stronger decoupling between the DMN and the SN in more mindful individuals may relate to a clearer functional segregation and thus more effective information flow (Clare Kelly, Uddin, Biswal, Castellanos, & Milham, 2008; Deco, Jirsa, McIntosh, Sporns, & Kötter, 2009; Lewis et al., 2009). This hypothesis is supported by findings that show SN activation during the detection of mind-wandering, activation of the DLPFC, within the CEN, during focus on the breath, and the DMN during mind-wandering (Hasenkamp et al., 2012). However, the functional significance of between network connectivity is not well understood, preventing an interpretation of the functional effects of increased between network anti-correlation. Further studies are needed that follow the development of activity and connectivity over the course of mindfulness training. From the study reported in paper three, two conclusions can be drawn: (1) the inter-network functional connectivity between subnetworks of the SN and the DMN and (2) between subnetworks of the DMN are sensitive to trait mindfulness.

10.4 SHIFTED INTRINSIC CONNECTIVITY OF CENTRAL EXECUTIVE AND SALIENCE NETWORK IN BORDERLINE PERSONALITY DISORDER

Borderline personality disorder is characterized by a “stable instability” of emotions and their regulation, impulsivity and social relations (Schmideberg, 1959). Consistent aberrant intrinsic functional connectivity may be a biomarker of this psychiatric disorder (Greicius, 2008). Resting state functional connectivity analysis was used to investigate the inter-iFC between three cognitive networks that have been hypothesized to be affected in affective psychiatric disorders (Menon, 2011). Networks were identified using data driven independent component analysis. Results suggest increased connectivity within the DMPFC for the DMN and SN and in fronto-parietal cortex within CEN networks. In addition, the overall mean amount of inter-iFC of the SN to the other networks was significantly increased, while the inter-iFC of the CEN was decreased. This shift in balance from CEN in healthy controls towards the SN in patients indicates a change from networks involved in cognitive control towards to those related to emotional processing. Two conclusions can be drawn from the study reported in paper four: (1) borderline personality disorder is associated with a shift of intrinsic functional connectivity leading to increased connectivity of the salience network and (2) decreased connectivity of the central executive network.

10.5 INVOLVEMENT OF THE AMYGDALA AND THE PUTAMEN IN FOCUSED ATTENTION MEDITATION

From the above summary, it is apparent, that ATB with visual-emotional stimulation in novices resulted in activations of fronto-parietal regions and interactions between subcortical and prefrontal structures related to emotional processing and aPE computations. In detail, the critical prefrontal regions activated during emotion regulation included dorsal ACC, DMPFC, with bilateral middle and left inferior frontal gyri. Activation within these regions was accompanied by deactivations of the amygdala during regulation. Similarly, during ATB and aPE computations, we find a deactivation of the putamen. Furthermore, the right amygdala showed increased connectivity with the left frontal cortex, specifically the left middle frontal gyrus, while the putamen showed increased connectivity with DMPFC regions, specifically the right middle frontal gyrus. Thus, connectivity patterns seemed to peak at different, opposing sites on the right and left DMPFC during ATB depending on the subcortical structure.

Although overlap between the regions showing increased connectivity was small, those areas that overlapped converged within frontal midline areas: the VMPFC and DMPFC (Figure 3). These midline regions are involved in self referential processing (Northoff et al., 2006), part of the DMN, and involved in the regulation of subcortical regions via the ACC and VMPFC (Kober et al., 2008; Kohn et al., 2013). The reported PFC regions have shown increased activation in previous studies on mindfulness meditation (Baerentsen et al., 2010; Brefczynski-Lewis et al., 2007; Hölzel et al., 2007; Tomasino et al., 2012). A meta-analysis on FA meditation not only confirmed activation in these regions, but also found activations in subcortical structures, specifically the putamen (Tomasino et al., 2012). Similarly, a recent study investigating modulation of reward PE computations during meditation also found effects in the right putamen, supporting the effectiveness of ATB in the modulation of aPE by mindfulness shown in our results (Kirk et al., 2015). Furthermore, a number of studies involving stimuli with negative valence during mindfulness have shown a decrease in activation within the amygdala (Creswell et al., 2007; Farb et al., 2007; Goldin & Gross, 2010; Hölzel et al., 2013; J. Lutz et al., 2013; Modinos et al., 2010; Taylor et al., 2011). Although these subcortical structures seem to play an integral part in the neural correlates of mindfulness, subcortical activations have received considerably less attention within the literature of mindfulness. Our data emphasize the importance of subcortical activations especially for the effects of mindfulness on emotion regulation and learning. Thus, together with fronto-parietal attention regulation and self-monitoring networks, subcortical activations are part of the regions involved in mindfulness meditation.

10.6 OVERLAP BETWEEN MINDFULNESS NETWORKS AND THE DMN – MINDWANDERING VS. SELF-MONITORING

The frontal regions identified in our analyses and the overlapping regions of the PPI in paper one and two (Figure 3) mainly consist of midline structures of the frontal cortex and show a strong overlap with regions of the anterior DMN involved in self-referential processing (Northoff et al., 2006) and stimulus unrelated thought or mind-wandering (Mason et al., 2007). Involvement of these areas in mindfulness has been observed in a number of other studies (Baerentsen et al., 2010; Brefczynski-Lewis et al., 2007; Hölzel et al., 2007; Tomasino et al., 2012) although mindfulness and mind wandering have been found to be opposing constructs (Mrazek, Smallwood, & Schooler, 2012). This raises the issue on how these processes differ in terms of brain processes. A possible explanation may lie in the additional lateral frontal and possibly the subcortical regions activated during mindfulness meditation. Different studies have reported DLPFC activations in inferior frontal gyrus and middle frontal gyrus (Brefczynski-Lewis et al., 2007; Dickenson et al., 2013; Farb et al., 2013) similar to our experiment (paper one). These regions might be involved in directing self-processing towards self-monitoring of cognitive and bodily processes and states.

Another hypothesis has been related to deactivation of the PCC as the critical neural correlate of the meditation experience (Brewer & Garrison, 2013). In their study Garrison et al. (K. A. Garrison et al., 2013) used real time biofeedback of the PCC during FA meditation in novices. Participants reported a strong correspondence between PCC deactivation and their personal feeling of focused attention vs. mind-wandering. Mindfulness teaches paying attention in a non evaluative manner (Kabat-Zinn, 1990). The PCC is activated during emotional processing (Kober et al., 2008) and related to making self-related evaluations of personality traits (Whitfield-Gabrieli et al., 2011). The hypothesis is that this very distinction in “evaluation” makes the difference between mindful and “mindless” or normal attention and could be related to PCC deactivation. Interestingly, in other experiments, only expert meditators show a deactivation within the core areas of the self referential processing network (Brefczynski-Lewis et al., 2007; Brewer et al., 2011), which may indicate that considerable training is necessary to reach a state of clear non-evaluativeness.

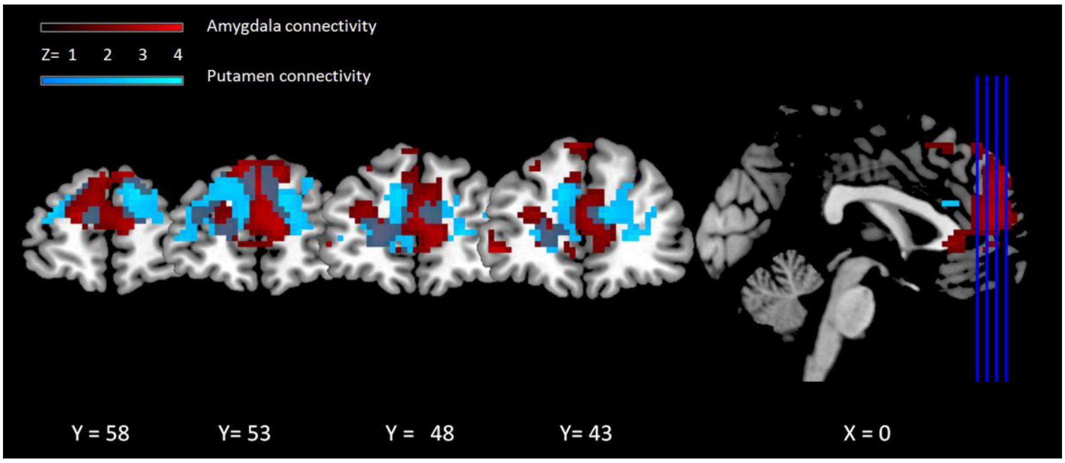

Figure 3.Overlap of connectivity patterns of the studies presented in paper one & two.

Increased functional connectivity during ATB of the right amygdala (red) and the right putamen (blue). Results of paired sample t-tests based on PPI analyses with factors picture (amygdala, study 1) or prediction error (a parametric modulation of picture, putamen, study 2) respectively and time-course of the seed ROI (amygdala or putamen). Statistical parametric maps are overlaid on a T1 anatomical image. Coordinates are given in MNI standard space.

10.7 MINDFULNESS TRAINS THE ACTIVATION OF DORSAL PREFRONTAL CORTEX IN RESPONSE TO MINDWANDERING

The results presented in papers one to three may provide evidence for a neural pathway of the beneficial effects, which mindfulness has shown on rumination (Brown & Ryan, 2003; Chambers, Lo, & Allen, 2008; Koszycki, Raab, Aldosary, & Bradwejn, 2010; Ramel, Goldin, Carmona, & McQuaid, 2004). For example, Chambers and colleagues (2008) found that novice meditators reported reduced rumination after a 10-Day intensive meditation course compared to a control group. Rumination is a pathological form of mind wandering that involves circular thinking and is associated with a prolonged negative emotional state, depression, and anxiety (Mor & Winquist, 2002; Rood, Roelofs, Bögels, Nolen-Hoeksema, & Schouten, 2009). The “upward spiral” model of depression gives a plausible neural explanation of the etiology of rumination in depression. The model assumes that information with negative valence receives increased salience while a striatal “blockade” prevents the normal involvement of DLPFC, which attributes contextual information, into the loop (Hamilton et al., 2012). In detail, high activity in the pulvinar feeds information forward to the amygdala, insula and dorsal ACC for negative stimuli. Via mutual feedback loops, this activation is sustained but not transmitted to DLPFC, potentially due to low dopamine levels in the striatum, which gates information to the cortex. The DLPFC hypothetically connects visceral information with context (i.e., creating a situated conceptualization), leading to emotionally attenuating appraisals (Hamilton et al., 2012). This model is supported by two meta-analyses showing that SSRI treatment alleviated depression via deactivation in areas of the salience network at rest (Fitzgerald, Laird, Maller, & Daskalakis, 2008) and of the amygdala during emotional stimulation (Delaveau et al., 2011) together with increased activation of the DLPFC. It has been hypothesized that mindfulness training reduces negative rumination (or the tendency to ruminate altogether, see Teasdale, Segal, & Williams, 1995). This anti-ruminating effect might be one of the critical therapeutic elements in mindfulness (Desrosiers, Vine, Klemanski, & Nolen-Hoeksema, 2013; Jain et al., 2007). Indeed, research indicates reduced rumination after mindfulness training (Brown & Ryan, 2003; Chambers et al., 2008; Koszycki et al., 2010; Ramel et al., 2004). As outlined above, rumination seems to be related to a reduced involvement of executive control regions like the DLPFC and increased involvement of regions of the salience network and the amygdala. Neuroscientific experiments into the neural correlates of mindfulness support this anti-rumination effect. Mindful focused attention meditation trains the detection and inhibition of mind wandering and self-related thoughts. While the detection of mind wandering is associated with activation within the salience network, the attentional switch from mind-wandering to focused attention is associated with activation in DLPFC (Hasenkamp et al., 2012). Furthermore, mindfulness meditation in trained meditators has been shown to be associated with increased activation of the DLPFC, a critical area of the central executive network together with a decreased tendency of default mode activation (Brewer et al., 2011). Thus, these data suggest that mindfulness meditation, may result in a higher sensitivity towards mood states and mind wandering (Hölzel et al., 2011), and trains students to activate the central executive regions, when mind wandering or rumination is detected (Hasenkamp et al., 2012).

10.8 RUMINATION AND RESTING STATE NETWORKS

The training of mind-wandering detection during mindfulness meditation may result in an additional effect, by which mindfulness can improve rumination: a change in the balance between key cognitive networks. Rumination is a symptom of depression, and predicts further and more severe depressive states in patients with major depressive disorder (Kuehner & Weber, 1999). While rumination is associated with brain activation of DMN, particularly the medial PFC and PCC (Cooney, Joormann, Eugène, Dennis, & Gotlib, 2010), the negativity of rumination is associated with the activation of the salience network in response to DMN activation during rest (Hamilton et al., 2011). Hamilton et al. (2011) investigated the resting state activations of the DMN, salience and central executive networks in depressed patients and controls. The authors found that aversive rumination in depression was associated with increased activation of the DMN during rest compared to controls, who showed increased activation of the CEN instead, which was associated more with observant self-reflection. Thus, this might indicate that the activation of the salience vs. the central executive network in response to default mode network activation during rumination may reflect the valence of ruminating thoughts. Our data presented in paper three indicated a stronger negative correlation between subnetworks of the SN and the DMN. This increased anti-synchrony may be a mechanism that could account for the beneficial effect of mindfulness on rumination.

Over time, mindfulness training may lead to a less noisy interplay between key cognitive networks which could be reflected in stronger anti-correlations during rest (Clare Kelly et al., 2008; Deco et al., 2009; Lewis et al., 2009). This assumption is supported by the behavioral correlates of these resting state networks. While the DMN is associated with self-related thought about past or future events (Buckner et al., 2008), the salience network is associated with personal importance and salience to the self (Seeley et al., 2007). This might also include emotional reactions towards stimuli. The central executive network is instead associated with task positive processes (Dosenbach et al., 2007), i.e., working memory and processing of sensory input. An activation of areas of the salience together with the DMN could result in a vivid emotional reaction, including associated memories (Lindquist et al., 2012). If instead of the salience network, the central executive network is activated in response to DMN activation, this may result in a more analytic or observant perspective of thoughts, which is associated with less negative feelings (Hamilton et al., 2011). In summary, mindfulness meditation is likely related to a training of the interplay between three cognitive networks, the SN, CEN and DMN, which are also related to rumination. This training may shift the balance between these networks towards the CEN, which may represent a neural pathway of an anti-rumination effect of mindfulness. Our data especially in paper three are consistent with this hypothesis.

10.9 MINDFULNESS AFFECTS FUNCTIONAL NETWORKS: A POSSIBLE PATHWAY OF THERAPEUTIC EFFECTS OF MINDFULNESS

As outlined above, mindfulness influences the triple networks that are involved in psychopathology: the DMN, CEN and SN (Menon, 2011). The salience network in particular has been shown to have aberrant connectivity with the amygdala and the hippocampus in depression (Tahmasian et al., 2013) and with the DMN and CEN in borderline personality disorder (Doll et al., 2013). Particularly the experiment on intrinsic functional networks in borderline personality disorder (Doll et al., 2013) focused on the disrupted balance between the SN and CEN, that seems similarly disrupted as for maladaptive rumination in depression (Hamilton et al., 2011). Since mindfulness has shown effective in the treatment of depression (Hofmann et al., 2010) and is a principal pillar of psychotherapy in borderline personality disorder (Linehan, 1993b), the effects of mindfulness training on internetwork connectivity may be one of the biomarkers of improvement. Based on the current evidence, we would expect treatment related changes in connectivity for the fronto-insular operculum due to its role in switching between DMN and CEN (Sridharan et al., 2008) and the balance between SN and CEN to shift towards increased connectivity between DMN and CEN. Since a number of studies emphasize increased activation of the DLPFC, changes may be specifically apparent in this region.

10.10 THE OVERLAP OF CONNECTIVITY EFFECTS OF MINDFULNESS AND BORDERLINE PERSONALITY DISORDER

The study described in paper four reported resting state connectivity alterations in patients with borderline disorder. Alterations were apparent as increased functional connectivity within the DMPFC in both SN and DMN and in fronto-parietal regions within the CENs. The clusters in the DMN and SN are overlapping with those that showed increased connectivity and activation with the amygdala and the putamen in the studies reported in paper one and two. This might indicate that mindfulness does modulate the connectivity of regions that are affected by BPD. Finding may explain a therapeutic effect of mindfulness by increasing connectivity between subcortical regions and prefrontal control regions, which are disconnected from the amygdala in BPD (New et al., 2007).

It is worthy to note that when comparing the inter-iFC data between the studies reported in papers three and four, connectivity values of the BPD patients behave more similarly to more mindful individuals. Thus, the data seem not to correspond well with the idea of mindfulness directly counteracting the intrinsic connectivity effects of BPD. Future studies that track the development of functional connectivity over the process of mindfulness training – in both controls and psychiatric patients - are required to elucidate the specific link between connectivity, mindfulness and psychiatric symptoms.

Overall, the increased inter-iFC of the aDMN and the pSN and decreased inter-iFC between the aDMN and the lCEN in BPD patients fits with the hypothesis that this pattern of connectivity is related to negative rumination , which can be assumed in hospitalized BPD patients (Hamilton et al., 2011). However, these data need to be replicated and linked with behavioral data in order to investigate the specificity of the triple network hypothesis (Menon, 2011). Thus, while mindfulness effects on amygdala – DMPFC connectivity correspond well with the neural findings in BPD, the effects of mindfulness on the functional connectivity architecture of psychiatric patients require further investigation.

10.11 LEARNING EFFECTS OF MINDFULNESS: POSSIBLE NEURAL PATHWAY FOR ANTI ANXIETY EFFECTS OF MINDFULNESS

Learning might be similarly affected by mindful breathing as emotion regulation, via top-down control originating from DMPFC. A firm attentional focus on the breath may reduce the inherent salience of emotional stimuli (Liberzon, Phan, Decker, & Taylor, 2003), which may reduce the associability of those stimuli through deactivation of the amygdala. The amygdala has been shown to code for the associability of cues, thereby affecting learning rates (Li, Schiller, Schoenbaum, Phelps, & Daw, 2011) together with the ACC (Behrens, Woolrich, Walton, & Rushworth, 2007) and the insula (Preuschoff, Quartz, & Bossaerts, 2008). This signal could affect PE computations in the putamen, since amygdala and putamen are strongly interconnected (Roy et al., 2009). Thus, the inhibitory effects of emotion regulation on the amygdala could be a neural pathway in reducing prediction error related signaling within the putamen.

The observed effects in paper two can be related to the idea that mindfulness may be efficiently used in the therapy of anxiety and obsessive compulsive disorder since both can be traced back to maladaptive learning mechanisms (Mineka & Zinbarg, 2006). While a behavioral effect of mindfulness in the treatment of these disorders has been found (Hofmann et al., 2010), the neural mechanisms behind these effects are not understood. The results reported in paper two, support the effectiveness of mindful breathing for modulating aPEs within the striatum. We concluded that a potential neural pathway how mindfulness training affects learning could be the control of emotional salience via the amygdala into the striatum.

Another open question is whether mindful breathing can support relearning or extinction processes in anxiety disorders an which role the modulation of aPEs in the striatum may play. Extinction usually relies on subgenual VMPFC regulating prediction error signaling in the amygdala, with hippocampal input signaling contextual information related to fear expression or inhibition (Myers & Davis, 2007). The role of the striatum in fear extinction seems to be to implement flexible adjustments of predictions. The striatum appears to track changes in predictability of a conditioned stimulus and is associated with prediction errors during acquisition and reversal learning (Schiller, Levy, Niv, LeDoux, & Phelps, 2008). As a consequence, a negative PE signal upon omission of an aversive event after a previously conditioned stimulus would be expected. Although negative PE signaling during extinction has not been confirmed in human striatum (Spoormaker et al., 2011), this might still exist. Such a signal would be difficult to detect as it is likely reduced in magnitude and spread out in time rather than focused on one time point (McNally, Johansen, & Blair, 2011). Mindfulness could exert effects by facilitating extinction related PE modulation. While the data presented in paper three support the reduction of prediction error during acquisition of conditioning, future studies are needed that investigate the link between mindfulness and anxiety processes during extinction.

11. CONCLUSION

The present dissertation explored the effects of mindfulness on emotion regulation, emotion learning and the interaction of neuro-cognitive key networks. Specifically, research questions were (1) what are the neural correlates of FA meditation and how does it affect emotional processing? (2) How do neural processes between mindfulness meditation and learning interact? (3) What are the effects of mindfulness on functional connectivity, particularly between key cognitive networks? (4) How do the changes in functional connectivity related to those seen in affective disorders, for example, borderline personality disorder? The studies reported papers one, two, three and four tried to answer these questions. Results indicate that mindfulness changes the connectivity of the amygdala during emotion regulation and the putamen during learning. In the prefrontal cortex, mindfulness effects were particularly apparent within DMPFC during task and between subnetworks of the SN and the DMN during rest. The connectivity effects of mindfulness on subcortical structures and alterations in functional connectivity in BPD patients overlapped in DMPFC. These results are particularly relevant for the understanding of beneficial effects of mindfulness during psychotherapy. The experiments described here provide evidence for possible neuronal pathways of improved emotion regulation abilities, relearning of maladaptive behavior and an anti-rumination effect. The data presented here may help understanding the underlying neural mechanisms of mindfulness based focused attention and its effects on emotional processing.

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13. LIST OF PUBLICATIONS

Mindful attention to breath regulates emotions via increased amygdala-prefrontal cortex connectivity
Anselm Doll, Britta K. Hölzel, Satja Mulej Bratec, Christine C. Boucard, Xiyao Xie, Afra Wohlschläger and Christian Sorg. The Manuscript was submitted to *NeuroImage* at the time of Thesis submission.

The effects of mindful attention to breath on aversive prediction error-based learning in the striatum
Anselm Doll, Satja Mulej Bratec, Afra Wohlschläger and Christian Sorg. The Manuscript was in preparation for submission at the time of Thesis submission.

Mindfulness is associated with intrinsic functional connectivity between default mode and salience networks
Anselm Doll, Britta K. Hölzel, Christine C. Boucard, Afra Wohlschläger and Christian Sorg. The Manuscript was in review with Frontiers in Human Neurosciences at the time of Thesis submission.

Shifted intrinsic connectivity of central executive and salience network in borderline personality disorder
Anselm Doll, Christian Sorg, Andrei Manoliu, Andreas Wöller, Chun Meng, Hans Förstl, Claus Zimmer, Afra M. Wohlschläger, Valentin Riedl. Frontiers in Human Neuroscience, 2013. *Frontiers in Human Neuroscience*, *7* (October), 1-13.

14. EIDESSTATTLICHE VERSICHERUNG/AFFIDAVIT

Hiermit versichere ich an Eides statt, dass ich die vorliegende Dissertation „Brain effects of mindfulness in three modalities: functional activation and connectivity during task and rest” selbstständig angefertigt habe, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

I hereby confirm that the dissertation “Brain effects of mindfulness in three modalities: functional activation and connectivity during task and rest” is the result of my own work and that I have only used sources or materials listed and specified in the dissertation.

München, den
Munich, Unterschrift signature

15. AUTHOR CONTRIBUTIONS

MINDFUL ATTENTION TO BREATH REGULATES EMOTIONS VIA INCREASED AMYGDALA-PREFRONTAL CORTEX CONNECTIVITY.

The following authors were involved in the creation of this manuscript: Britta K. Hölzel, Satja Mulej Bratec, Christine C. Boucard, Xiyao Xie, Afra Wohlschläger and Christian Sorg.
The author of this thesis contributed to the idea of the article (together with C. Sorg and A. Wohlschläger) and performed both data acquisition, i.e. recruiting participants, psychometric testing, training and scanning (together with C. C. Boucard, who helped during the training and scanning) and –analysis (together with S. Mulej Bratec, who assisted with the analysis of the behavioral data). Writing all parts of the manuscript was also performed by the author of the thesis, while co-authors were involved in the editing of introduction, methods, results and discussion.

THE EFFECTS OF MINDFUL ATTENTION TO BREATH ON AVERSIVE PREDICTION ERROR-BASED LEARNING IN THE STRIATUM.

The following authors were involved in the creation of this manuscript: Anselm Doll, Satja Mulej Bratec, Afra Wohlschläger and Christian Sorg. The author of this thesis performed both data acquisition i.e. recruiting participants, psychometric testing, training and scanning (together with C. C. Boucard, who helped during the training and scanning) and –analysis (together with S. Mulej Bratec, who assisted with the analysis of the behavioral data). Writing of all parts of the manuscript was also performed by the author of the thesis, while co-authors were involved in the editing of introduction, methods, results and discussion.

MINDFULNESS IS ASSOCIATED WITH INTRINSIC FUNCTIONAL CONNECTIVITY BETWEEN DEFAULT MODE AND SALIENCE NETWORKS.

The following authors were involved in the creation of this manuscript: Anselm Doll, Satja Mulej Bratec, Afra Wohlschläger and Christian Sorg. The author of this thesis performed both data acquisition i.e. recruiting participants, psychometric testing, training and scanning (together with C. C. Boucard, who helped during the training and scanning). Writing of all parts of the manuscript was also performed by the author of the thesis, while co-authors were involved in the editing of introduction, methods, results and discussion.

SHIFTED INTRINSIC CONNECTIVITY OF CENTRAL EXECUTIVE AND SALIENCE NETWORK IN BORDERLINE PERSONALITY DISORDER

The following authors were involved in the creation of this manuscript: Anselm Doll, Christian Sorg, Andrei Manoliu, Andreas Wöller, Chun Meng, Hans Förstl, Claus Zimmer, Afra M. Wohlschläger, Valentin Riedl. The idea of the study was contributed by C. Sorg & V. Riedl. Data acquisition was performed by A. Wöller. The author of this thesis performed the data analysis (with the assistance of A. Manoliu, who helped with the ICA technique). Writing of all parts of the manuscript was performed by the author of the thesis together with C. Sorg, thus sharing first authorship. The co-authors were involved in the editing of introduction, methods, results and discussion.

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16. CURRICULUM VITAE

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Work experience

09.2010 – today	Department of Neuroradiology, Psychiatry, Klinikum rechts der Isar, Neuroimaging Centre, Technische Universität München
Function	Ph. D. Student
Activity	Preparing and executing functional neuroimaging experiments

09.2006 – 01.2007	Maastricht University, the Netherlands
Function	Tutor
Activity	Supervision of weekly group discussions and learning progression, Biopsychology and Perception.

Educational background

09.2010 – today	Study at Ludwig-Maximilians-University Munich, Germany
Degree	Doctoral
Specialization	*Neural correlates of emotion regulation and learning by mindfulness & resting state connectivity in psychiatric disorders*

10.2008 – 09.2010	Study at Ludwig-Maximilians-University Munich, Germany
Degree	Master of Science (final grade 1.12)
Specialization	Neuro-Cognitive Psychology (elite study program)
Thesis	Intrinsic Brain Networks in Borderline Personality Disorder

06.2004 – 06.2007	Study at University Maastricht, the Netherlands
Degree	Bachelor of Science (final grade 1.18)
Specialization	Biopsychology
Thesis	An evolutionary framework for eudaimonic and hedonic happiness

07.1994 – 07.2003	Stadtgymnasium Dortmund
Degree	Abitur

Research Experience

03.2010 – today	Department of Neuroradiology, Klinikum rechts der Isar, Technische Universität Munich
Topics	Intrinsic functional network connectivity in Borderline Disorder. Emotion regulation by meditation and emotional learning
Supervisor	**Dr. Christian Sorg & Dr. Afra M. Wohlaschläger**

08.2009 – 10.2009	Psychiatric Clinic, LMU Munich
Topic	Humor processing in Asperger syndom patients - an fMRI study
Supervisor	**Dr. Kristina Henning-Fast**

02.2009 – 04.2009	Department of Psychology, LMU Munich, Germany
Topic	Biofeedback of cerebral blood flow with Doppler sonography
Supervisor	**Dr. Stefan Duschek**

Scholarships

06.2012 – today	Stipandiary of the Bayrische Eliteförderungsgesetz, supported by the department of Psychiatry, Klinikum rechts der Isar.
04.2009- 09.2010	Stipendiary of the Max-Weber-Program

Publications

Doll, A., Sorg, C., Manoliu, A., Wöller, A., Meng, C., Förstl, H., Zimmer, C., Wohlschläger, A. M., Riedl, V., (2013). Shifted intrinsic connectivity of central executive and salience network in borderline personality disorder. *Frontiers in Human Neuroscience, 7*, 1-13.

Methodological Skills

Very experienced	Functional magnetic resonance imaging
	Behavioural methods
Experienced	Doppler Sonography
	Heart rate
	Galvanic skin response
Basic knowledge	Eye tracking
	Transcranial magnetic stimulation