

# **Emotion Regulation, Social Cognitive and Neurobiological mechanisms of Mindfulness, from Dispositions to Behavior and Interventions.**

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*von Simón Guendelman*

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Dissertation

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*Simón Guendelman*

“Our suffering arises because our minds react to our experiences in ways are often uncontrollable. We cannot always change the world and make the rain stop, but we can change our internal response to what is happening”.

*Rob Preece. (2006).*

“If with kind generosity one merely has the wish to soothe the aching heads of others beings, such merit knows no bounds”.

*Shantideva. (2008).*

Erklärung:

Hiermit erkläre ich, die Dissertation selbstständig und nur unter Verwendung der angegebenen Hilfen und Hilfsmittel angefertigt zu haben.

Declaration:

I hereby declare that I completed the doctoral thesis independently based on the stated resources and aids.

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Datum, Unterschrift



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# Abstract

Mindfulness, the capacity to fully attend to the present experience, has been linked to a myriad of mental health benefits, being socio-emotional abilities such as emotion regulation (ER) and social cognition of the main potential active mechanisms. The current doctorate thesis investigated the relationship between mindfulness and ER and social cognition, using a range of methodological approaches from conceptual -evidence revision to trait level individual differences and behavioral mechanisms and functional brain correlates. *Study one* explored the relationship between mindfulness and ER by examining the diverse literature and existing empirical models (i.e. mindfulness as a trait, interventions and experts), discussing different psychological and neuro-cognitive active mechanisms. *Study two* intended to unravel the ER mechanism of dispositional mindfulness, showing in both borderline personality and healthy subjects the mediating effect of self-compassion linking mindfulness and ER traits. *Study three* further investigated the link between ER and social cognition using behavioral and neuro-imaging experiments, addressing the newly developed notion of social ER (the capacity to modulate others' emotions). It showed that when regulating others' emotions, an individual's own distress is reduced, being key 'socio-cognitive' brain regions (i.e. precuneus) engaged in mediating these effects. Furthermore, this study revealed that subjects with lower ER abilities have higher emotional empathy (i.e. compassion feelings), linking individual level with socio-cognitive processes. *Study four* investigated the fine-grained ER mechanisms of a mindfulness intervention, comparing the mindfulness based stress reduction (MBSR) with a reading/listening group (READ), in the context of a neuroimaging-based randomized controlled trial. This study revealed ER brain-behavioral plasticity induced by the MBSR, for both self and social ER, differently for cognitive reappraisal and acceptance, indicating both as effective stress reducing psychological strategies. Additionally, it showed a lack of effect over social cognition (cognitive and emotional empathy), suggesting a stepped effect of MBSR from self to social functioning. Articulating empirical and conceptual approaches, a model that integrates *exchanges* and *regulation* of emotions in the context of social interactions is proposed. The dissertation offers new insights into mindfulness' ER mechanisms, from dispositions to neuro-behavioral levels, and also sheds light onto individual level determinants of social processes, linking ER and social cognition.

## Kurzfassung

Achtsamkeit wird mit einer Vielzahl positiver Effekte für die psychische Gesundheit in Verbindung gebracht, wobei Fähigkeiten wie die Emotionsregulation (ER) und die soziale Kognition zu den wichtigsten Mechanismen gehören. In der vorliegenden Doktorarbeit wurde die Beziehung zwischen Achtsamkeit, ER und sozialer Kognition untersucht. In *Studie Eins* wurde die Beziehung zwischen Achtsamkeit und ER anhand diverser Forschungsliteratur und empirischer Modelle beleuchtet und verschiedene psychologische und neurokognitive Wirkmechanismen diskutiert. *Studie Zwei* zielte darauf ab, den ER-Mechanismus der dispositionellen Achtsamkeit aufzuklären, wobei sowohl bei der Borderline-Persönlichkeitsstörung als auch bei gesunden Probanden der medierende Effekt von Selbstmitgefühl auf den Zusammenhang von Achtsamkeit und ER-Merkmalen gezeigt werden konnte. In *Studie Drei* wurde die Verbindung zwischen ER und sozialer Kognition mit Hilfe von Verhaltens- und Neuroimaging-Experimenten untersucht. Hier wurde besonders das neu entwickelte Konzept der sozialen ER (die Fähigkeit, die Emotionen anderer zu modulieren) adressiert. Es zeigte sich, dass durch die soziale ER eigener Stress reduziert wird und „sozio-kognitive“ Gehirnregionen (z.B. Precuneus) als Schlüsselregionen an der Vermittlung dieser Effekte beteiligt sind. Zudem konnten Verknüpfungen zwischen individueller Ebene und sozio-kognitiven Prozessen hergestellt werden. In *Studie Vier* wurden die ER-Mechanismen einer Achtsamkeitsintervention untersucht, wobei die achtsamkeitsbasierte Stressreduktion (MBSR) mit einer Lese-/Hörgruppe (READ) im Rahmen einer randomisierten kontrollierten Neuroimagingstudie verglichen wurde. Diese Studie zeigte eine durch die MBSR induzierte Hirn-, sowie Verhaltens-Plastizität für die selbstbezogene und die soziale ER, die sich für kognitive Neubewertung und Akzeptanz unterschied, was beide als effektive stressreduzierende psychologische Strategien ausweist. Maße der sozialen Kognition waren davon unbeeinflusst und lassen somit auf einen abgestuften Effekt der MBSR von selbstbezogener zu sozialer Funktionalität schließen. Durch die Verwendung empirischer und konzeptioneller Ansätze wird ein Modell entwickelt, welches den *Austausch* und die *Regulierung* von Emotionen im Kontext sozialer Interaktionen integriert. Die Dissertation bietet neue Einsichten in die Mechanismen der Achtsamkeit, von Dispositionen bis hin zu neuro-behavioralen Ebenen, und beleuchtet zudem die Determinanten sozialer Prozesse auf der individuellen Ebene, wodurch eine Verbindung zwischen ER und sozialer Kognition hergestellt wird.

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# Introduction

## 1.1. Mindfulness, from trait to clinical interventions

### 1.1.1. Operational definitions of Mindfulness

During the last years, mindfulness has gained momentum as one the most promising and newest psychological interventions. Mindfulness as a particular type of meditation practice originated from Buddhist psychology; mindfulness corresponds to the Sanskrit term *Smṛti*, which points to the capacity of the mind to retain and to be aware of an object, including the present moment experience (Anālayo, 2019; Trungpa, Baker, & Casper, 2002). In the context of western psychology, mindfulness has been defined as the capacity of *paying attention* to the present experience, *intentionally* and *without judgments* (Shapiro, Carlson, Astin, & Freedman, 2006), which has been distilled as a “non-elaborative, non-reactive awareness” (Kabat-Zinn, 2005). Mindfulness has been introduced to scientific and clinical psychology through the development of the so-called Mindfulness-based interventions (MBIs), which are systematized 8 week-programs, teaching mindfulness through different types of meditations, yoga and body-awareness exercises and psycho-education components (Shonin, Gordon, & Griffiths, 2013).

In order to disentangle its varied use as a construct in clinical psychology, it is important to notice that mindfulness can be understood in three different ways, as *dispositional mindfulness*, this means individual differences in mindfulness measured as a trait, *mindfulness meditation*, the practice of cultivating the present centered non-judgmental awareness itself, and *mindfulness states*, as the first-person experience of being aware without judgments (Chambers, Gullone, & Allen, 2009; Davidson, 2010). Scientific investigations have started to explore the mechanisms and effects involved in these different notions of mindfulness, using diverse healthy and clinical populations, but also expert meditators.

Regarding *dispositional mindfulness*, studies have shown that individuals with higher levels of self-reported mindfulness have better health-related coping behaviors (Slonim, Kienhuis, Di Benedetto, & Reece, 2015) and a meta-analysis evidenced that trait mindfulness shows a negative relationship with neuroticism and negative emotionality (Giluk, 2009). Thus, mindfulness as a trait has shown to

be linked with positive mental health outcomes. This is coherent with clinical implementations of mindfulness, in which deficits in dispositional mindfulness are specifically targeted by MBIs, i.e. as in dialectical behavioral therapy for borderline personality disorder (BPD) (Linehan, 1993). In connection to this, self-compassion, a self-oriented accepting and kind attitude towards emotional pain, has been proposed as a novel individual disposition and construct linking mindfulness and its emotional health benefits (Neff, 2003).

### **1.1.2. Mindfulness Based Stress Reduction (MBSR)**

The mindfulness-based stress reduction (MBSR), the oldest, most widely used and validated MBI, was developed by Jon Kabat-Zinn in the late seventies (Kabat-Zinn, 2005); it is a program that specially targets stress-related mal-adaptive behaviors and enhances stress regulation capacity through mindfulness meditation. This 8-week training teaches mindfulness by means of different formal meditation techniques (body scan, mindful-awareness, etc.), informal meditation practices (e.g. mindful eating), yoga exercises, and psycho-education (e.g. how to approach emotional stress with mindfulness techniques).

Meta-analyses of studies on healthy population have shown its beneficial effects in reducing perceived stress, negative emotions and increasing well-being (in general with moderate effect sizes; Eberth & Sedlmeier, 2012; Khoury, Sharma, Rush, & Fournier, 2015). Meta-analyses of studies on diverse medical or psychiatric populations have shown the same pattern of results – a decrease of negative emotions and increased quality of life (Goldberg et al., 2018; M Goyal et al., 2014), demonstrating that its effectiveness is comparable to others evidence based psychological treatments, i.e. cognitive behavioral therapy (Goldberg et al., 2018; M Goyal et al., 2014). MBIs have shown to be especially effective in conditions such as chronic stress, depression, chronic pain and addictions (Goldberg et al., 2018), which are characterized by negative emotionality and deficits in emotion regulation as a core aspect.

## **1.2. Emotion Regulation, Social Cognition and Social Emotion Regulation**

### **1.2.1. Emotion Regulation**

One key factor for general adaptability and social functioning is emotion regulation

(ER). ER has been defined as all the conscious and non-conscious strategies that modulate one or more component of the emotional response (Gross, 1998). Literature in ER has shown that subjects who preferentially use cognitive reappraisal (the capacity to reinterpret or change the cognitive frame of a stressful stimuli) have better emotional health, well-being and interpersonal functioning (Gross & John, 2003). Indeed, experimental studies inducing stress have shown that cognitive reappraisal can reduce self-reported and physiological response of stress (Cutuli, 2014). A meta-analysis of individual differences in ER strategies across mental health disorders demonstrated that dysfunctional strategies such as avoidance, rumination and suppression were positively associated with depression, anxiety, eating and substance use disorders. Regarding adaptive strategies, cognitive reappraisal was negatively associated with those psychopathologies, but acceptance (the capacity to tolerate the experience of emotional stress without reacting on it) did not (Aldao, Nolen-Hoeksema, & Schweizer, 2010). In this way, theoretical and empirical studies in psychotherapy research have suggested ER as one key mechanistic target for improving outcomes in psychological interventions (Cuijpers, Cristea, Karyotaki, Reijnders, & Hollon, 2019; Schnell & Herpertz, 2018). Nowadays ER is considered a transdiagnostic psychopathological and treatment construct across different mental disorders (Sloan et al., 2017), but even more, for several conditions (i.e, like in depression or BPD), ER seems to be at the core of its social impairments (Demenescu, Kortekaas, den Boer, & Aleman, 2010; Euler et al., 2019; Park et al., 2019).

### **1.2.2. Social Cognition**

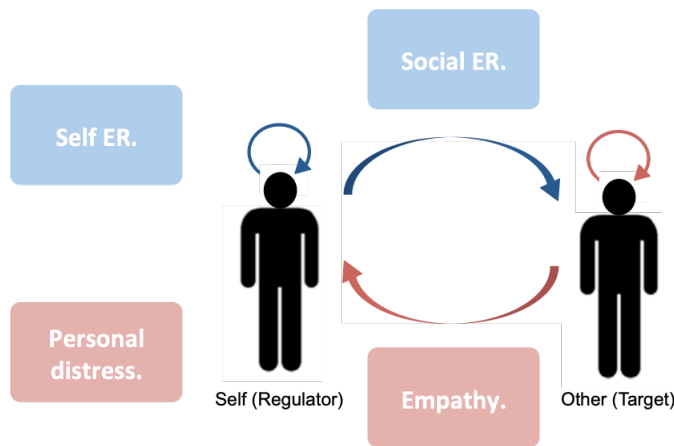
Social cognition, that is, how humans share and understand other's mental states, is considered an umbrella term for the different bio-behavioral processes underlying the *making sense-of* and *interaction-with* others (Happé, Cook, & Bird, 2017). Literature differentiate two routes or mechanisms for social cognition, the affective one which consists of the sharing of emotional states (e.g. traditionally called empathy) and the cognitive route consisting of propositional knowledge (or inference) about other person's mental state (e.g. often called theory of mind, cognitive empathy or mentalizing) (Frith & Frith, 2005; Kanske, Böckler, Trautwein, & Singer, 2015; Shamay-Tsoory & Aharon-Peretz, 2007). Differently, compassion or empathic concern stands as the intention of alleviating other's suffering – which can be manifested behaviorally or mentally – can be derived from



both cognitive and affective routes (De Waal & Preston, 2017). Interestingly, regarding the sharing of affective states (hence after empathy) theoretical models that have tried to disentangle its components have suggested ER as a central building block (De Waal & Preston, 2017; Decety, Bartal, Uzefovsky, & Knafo-Noam, 2016). For example, when exposed to others in suffering, due to empathy, emotional pain can arise in the observer (empathic or personal distress), and this would be related to lower ER. As many studies have asserted, when empathizing with others in distress, major stress for the observer is ensued (Batson, Fultz, & Schoenrade, 1987; Hein & Singer, 2008; Saarela et al., 2007).

### **1.2.3. Social Emotion Regulation**

In the same situations, when interacting with others in emotional pain, we can not only empathize with other's emotional states, but also very often we try to change or modulate them; this has been defined as social or other ER (Niven, Totterdell, & Holman, 2009; Zaki & Williams, 2013). Social ER is a new exciting and growing field of research, that only recently has received attention in the social neurosciences (Reeck, Ames, & Ochsner, 2016). For some authors social ER includes both the cases when one attempts to regulating own emotions through actively looking for others (being regulated by another), but also the cases when one actively regulates the other (regulating the other) (Zaki & Williams, 2013). Typical experiments consist in one person (the regulator) intending to downregulate another person in distress (the target), using certain strategies or interactive behaviors. Interestingly, initial studies have shown contradictory results in terms that regulating other's in distress could either decrease or increase own stress levels in the regulator (Martínez-Íñigo, Mercado, & Totterdell, 2015; Niven, Totterdell, Holman, & Headley, 2012), thus leaving an open question regarding the "emotional costs" for the regulator of regulating another person's emotions. See figure I for a summary of constructs including self, social ER and empathy.



**Figure I.** A schematic diagram depicting self, social ER and empathy in the context of a social interaction.

### 1.3. Psychological Effects of Mindfulness on Emotion Regulation and Social Cognition

#### 1.3.1. Psychological Effects of Mindfulness on Emotion Regulation

Despite its clinical utility and widespread use, MBI's underlying mechanisms have not been fully unraveled. Authors have proposed self-awareness, attention and emotion regulation as active ingredients mediating its beneficial effects (Tang, Hölzel, & Posner, 2015). A study using self-reported measurements have found that higher trait mindfulness predicts lower depressive symptoms and trait anger, independently of neuroticism (Feltman, Robinson, & Ode, 2009). Other studies using different mediation analyses have shown that mindfulness through higher ER leads to decreases in negative emotions and perceived stress (Bao, Xue, & Kong, 2015; Coffey, Hartman, & Fredrickson, 2010). Thus, ER has been suggested as a potential mechanism for mindfulness benefits.

In this vein, a meta-analysis of MBIs (including MBSR) longitudinal studies exploring mediation factors found strong evidence for emotional and cognitive reactivity, among others as active change mechanisms leading to clinical gains (Gu, Strauss, Bond, & Cavanagh, 2015). Furthermore, longitudinal studies investigating specific ER strategies have evidenced divergent results, on one hand, authors have shown that MBIs increase cognitive reappraisal (Garland, Gaylord, & Fredrickson, 2011; Garland, Hanley, Farb, & Froeliger, 2015; Garland, Hanley, Goldin, & Gross, 2017), while others have found acceptance as the key active factor (Britton et al.,

2017; Lindsay, et al., 2018; Lindsay, Young, Brown, Smyth, & David Creswell, 2019). Authors have argued that indeed both strategies might be coherently enhanced by specific mental domains implicitly trained in MBIs, for example, *broadened observation* and *awareness* (the paying-attention component) would lead to higher cognitive reappraisal, which then predicts lower emotional distress (Desrosiers, Vine, Curtiss, & Klemanski, 2014; Garland et al., 2017). On the other hand, the accepting, *non-reactive* and *non-judgmental* stance (towards experience) of mindfulness may also lead to adaptive ER and salutary outcomes (Curtiss, Klemanski, Andrews, Ito, & Hofmann, 2017; Lindsay & Creswell, 2017). Nevertheless, these studies have mainly relied on self-report questionnaires and cross-sectional designs, also, they did not directly compare the acquisition of both ER strategies (acceptance vs cognitive reappraisal), and more importantly, they have not used behavioral experiments in order to evaluate the efficacy and the potential generalization training effects for each strategy.

### **1.3.2. Psychological Effects of Mindfulness on Social Cognition**

Despite the fact that mindfulness meditation is mainly a self-focus practice, previous literature suggested that its effects might generalize to the social domain. An early study showed that mindfulness as trait was associated with higher empathy and interpersonal assertiveness (Dekeyser, Raes, Leijssen, Leysen, & Dewulf, 2008), and a meta-analysis of intervention studies suggested that MBIs might increase empathy, such as empathic concern (using self-reported questionnaires) (Luberto et al., 2018). However, a recent large longitudinal study comparing newly developed mindfulness and compassion interventions evidenced that only the latter increased empathy and compassion levels (Hildebrandt, McCall, & Singer, 2017). Also, a recent meta-analysis demonstrated a lack of effect of MBIs on empathy and compassion when compared to active control groups, though most of those studies used self-reported questionnaires (Kreplin, Farias, & Brazil, 2018). Despite these findings, no studies to date have evaluated the effects of the MBSR on empathy, using established behavioral measurements. Even more, how MBIs (specifically MBSR) might influence personal distress and social ER in the context social interaction remains largely unknown. Likewise, given the crucial role of ER processes in counteracting empathic distress but also in social ER, it is expected that a MBI (MBSR) would increase social ER capacities, as a middle-step generalization effect to the social domain.

## **1.4. Neurocognitive mechanisms of Emotion Regulation, Social Cognition & Social Emotion Regulation & the impact of Mindfulness Based Interventions**

### **1.4.1. Neurocognitive mechanisms of Emotion Regulation**

From the perspective of functional neuroimaging studies, ER has been described as the interaction of emotion generation and emotion regulation brain regions. Traditionally, areas such as the amygdala, basal ganglia, anterior insula would encode the physiological arousal and valence of the triggering stimuli (known as emotion generation or reactivity). Regions like the dorsal and ventral-lateral prefrontal cortex, the pre-supplementary and supplementary motor area and parietal cortex (including supra-marginal and angular gyrus) have been linked to explicit and voluntary efforts of regulating own emotions (Etkin, Büchel, & Gross, 2015; Frank et al., 2014; Kohn et al., 2014). A recent meta-analysis investigating the different types of ER strategies revealed that cognitive reappraisal relies on activations in similar regions already described, but also in middle and superior temporal cortex (Morawetz, Bode, Derntl, & Heekeren, 2017), suggesting semantic and memory processes as constituents of reappraisal (Buhle et al., 2014; Engen & Anderson, 2018; Morawetz et al., 2017). Interestingly, for attention-based strategies, like increasing awareness of bodily features of emotions (a crucial aspect of acceptance strategy), the anterior insula and pre-supplementary motor appeared as important differential regions (Morawetz et al., 2017).

### **1.4.2. Neurocognitive mechanisms of Social Cognition & Social Emotion Regulation**

Regarding neuro-cognitive mechanisms of social cognition routes, brain studies have shown that mentalizing or cognitive empathy engages a neuronal network including the superior temporal cortex, the temporo-parietal junction, the precuneus and the dorso-medial prefrontal cortex among others (Bzdok et al., 2012; Kanske et al., 2015; Oliver, Vieira, Neufeld, Dziobek, & Mitchell, 2018). Regarding the affective route, behavioral and neuroimaging studies on empathy for pain and negative affect have shown that being exposed to other's suffering elicits emotional distress in the observer/receptor (Batson et al., 1987; Gleichgerrcht & Decety, 2014), which in turn engages the activation of a core brain – *empathy* - network including the anterior insula and the middle anterior cingulate cortex

among others (Jabbi, Swart, & Keysers, 2007; Lamm, Silani, & Singer, 2015; for meta-analyses: Lamm, Decety, & Singer, 2011; Fan, Duncan, de Greck, & Northoff, 2011).

Interestingly, for social ER, initial studies have used neuroimaging experiments where one person (the regulator – being measured in the scanner) had the task to decrease another subject's emotional distress. These have revealed brain activation in regions such as the prefrontal (as dorso-lateral), parietal (as the temporo-parietal junction) and temporal cortices, overall suggesting ER and social cognition as basic processes for social ER (Hallam, et al., 2014; Jensen et al. 2014). However, the correspondance between these cognitive proceses and its brain regions is still unclear (Reeck et al., 2016). Evenmore, these studies suffer from methodological deficiencies, i.e. inadequate control of type I error in imaging analysis and small sample size (i.e. lower than 30 subjects), among others.

### **1.4.3. Neurocognitive Effects of Mindfulness on Emotion Regulation & Social Cognition**

During the last years, functional brain longitudinal studies have shown that MBIs can increase brain activation in regions like the prefrontal and cingulate cortex, anterior insula and hippocampus (for meta-analyses: Gotink, Meijboom, Vernooij, Smits, & Hunink, 2016; Young et al., 2017), but also in parietal cortex (Goldin & Gross, 2010; Goldin, Ziv, Jazaieri, Hahn, & Gross, 2013), all regions that have been associated with ER and social cognition (i.e. Bzdok et al., 2012; Kohn et al., 2014). Lately, a large longitudinal study compared different meditation based programs (mindfulness *versus* compassion *versus* mentalizing training), evidencing differential structural and functional brain changes in the three groups (mindfulness – prefrontal regions; compassion – fronto-insular regions; mentalizing – inferior frontal & lateral temporal regions). Noteworthy, these brain changes covaried with respective behavioral improvements in attention, compassion and theory of mind (Valk et al., 2017). Nevertheless, these studies did not specifically examine ER changes at the cognitive or brain level.

Studies evaluating ER neuro-cognitive mechanisms underlying MBIs have shown that MBSR compared to waiting-list displayed higher activation in the right anterior insula, right lateral prefrontal and subgenual-anterior cingulate cortex using a sadness induction paradigm. Interestingly, activation gains in anterior

insula correlated with lower depressive symptoms (Farb et al., 2010). An RCT comparing a mindfulness training with a reading group found that both groups improved their performance in a response inhibition task, but only the MBI group showed reduced emotional interference using an affective Stroop task (a conflict resolution paradigm that targets affective processes). Importantly, there were no differences between groups over time in neuronal activations during negative affect processing. Nevertheless, brain activation gains in anterior insula, dorsal-anterior cingulate cortex and middle prefrontal cortex scaled positively with meditation practice only in the MBI group (Allen et al., 2012). Finally, a study with generalized anxiety disorder patients compared MBSR with a psycho-education program under an affect labeling task, evidencing major activation of the ventro-lateral prefrontal cortex, and higher functional connectivity between this region and the amygdala in the MBI group (Hölzel et al., 2013). Nevertheless, these studies were based on small sample sizes, most of them lacking active control groups (as in meta-analyses: Gotink et al., 2016; Young et al., 2017), but also they did not explore active ER strategies (such as cognitive reappraisal), and the experimental designs had limited ecological validity, e.g. they did not employ stressful social interactions

## **Research Questions and Hypotheses**

Despite evidence that mindfulness is related to mental health benefits, its active mechanisms and gains at social level remain uncertain. This thesis investigated the relationship between mindfulness, ER and social cognition, focusing on mechanisms involved in mindfulness, using diverse methodological approaches ranging from behavioral and brain functional assessments to individual differences in healthy and clinical population (BPD patients). The project also investigated the link between ER and social cognition (emotional and cognitive empathy), disentangling the psychological and brain mechanisms of social ER. The main original research article focuses on the ER and socio-cognitive mechanisms of an MBI (MBSR) in the context of an active-controlled randomized neuro-imaging trial, looking at fine grained ER mechanisms at behavioral and brain levels. Furthermore, it reveals its subsequent generalization effects, from personal to social functioning using the lens of self and social ER and social cognition. Overall, through the advancement of the Distress-Regulation model of social interactions, the thesis intends to further the understanding of the interplay of personal (like ER) and social level (like empathy) phenomena within the context social interactions. Figure II depicts the main constructs targeted by each article.

### **2.1. Mindfulness and Emotion Regulation: Insights from Neurobiological, Psychological and Clinical Studies (the MFN-ER review study)**

The aim of this study was to evaluate how mindfulness and ER are related at the conceptual and empirical level, using different empirically derived models: mindfulness as trait, as state induction, as intervention (MBIs) and mindfulness experts. A comprehensive-narrative review was performed, including studies using psychological questionnaires, behavioral and neuroimaging experiments concerned with ER. Mindfulness effects over ER are described in terms of top-down and bottom-up ER mechanisms. Further conceptual clarifications are derived regarding specific ER mechanisms involved in MBIs.

Completing a narrative review using key terms as mindfulness, mindfulness inductions, mindfulness based interventions (MBI), expert meditators and emotion regulation, allowed to explore the following research questions.



*Question 1.1)* Is dispositional mindfulness (as trait) associated with individual differences in ER (e.g. neuroticism)? *Question 1.2)* Are MBIs clinical benefits mediated by ER gains? *Question 1.3)* Does mindfulness influence neuronal activation in ER brain regions? Are there similar brain effects found in MBI and expert meditators?

*Hypothesis 1.1)* Mindfulness as trait will be both positively associated with ER health/resilience factors, and negatively associated with ER traits linked with psychopathological/vulnerability.

*Hypothesis 1.2)* Changes in ER skills will mediate clinical outcomes in MBI.

*Hypothesis 1.3)* Mindfulness will have an effect on ER brain regions, including bottom-up (e.g. amygdala) and top-down systems (e.g. frontal cortex).

## **2.2. Self compassion mediates the relationship between mindfulness and emotion dysregulation (the MFN-SC study)**

The aim of the study was to further elucidate the psychological mechanisms of Mindfulness (as a trait) and its effect on ER and borderline features, exploring the mediating role of self-compassion. Despite the fact that the relationship between Mindfulness and ER has already been suggested in healthy and borderline personality disorder (BPD) patients, the mediating factors are still unknown. Defining these might help clinicians to optimize the design of new interventions.

In a group of BPD and two healthy subjects samples (matched and unmatched), we evaluated mindfulness, self-compassion and ER traits (difficulties in emotion regulation and borderline symptoms), enabling to investigate the following research questions.

*Question 2.1)* How is the relationship between mindfulness and self-compassion with ER and borderline symptoms? *Question 2.2)* Is the relationship between mindfulness and ER and borderline features mediated by self-compassion?

*Hypothesis 2.1)* Mindfulness and self-compassion will be both negatively associated with difficulties in emotion regulation and borderline symptoms.

*Hypothesis 2.2)* The relationship between mindfulness and ER and borderline features will be mediated by self-compassion.



### **2.3. Regulating negative emotions of others reduces own stress: neurobiological correlates and the role of individual differences in empathy (the ER-EMP study)**

It is a very common experience that witnessing the suffering of others results in personal distress. One way of reducing this distress is through regulation of one's own emotions. Moreover, in these situations people frequently and readily intend to regulate the *other* person's emotional state; nevertheless it is not yet known whether this comes at an emotional cost (or benefit) for the observer. Even though theoretical models (Decety & Jackson, 2004; de Waal & Preston, 2017) have long argued for the role of emotion regulation in empathy, no empirical studies have directly explored how both are related.

The present study aimed to investigate behavioral and functional brain mechanisms of self and other ER via reappraisal and their relationship with individual differences in empathy (compassion and cognitive empathy).

In a sample of healthy subjects we applied the newly developed self and other emotion regulation task (SORT) for the fMRI environment, and a well established behavioral social cognition task (the multifaceted empathy test - MET), these enabled us to explore the following research questions.

*Question 3.1)* How are individual differences in ER and compassion/cognitive empathy related? *Question 3.2)* What are the neurobiological mechanisms, and behavioral subjective benefits (stress level) of other ER?

*Hypothesis 3.1a)* Subjects with lower ER (higher personal distress) will show higher levels of compassion (emotional empathy).

*Hypothesis 3.1b)* No relationship between ER and cognitive empathy will be observed.

*Hypothesis 3.2a)* Behaviorally, social ER will decrease personal distress in the regulator.

*Hypothesis 3.2b)* Regulating other's emotions will recruit brain regions related both to social cognition (e.g. TPJ) and ER (e.g. parietal, prefrontal cortex) processes.

## **2.4 Towards a mechanistic understanding of mindfulness-based stress reduction (MBSR) using an RCT neuroimaging approach: Effects on self and other emotion regulation (the MBI ER-EMP study)**

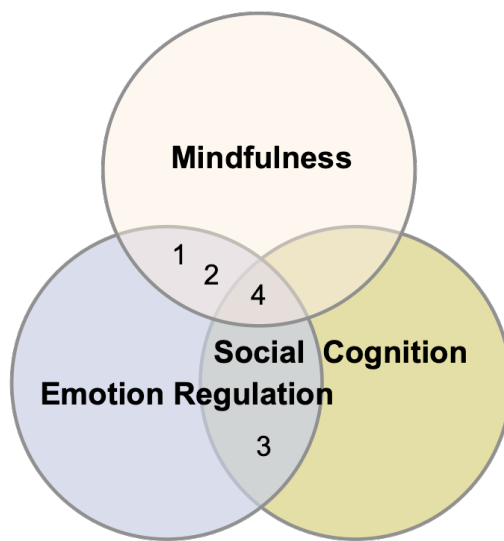
Through the implementation of an active controlled randomized controlled trial, the aim of the study was to evaluate a MBI (MBSR) effects on ER skills, for self and social ER and its functional brain correlates (as primary outcome). Particularly, we compared fine-grained ER strategies such as cognitive reappraisal and acceptance as active strategies involved in MBI. Alongside this, the study investigated the underlying ER functional neuro-plasticity involved in the intervention and its association with meditation practice (home assignments) and behavioral benefits (stress reduction). Furthermore, we evaluated the generalization effects of MBI on social cognition, exploring its effects on compassion and cognitive empathy (as secondary outcome).

*Question 4.1.a)* Does the MBSR, compared with an active-control group, increase capacities for self and social ER? *Question 4.1.b)* In doing so, is there a preferential effect over cognitive reappraisal or acceptance strategies? *Question 4.1.c)* Does the MBSR, compared with an active-control group, increase socio-emotional capacities as cognitive empathy and empathy/compassion? *Question 4.2)* What are the functional brain mechanisms underlying the gains in self and social ER, using cognitive reappraisal and acceptance strategies?

*Hypothesis 4.1.a)* The MBI (MBSR), compared with the active-control group, will increase capacity for self and social emotion regulation, in both cases using cognitive reappraisal and acceptance strategies.

*Hypothesis 4.1.b)* The MBI (MBSR), compared with the active-control group, will increase socio-emotional capacities such as cognitive empathy and compassion.

*Hypothesis 4.2)* The MBI (MBSR), compared with the active-control group, will display functional neuro-plasticity, in regions associated with self ER (e.g. prefrontal, parietal and insular cortices) and social ER (e.g. TPJ, precuneus).



**Figure II.** Main constructs targeted by each study:

1 = the MFN-ER review study.

2 = the MFN-SC study.

3 = the ER-EMP study.

4 = the MBI-ER-EMP study.

# Original Research Articles

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## Mindfulness and Emotion Regulation: Insights from Neurobiological, Psychological, and Clinical Studies

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There is increasing interest in the beneficial clinical effects of mindfulness-based interventions (MBIs). Research has demonstrated their efficacy in a wide range of psychological conditions characterized by emotion dysregulation. Neuroimaging studies have evidenced functional and structural changes in a myriad of brain regions mainly involved in attention systems, emotion regulation, and self-referential processing. In this article we review studies on psychological and neurobiological correlates across different empirically derived models of research, including dispositional mindfulness, mindfulness induction, MBIs, and expert meditators in relation to emotion regulation. From the perspective of recent findings in the neuroscience of emotion regulation, we discuss the interplay of top-down and bottom-up emotion regulation mechanisms associated with different mindfulness models. From a phenomenological and cognitive perspective, authors have argued that mindfulness elicits a “mindful emotion regulation” strategy; however, from a clinical perspective, this construct has not been properly differentiated from other strategies and interventions within MBIs. In this context we propose the distinction between top-down and bottom-up mindfulness based emotion regulation strategies. Furthermore, we propose an *embodied emotion regulation* framework as a multilevel approach for understanding psychobiological changes due to mindfulness meditation regarding its effect on emotion regulation. Finally, based on clinical neuroscientific evidence on mindfulness, we open perspectives and dialogues regarding commonalities and differences between MBIs and other psychotherapeutic strategies for emotion regulation.

Increasing interest has emerged about the therapeutic effects of mindfulness meditation and its clinical applications. Several studies have shown positive results in fostering emotional mental health among clinical and healthy populations (Bohlmeijer et al., 2010; Fjorback et al., 2011; Gotink et al., 2015). Neurobiological studies indicate that this type of mental training may have an effect on the

plasticity of brain structure and functioning (Tomasino et al., 2013; Fox et al., 2014). Some of the main neurocognitive mechanisms implicated in mindfulness meditation include attention control, emotion regulation, and self-awareness (Tang et al., 2015). In this article, we will focus on the relationship between mindfulness and emotion regulation, taking into account diverse psychological, clinical and neuroimaging evidence.

Unlike other reviews on the topic, this article does not focus on the problematic aspects involved in the operationalization and definition of mindfulness itself. Instead, the intention is to offer a comprehensive perspective linking different empirical models including mindfulness as a trait, mindfulness inductions, MBIs and mindfulness experts, and emotion regulation-related mechanisms including psychological and top-down/bottom-up brain systems. Moreover, we propose a preliminary framework for better understanding of emotion regulation changes due to mindfulness practice, tackling problematic aspects of the notion of “mindful emotion regulation” widely used in mindfulness clinical research, and complex involvement of top-down and bottom-up mechanisms in MBIs.

## **MINDFULNESS, EMOTION REGULATION, AND CLINICAL APPLICATIONS**

Contemporary psychology considers emotion regulation a central component of mental health, and its imbalances might underlie several mental disorders (Berenbaum et al., 2003; Mennin and Farach, 2007). Emotion regulation includes all of the conscious and non-conscious strategies we use to increase, to maintain or decrease one or more components of an emotional response (Gross, 1998). Originally, trying to bring together ideas from psychoanalysis and the field of stress and coping behaviors, Gross developed a *process* or *time model* of emotion regulation, in which emotions can be modulated in five different stages: selecting a situation, modifying a situation, deployment of attention, changing cognition (cognitive reappraisal), and modulating the experience, behavior or physiological response (Gross, 2001). Gross and John in a correlational study demonstrated that individual differences in the usage of these strategies (more cognitive reappraisal) were related to better emotional health, well-being and interpersonal functioning (Gross and John, 2003).

In line with this approach, Aldao et al. performed a meta-analytic review focused

on how emotion regulation strategies, measured by self-report scales, vary across different psychopathological conditions. The main findings showed that *avoidance*, *ruminat*ion, and *suppression* (as strategies) were each positively associated with anxiety, depression and eating disorders. *Problem-solving* was negatively associated with anxiety, depression and eating disorders. *Reappraisal* and *acceptance*-based strategies were negatively associated, but not significantly, with anxiety and depression (Aldao et al., 2010). Emotion dysregulation has been recognized as a core psychopathological factor in many other psychological disorders such as borderline personality disorder (BPD; Linehan, 1993; Schore, 2003), emotional trauma (Corrigan et al., 2011), attention deficit hyperactivity disorder (ADHD; Shaw et al., 2014), bipolar disorder (Van Rheenen et al., 2015), and anorexia and bulimia nervosa (Lavender et al., 2015). Emotion dysregulation has been demonstrated to mediate the link between child abuse/neglect and later depressive disorder (Crow et al., 2014), and also the link between cumulative adversity in lifetime and depressive symptoms (Abravanel and Sinha, 2015).

Taking into account how individual differences in emotion regulation strategies influence mental health, and the extensive role of emotion dysregulation in many psychopathological conditions, it is reasonable to believe that clinical interventions focused on emotion regulation/dysregulation might have substantial benefits for these psychological disorders. This argument is in line with several studies in which MBIs seem to be particularly effective in clinical and non-clinical conditions characterized by distress and negative emotions.

Mindfulness meditation has its origin in the Buddhist psychology tradition, more specifically in the texts known as *Satipatthana Sutra* (Analayo, 2003) and the *Abhidharma* (from Sanskrit, means higher teachings), a cycle of teachings concern about how the mind, including emotions and consciousness work (Trungpa, 2001; Analayo, 2003; Rapgay and Bystrisky, 2009). The word “mindfulness” corresponds to the translation of the original terms *smṛti* (from Sanskrit) or *sati* (Pali), which captures the capacity to retain an object in the mind, but in a broad sense also implies being aware of and attentive to the present moment (Lutz et al., 2015). In clinical and research contexts, mindfulness as a specific type of meditation practice has been described as a “non- elaborative, non-judgmental awareness” of present-moment experience (Kabat-Zinn, 2005), a non-reactive awareness that emerges as a result of intentionally paying attention to present experience, and a capacity that

can be trained through formal meditation practice. Several MBIs have been developed, including mindfulness meditation and other components, such as body awareness, yoga, and psychoeducation. These are group interventions, specially designed for targeting specific psychopathological substrates (like emotion dysregulation), in particular those related to psychiatric conditions (Shonin et al., 2013).

The mindfulness-based stress reduction (MBSR) program was developed by Jon Kabat-Zinn during the late seventies (Kabat-Zinn, 2005). Several revisions and meta-analyses have highlighted its robust benefits for healthy subjects, increasing well-being, and decreasing stress and negative emotions (Eberth and Sedlmeier, 2012). For clinical population, highlights the decrease in pain intensity, stress, and psychological complaints among patients suffering from diverse chronic pain/inflammatory diseases (Cramer et al., 2012; Lauche et al., 2013) and cancer (Ledesma and Kumano, 2009). Recently, a standardized review of meta-analysis of randomized controlled trials (RCTs) for MBSR and mindfulness-based cognitive therapy (MBCT) demonstrated a significant improvement in different domains (calculated as Cohen's  $d$  effect sizes): depressive symptoms ( $d = 0.37$ ), anxiety ( $d = 0.49$ ), stress ( $d = 0.51$ ), quality of life ( $d = 0.39$ ), physical functioning ( $d = 0.27$ ; Gotink et al., 2015).

MBCT is a program derived from MBSR, developed for preventing recurrence/relapse in recurrent major depressive disorder (MDD; Segal et al., 2002). Several RCT and systematic reviews have demonstrated its effectiveness in relapse prevention and residual symptoms (Chiesa and Serretti, 2011; Piet and Hougaard, 2011; Clarke et al., 2015), and lately, also, in depressive symptoms in MDD (Jain et al., 2015). Another MBI is mindfulness-based relapse prevention (MBRP), which is designed for preventing relapse in substance use disorders (Bowen et al., 2010). Available studies have demonstrated its efficacy in reducing relapse into drug and drinking use, as well as substance usage after a period of abstinence (Bowen et al., 2014; for summary of results, see Table 1).



**Table 1:** Summary of mindfulness-based interventions (MBIs) and main evidence-based targeted conditions.

<i>MBI</i>	<i>Main conditions with evidence support for MBI.</i>
MBSR	Stress, burnout (health professions) Chronic pain (low-back pain, fibromyalgia), Cancer
MBCT	MDD (relapse prevention and acute treatment), BD
MBRP	Substance use disorders (relapse prevention)
ACT	Chronic pain, anxiety and depressive disorders
DBT	Borderline personality disorder, substance use disorders

*MBSR (mindfulness based stress reduction); MBCT (mindfulness based cognitive therapy); MBRP (mindfulness based relapse prevention); ACT (acceptance and commitment therapy); DBT (dialectical behavioral therapy).*

Acceptance and commitment therapy (ACT) is a particular psychotherapeutic orientation developed from behavioral analysis, with mindfulness and acceptance as core principles (Hayes et al., 1999), whose effectiveness is similar to that of cognitive behavioral therapy (CBT) for relevant mental disorders (A-Tjak et al., 2015). Dialectical behavioral therapy (DBT) was developed within a CBT framework, and combines mindfulness and ACT elements. It is organized as a yearlong program, targeting self-harm, and chronic suicidal behavior in BPD (Linehan, 1993). Systematic reviews of ACT find decreases in impulsivity and suicidal attempts, and improvements in general mental health (Stoffers et al., 2012). Interestingly, for the MBIs clinical programs, the central aim is to target dysfunctional strategies of emotion regulation, which are claimed to drive the maintenance and recurrence of these disorders. In this sense, the claim is that mindfulness might re-establish emotion regulation capacities, which leads to symptomatic and clinical recovery.

## **PSYCHOLOGICAL MECHANISMS OF EMOTION REGULATION INVOLVED IN MINDFULNESS**

Despite the effectiveness of MBIs in different psychological disorders, the underlying psychological and neurobiological mechanisms are still unclear. Several authors have proposed psychological models to account for the therapeutic effects of MBIs. Shapiro et al. claim that mindfulness might act through changing attention, intention, and attitude (Shapiro et al., 2006). Others suggest that



positive effects of MBIs could be explained by mechanisms such as observing, describing, acting with awareness, non-judging of inner experiences, and non-reactivity to inner experiences (Baer et al., 2006). Based on an integration of Buddhist psychology and empirical evidence, Grabovac et al. proposed a model in which changes in acceptance, attention regulation, ethical practice, and attachment/aversion to feelings lead to decreased mental proliferation (rumination narrative based), and through this to salutary effects (Grabovac et al., 2011). Other authors have proposed neurocognitive models integrating psychological and neuroscientific data. Vago and Silbersweig proposed that mindfulness leads to changes in self-processing, through the development of self-awareness (meta-awareness), self-regulation (modulation of behavior), and self-transcendence (prosocial characteristics). These changes reflect modulation in neurocognitive networks related to intention and motivation, attention and emotion regulation, extinction and reconsolidation, prosociality, non-attachment, and decentering (Vago and Silbersweig, 2012). Hölzel et al. proposed that mindfulness enacts its effects through plastic changes of mental and brain functions related to attention regulation, body awareness, emotion regulation and self-perspectives (Hölzel et al., 2011a). Recently, Lutz et al. developed a multidimensional model for understanding mindfulness in expert meditators and MBIs, proposing a neurophenomenological “matrix model” in which categorical orthogonal dimensions, including object orientation, dereification and meta-awareness, are central cognitive mechanisms underlying contemplative practices (Lutz et al., 2015; for summary of models, see Table 2).

**Table 2:** Psychological and neurocognitive models of mechanisms of MBIs

<i>Author</i>	<i>Type of Model</i>	<i>Components</i>
Shapiro et al. 2006.	Psychological	Attention, attitude, intention
Baer et al. 2006.	Psychological	Observing, describing, acting with awareness, nonjudging of inner experiences and nonreactivity to inner experiences
Grabovac et al. 2011.	Psychological	Acceptance, attention regulation, ethical practice and decreased attachment/aversion to feelings. Final pathway: <i>decreased mental proliferation</i> (rumination narrative based)
Vago & Silbersweig. 2012.	Psychological-Neurocognitive	Intention and motivation, attention and emotion regulation, extinction and reconsolidation, prosociality, nonattachment and decentering. Final pathway: <i>increasing self-awareness, self-regulation, self-transcendence</i>

Hölzel <i>et al.</i> 2011b.	Psychological- Neurocognitive	Attention regulation, body awareness, emotion regulation and change in perspective of the self. Final pathway: <i>increasing self-regulation</i>
Lutz <i>et al.</i> , 2015.	Phenomenolog ical- Neurocognitive	Primary (orthogonal) dimensions: object orientation, dereification and meta-awareness. Secondary qualities: aperture, clarity, stability and effort

As can be seen, the nature and usage of the construct of mindfulness are complex and elusive. In order to understand the myriad of studies reviewed in this article, it's necessary to clarify the different usage of the mindfulness construct. Dispositional mindfulness is understood as a mental trait or stable characteristic of personality, which can vary between and within individuals across time. Mindfulness as practice refers to the concrete practice of mindfulness meditation, the deployment (and training) of a non-elaborative (non- conceptual), present-centered, exploratory and non-judgmental (non-valorative) awareness. Mindfulness as a state corresponds to the actual proper first-person experience of the non-elaborative, present-centered, non-judgmental awareness (Chambers et al., 2009; Davidson, 2010).

Although most of these models include cognitive, self- awareness, emotional, and attitudinal components, none of them provide an in-depth understanding of the relationship between mindfulness and emotion regulation changes. As can be derived from previous section, a lot of clinical evidence indicates that MBIs seem to be particularly effective in psychological conditions characterized by different forms of emotion dysregulation (see Table 1). In accordance with this, authors studying the psychological mechanisms underlying *mindfulness as a trait* or *as a practice* have focused specially on the relationship between mindfulness and its capacity to enhance emotion regulation as a key route to yielding mental health benefits.

## Cross-Sectional Studies

Studies measuring dispositional mindfulness consist of cross- sectional surveys using self-report scales in a healthy population. The frequency of these studies has grown exponentially and their scope has moved beyond psychiatry and psychology issues to include several other positive health-related outcomes. For example, recent studies suggest that higher dispositional mindfulness is correlated to

improved self-care behaviors (Slonim et al., 2015), and among people with adverse childhood experiences, mindfulness as a trait is related to fewer medical conditions, and better health behaviors (Whitaker et al., 2014).

Giluk performed a meta-analysis of 29 studies investigating the relationship between mindfulness and personality (Big Five) and aspects of affect/mood, finding a negative correlation between mindfulness, neuroticism and negative affect, and a positive correlation between mindfulness and conscientiousness and positive affect (Giluk, 2009). Feltman et al., in a study with 289 participants, found that mindfulness and neuroticism were independent and inverse predictors of depressive symptoms and trait anger; importantly the relationship between neuroticism and symptoms was stronger with low mindfulness, suggesting that mindfulness might play a role in buffering the negative emotionality of neuroticism (Feltman et al., 2009). In line with this, Wupperman et al. found that deficits in mindfulness predict borderline symptoms in a healthy population, independently of neuroticism (Wupperman et al., 2008).

Other studies have evaluated what factors mediate the effect of mindfulness on emotion symptomatology. Bao et al. found a mediation effect of mindfulness, through increases in emotional intelligence (including factors such as emotion regulation) over perceived stress (Bao et al., 2015). Selby et al. looked at how borderline symptoms predict low mindfulness levels. Performing a bootstrapping mediation analysis revealed a significant effect of rumination as a mediator between borderline features and mindfulness deficits, indicating the maladaptive role of rumination as a regulatory strategy (Selby et al., 2016). These results are congruent with intervention studies that highlight the positive effect of DBT and ACT in the BPD population (Gratz and Gunderson, 2006; Stoffers et al., 2012).

Looking to further clarify and understand psychological mechanisms of mindfulness, Coffey et al. conducted a correlational study with 399 healthy people using the five-factor mindfulness questionnaire, the difficulties in emotion regulation scale and the trait meta-mood scale. Using factor analysis and structural equation modeling, the authors found that mindfulness and emotion regulation corresponded to shared and distinct constructs, distinguishing four factors: present-centered attention and acceptance of experience (for mindfulness), clarity about one's internal experience, and the ability to manage negative emotions (for emotion regulation). A path analysis supported the stance that mindfulness

(including the factors “present-centered attention” and “acceptance of experience”), through clarity about one’s own experience, improves the ability to deal with negative emotions (the model had a good data fit, having a RMSEA of 0.059;  $p < 0.0001$ ). The authors also found that clarity about experience was negatively correlated to rumination and psychological distress, and positively related to flourishing (Coffey et al., 2010). Acknowledging methodological limitations, studies using dispositional mindfulness as a trait or personality characteristic (statistically as independent variable or predictor) provide interesting preliminary evidence that mindfulness, even though partially overlapping with emotion regulation constructs, might exert its beneficial salutary effects through higher emotion regulation capacities.

### **Longitudinal Studies**

In the area of clinical and psychotherapy research, the question of change mechanisms, or “active ingredients,” that drive therapeutic effects has been a central concern over the last 20 years (Kazdin, 2007; Nock, 2007). As we stated in previous sections, hundreds of longitudinal studies have demonstrated the efficacy of MBIs in a healthy or clinical population, but also studies have evaluated change factors that might mediate the salutary effects of these interventions.

Recently, Gu et al. performed a systematic review and meta-analysis only of MBSR and MBCT studies that included mediation analysis. Starting from 169 trials and ending with 20 included in further analyses, the authors found consistent and strong evidence of emotional and cognitive reactivity, repetitive negative thinking (such as rumination and worry), and mindfulness itself as change factors/mechanisms. Only for mechanisms with sufficient studies (mindfulness and repetitive negative thinking) was quantitative synthesis using two-stage meta-analytic structural equation modeling used, further confirming mindfulness and rumination/worry as mediators of the effects of MBIs (Gu et al., 2015). In the same vein, intending to understand change mechanisms using MBCT for recurrent depressive disorder, Maj van der Velden et al. performed a systematic review of mediation studies. Out of 23 studies, 12 showed that mindfulness skills, worry, rumination, self-compassion and meta-awareness mediated or predicted treatment outcomes of MBCT (Van der Velden et al., 2015).

From these meta-analytic reviews, including high-quality RCT mediation studies, it

is possible to state that mindfulness, emotional and cognitive reactivity, rumination/worry, self-compassion, and meta-awareness might be mechanisms underlying the therapeutic effects of MBIs (for summary of mechanisms, see Table 3). On the one hand, increases in mindfulness, self-compassion, and meta-awareness might account for adaptive emotion regulation strategies; on the other hand, decreases in emotional, cognitive reactivity, and rumination/worry might represent the dismantling of dysfunctional emotional-cognitive and self-processing strategies of emotion regulation. This evidence is concordant with the work of Aldao et al. in which avoidance, rumination, and suppression as emotion regulation strategies were correlated to anxiety, depression, and eating disorders (Aldao et al., 2010). Therefore, MBIs might target specific emotion regulation deficits of emotion-related disorders.

**Table 3:** Evidence-based putative psychological mechanisms of MBIs (MBSR/MBCT)

<i>Author</i>	<i>Emotional</i>	<i>Cognitive</i>	<i>Attitudinal</i>
Gu et al., 2015.	< emotional reactivity	< cognitive reactivity < rumination < worry	> mindfulness
Van der Velden et al., 2015.	> self-compassion	> meta-awareness < worry < rumination	> mindfulness

## NEURAL MECHANISMS OF EMOTION REGULATION INVOLVED IN MINDFULNESS

As we have stated before, emotion regulation can be defined as all the conscious and non-conscious strategies we use to increase, maintain or decrease one or more components of an emotional response (Gross, 2001), including *implicit*, non-conscious, and automatic processes, as well as *explicit*, voluntary and conscious mental processes (Gyurak et al., 2011). From a neural perspective, these processes are realized by different and complex distributed brain systems. Subcortical regions like the amygdala, periaqueductal gray, ventral striatum (VS), anterior insula (AI), and dorsal-anterior cingulate cortex (dACC) are involved in *emotional reactivity*, as emotion generation regions leading changes in arousal and valence regarding the triggering stimuli. Cortical regions such as the dorso-lateral prefrontal cortex (dLPFC), the ventro-lateral prefrontal cortex (vLPFC), the pre-supplementary and supplementary motor area (pre-SMA and SMA) and parietal cortex are involved in

*explicit emotion regulation*. These regions conform to the so-called *central executive network* (CEN), usually involved in top-down emotion regulation, but also in attention and voluntary cognitive control. Finally, the ventral-anterior cingulate cortex (vACC) and the ventro-medial prefrontal cortex (vMPFC) are involved in *implicit emotion regulation*, the outside of awareness processing of emotion, but also in encoding subjective value of the stimuli or condition experienced by the subject (Frank et al., 2014; Kohn et al., 2014; Etkin et al., 2015). From now on, we will refer to the explicit emotion regulation system as the top-down system, and to the emotion generation and the implicit emotion regulation systems as both part of a bottom-up system, since both feed up the top-down system with information regarding arousal, visceral homeostasis, aversiveness and rewardingness of a given stimuli or situation, among others.

It has been stated that different emotion regulation strategies might differentially activate these brain systems implicated in emotion regulation processes. For example, Dörfel et al. found that *detachment*, *distraction (two forms of reappraisal)*, and *expressive suppression* increase brain activation in the same regions of the right fronto-parietal network, reducing activation of the left amygdala. This suggests a common underlying neural process for these strategies, but somewhat contrary to theoretical predictions, since *expressive suppression* as a less adaptive strategy might have a different neural correlate from reappraisal strategies. Interestingly, only *reinterpretation* induced a different activation pattern, recruiting the left vLPFC and orbitofrontal gyrus, but not decreasing amygdala activation (Dörfel et al., 2014). In another study comparing *reappraisal* and *affect labeling*, authors found a common activation pattern including activation in the right and left dLPFC, right and left vLPFC, and pre-SMA, and decreased amygdala and vMPFC activation (Burklund et al., 2014). Recently, a meta-analysis of 48 studies of cognitive reappraisal emotion regulation neuroimaging studies concluded that this strategy particularly activates the bilateral dLPFC, vLPFC, dMPFC, posterior parietal cortex, and left-middle temporal gyrus, and deactivates the amygdala bilaterally. Clearly involving the explicit emotion regulation network. Unexpectedly, no other regions related to emotion reactivity decreased their activation level during reappraisal down regulation (Buhle et al., 2014).

Interestingly, some studies have demonstrated that the top- down or explicit



emotion regulation system (dLPFC, vLPFC, parietal cortex) can also be involved in generating emotional states and not only in controlling them, in conjunction or in parallel with the implicit emotion generation system (Ochsner et al., 2009; McRae et al., 2012). In particular, in two studies, applying cognitive reappraisal to emotions generated via implicit stimulation resulted in a paradoxical increased activation of the amygdala (Herwig et al., 2010; McRae et al., 2012). In Herwig et al.'s study, the usage of emotional body-awareness strategy decreased amygdala activation compared to reappraisal strategy (Herwig et al., 2010). These studies highlight the question of whether top-down emotion regulation strategies are always the most appropriate, and whether there are other effective forms of emotion regulation that are not based on top-down mechanism.

Of particular interest for the mindfulness-based emotion regulation field is the notion of bottom-up emotion regulation. At the brain mechanisms level, the main assumption of this model is that the bottom-up systems implying emotional generation regions (like the amygdala, dACC and AI) and implicit emotion regulation regions (like the vMPFC) can also be modulated without the involvement of cognitive control (like the v-d LPFC), or semantic processing regions (temporal cortex). Several authors have argued that mindfulness might exert a unique emotion regulation strategy, termed “mindful emotion regulation,” different from cognitive reappraisal (based on top-down system), mainly through the privileged engagement of these bottom-up emotion regulation systems (Chambers et al., 2009; Farb and Segal, 2012; Chiesa et al., 2013; Grecucci et al., 2015a). Nevertheless, whether mindfulness-based emotion regulation is a unique phenomena, and whether it only relies on the involvement of bottom-up systems excluding cognitive control regions (top-down systems), and what the exact brain signature of mindfulness is as an emotion regulation strategy, among other questions, are still a matter of debate and will be addressed in the following sections of the article.

## **Structural Brain Changes in Mindfulness Experts and Mindfulness-Based Interventions**

Several studies have investigated the effect of MBIs and long-term mindfulness meditation practice using structural brain imaging, like morphometry-based magnetic resonance imaging (MRI) techniques. Cross-sectional design studies

comparing healthy controls with expert meditators (EMs) from different meditation traditions have demonstrated structural MRI changes in: the hippocampus (Hölzel et al., 2008; Luders et al., 2009; Kang et al., 2013); right anterior insula (AI; Lazar et al., 2005; Hölzel et al., 2008); orbitofrontal cortex (OFC; Hölzel et al., 2008; Luders et al., 2009; Kang et al., 2013); anterior cingulate cortex (ACC; Grant et al., 2013); left temporal pole (TP; Hölzel et al., 2008; Luders et al., 2009; Kang et al., 2013); left frontal gyrus (Vestergaard-Poulsen et al., 2009; Kang et al., 2013); right frontal sulcus (Lazar et al., 2005); corpus callosum (Luders et al., 2012; Kang et al., 2013); and regions in the brainstem (Vestergaard-Poulsen et al., 2009). Moreover, a study using machine learning structural pattern recognition analysis estimated that brains of meditators were 7.5 years younger than matched control subjects (Luders et al., 2016).

As can be seen, covering a wide range of brain regions, according to recent reviews and meta-analysis of neural bases of emotion regulation (Frank et al., 2014; Kohn et al., 2014; Etkin et al., 2015), would partially overlap with emotion reactivity (AI, ACC), and with implicit emotion regulation regions (OFC and vMPFC), and very loosely with explicit emotion regulation (medial PFC, but not lateral PFC regions) systems. From this, if mindfulness meditation would involve cognitive reappraisal, or top-down emotion regulation strategies, one would expect changes in lateral PFC morphometry. It is important to note that due to the design of the studies, it is not possible to infer causality between brain changes and long-term meditation practice; also, because of the nature of brain structural imaging, it is not possible to derive any information about brain regions' functions. Another limitation of these studies is the variability of hours of meditation practice within this population, ranging from 1,000 to 10,000 or more hours. Nevertheless, they might offer preliminary evidence of the effects of long-term mindfulness practice on brain plasticity.

During the last few years, longitudinal studies have assessed the impact of MBIs on brain morphology, particularly the MBSR 8-week program. Hölzel et al., using MRI voxel-based morphometry (VBM), found changes in gray matter density in the left hippocampus, posterior cingulate cortex, right temporo-parietal junction (TPJ), some small regions in the brainstem, and cerebellum (Hölzel et al., 2011b). In a similar uncontrolled longitudinal study with MBSR, the authors found that decreases in perceived stress were correlated to a decreased gray matter density in



the right amygdala (Hölzel et al., 2009). They also found a correlation between major psychological well-being and plastic changes in the brainstem (Singleton et al., 2014). Santarnecchi et al. performed a controlled longitudinal study with MBSR, finding a significant increase in cortical thickness in two clusters: the right SSC and right paracentral lobule, and AI and right inferior frontal gyrus (operculum). The authors found a significant interaction between structural changes in the right insula and a decrease in alexithymia levels, suggesting “body or interoceptive awareness” as a possible mechanism responsible for salutary effects of mindfulness practice (Santarnecchi et al., 2014). These studies suggest that an 8-week MBI (MBSR) might induce neuroplastic changes in key areas for emotional reactivity (amygdala, insula), body awareness or interoception/exteroception (insula, somatosensory cortex), self-consciousness (posterior cingulate cortex, pons), mood, and arousal regulation (brainstem regions—locus coeruleus, and raphe nuclei), perspective taking (TPJ) and memory systems (hippocampus, cerebellum). Interestingly, none of these studies suggest changes in PFC areas or regions involved in the top-down emotion regulation system, thereby indicating that salutary effects of MBI might be mediated mainly by changes in particular relevant subcortical and cortical regions related to bottom-up or non-emotion regulation related functional systems.

## **Functional Brain Changes in Emotion Tasks in Mindfulness Studies**

### ***Dispositional Mindfulness***

Cross-sectional studies in healthy populations have investigated how individual differences in mindfulness as trait might be related to specific brain functions during emotion elicitation task experiments. Creswell et al., in an affect labeling task during fMRI, found that levels of dispositional mindfulness were related to higher activations in the right vMPFC and right vLPFC and major deactivation of the right amygdala (Creswell et al., 2007). In a similar study, participants were asked to observe emotional faces during fMRI, and higher levels of DM were correlated to less amygdala reactivity. Using resting-state functional connectivity (rs-fMRI) analysis, the authors found a relationship between higher dispositional mindfulness and decreased connectivity within the midline regions, including the PCC and MPFC (Way et al., 2010). Importantly, the midline regions like the MPRC,

PCC, precuneus, ACC, and parietal cortex are part of the so-called default mode network (DMN; Raichle and Snyder, 2007), which has been related to mind-wandering (task-unrelated thought) and self-referential processing (Qin and Northoff, 2011). Brown et al. assessed 46 participants with an electroencephalogram (EEG) while viewing emotionally laden pictures, particularly looking at the late positive potential (LPP) as a marker of affective processing. Authors found that higher dispositional mindfulness correlated to lower LPP during high-arousal negative images (Brown et al., 2013). Finally, Kong et al., using rs-fMRI and local synchronization measurements (estimated by regional homogeneity) with 290 subjects, found that major dispositional mindfulness correlated to local synchronization in the right insula, left OFC, left parahippocampal gyrus (regions involving emotion reactivity, implicit emotion regulation), and decreased local synchronization with the inferior frontal gyrus (IFG; related to explicit emotion-regulation). Furthermore, levels of local synchronization in the OFC predicted positive emotions, and in the IFG predicted a sense of meaning and purpose in life, both effects mediated by DM (Kong et al., 2016). This study suggests that local synchronization in key regions of emotion regulation might engage differently in subjects high in dispositional mindfulness, accounting for positive emotions' salutary effects. Also it shows no correlation between lateral PFC local synchrony and dispositional mindfulness in emotion regulation-related variables, suggesting that individuals high in dispositional mindfulness might engage in emotion-related processes involving different regulatory systems than top-down ones (for summary of results, see Table 4).

Interestingly, these findings are concordant with psychological studies linking dispositional mindfulness to better emotional life outcomes (positive affect and emotional intelligence and minor neuroticism, negative affect, rumination, and borderline symptoms) thereby providing preliminary support for the construct validity of DM. These studies face many limitations, such as the difficulty in deriving causal inferences, and disentangling relevant confounders such as psychological traits and biological differences. Another problematic claim of these studies is the assumption that dispositional mindfulness really reflects daily-life mindful attitudes. At this time, to the best of our knowledge, no study has empirically clarified this point.

## ***Mindfulness Inductions***

Studies using brief meditation practice, or mindfulness inductions, have started to explore the clinical utility (effectiveness) and neural underpinnings of these types of interventions. Westbrook et al. performed a cross-sectional study with smokers looking to stop smoking. Participants were asked to watch specific craving-inducing images during fMRI, using “mindful attention” vs. “passive viewing” as strategies. When applying “mindful attention,” subjects reported less craving impulse; additionally, they presented decreased activation in the subgenual ACC (sg-ACC), and reduced functional connectivity between this same region and bilateral AI and VS. At the same time, no involvement of the PFC was detected (Westbrook et al., 2013). Interestingly, sg-ACC, AI, and VS correspond to emotion generation regions, but are also implicated in other relevant affective functions such as craving and reward processing (VS), processing of salient stimuli and interoception (AI), and the subjective encoding of value and processing of emotional conflict (sgACC; Wilcox et al., 2016).

Lutz et al., in a cross-sectional study with healthy participants, compared one group applying mindfulness with a no-strategy group while looking at a set of emotional pictures during fMRI. When expecting negative pictures, the mindfulness group displayed increased activation of the left AI, right and left dMPFC, and left dLPFC. During perception of negative pictures, the mindfulness group showed reduced activation in the right amygdala and parahippocampal gyrus, with no involvement of the PFC (Lutz J. et al., 2013). The same researchers also compared groups using mindfulness vs. cognitive reappraisal using the same emotional task as in fMRI. During the expectation of negative pictures, both groups showed a similar pattern of activation of the MPFC and the amygdala, and during the perception of negative images, decreased activation of the head of the right caudate in the mindfulness group was the only difference (Opiella et al., 2014). Interestingly, the first experiment comparing mindfulness vs. baseline conditions suggests a bottom-up (targeting emotion reactivity regions, with no changes in PFC) mechanism of mindfulness as emotion regulation strategy; instead, when adding an active regulatory strategy as comparison, it is almost impossible to differentiate at the neural level between the two emotion regulation strategies. However, the observed deactivation of the right caudate head might index decreased engagement of automated cognitive and motor responses (Parent

and Hazrati, 1995), which might be linked to decreased automatic cognitive reactivity, known as a mindfulness mechanism (Gu et al., 2015).

Interestingly, this draws attention to the fact that even a short mindfulness induction, in people naive about meditation, can induce a distinguishable bottom-up brain activation pattern when comparing mindfulness as a strategy to baseline or no- strategy condition. Nevertheless, when compared to cognitive reappraisal, differences seem to vanish. This suggests that mindfulness meditation in naive practitioners is performed with the engagement of widespread brain regions including top-down and bottom-up regulatory systems. From the clinical perspective, these studies provide a valuable outlook for understanding neurobiological substrates of brief meditation practices, which are central components of many MBIs, like MBCT, ACT, or DBT, that intend to elicit “mindfulness states” to face difficult emotions and emotion dysregulation states.

As previously stated, these studies share limitations with cross-sectional design studies. These investigations raise particularly relevant problems in the discussion of mindfulness and emotion regulation mechanisms, starting with the question of the acquisition of the so-called mindfulness emotion regulation strategies—in other words, when and how a person acquires the capacity to elicit a “mindfulness state,” different from other mental states. And also, when and how a person acquires the capacity to use mindfulness as an emotion regulation strategy. Finally, the question of how this learning process can be distinctly measured from behavioral and brain signatures. These are central questions that future studies need to unravel.

### ***Mindfulness-Based Interventions: Longitudinal Studies on Emotion, Pain, and Anxiety***

Over the last few years, longitudinal studies using fMRI have used a myriad of experimental tasks investigating emotion regulation changes secondary to MBIs. Farb et al. studied the impact of MBSR using fMRI under a sadness induction paradigm. After the intervention, the mindfulness group changed the activation pattern in key diverse emotion regulation regions: comparatively increased activation in the right AI, right LPFC and sg-ACC. The control group showed major activation in the left PFC, left superior temporal sulcus (STS), precuneus, and PCC, areas usually involved in self-awareness and semantic processing (Farb et al., 2010). From the same lab, using a self-referential task (self-narrative vs. self-

experiential) during fMRI, an increased activation was found in similar right brain regions, LPFC, AI, second SSC and inferior parietal lobule (IPL), for the self-experiential focus. Conversely, a self-narrative focus engaged major activation in the left vMPFC, dMPFC, and PCC, all midline regions that mainly correspond with the DMN (Farb et al., 2007). These studies indicate a different engagement of brain regions during emotion regulation; although both groups displayed top-down mechanisms linked to explicit emotion regulation systems (right or left LPFC), only the MBI groups employed regions related to emotion reactivity (AI, ACC), interoception (AI) and somatosensory awareness (SSC, IPL).

Attempting to unravel the involvement of different emotion regulation systems implicated in mindfulness meditation, Allen et al. performed an RCT comparing a 6-week mindfulness training and an active control (sharing and listening training). Despite both groups improving significantly in a response inhibition task, only the MBI group showed reduced emotional interference under an affective Stroop conflict resolution paradigm (a task known to activate implicit emotion regulation processes). The authors found no differences between groups in behavioral and neural activations during negative affect processing. Nevertheless, the greater amount of mindfulness practice predicted increased activation of bilateral dACC, right AI, and MPFC during implicit negative emotional processing, suggesting both implicit and explicit emotion regulation plasticity as mechanisms underlying mindfulness training (Allen et al., 2012). Another RCT study compared the effects of an 8-week Mindful Attention Training (MAT) vs. Cognitively Based Compassion Training (CBCT) vs. active control while participants passively viewed affective pictures during fMRI. In a region of interest analysis, the authors found decreased activation in the right amygdala in the MAT group in response to images of all valences. Interestingly, a trend increase in activation of the right amygdala when viewing negative images in the CBCT group was found, and the extent of this increase was significantly correlated to reductions in depressive symptoms (Desbordes et al., 2012). Although not conclusive, both RCT studies provide evidence that MBIs might exert their effects on the level of emotion reactivity and implicit emotion regulation.

Other studies have evaluated the impact of MBIs on pain processing. Zeidan et al. performed a longitudinal uncontrolled study with 4-day MBI training, using Arterial Spin Labeling (ASL), a technique for estimating cerebral blood flow with

MRI across time points. After the intervention, during a breathing meditation task, the authors found decreased perfusion of the MPFC and PCC (DMN), and a major activation of the AI, ACC, pre-SMA, OFC, VS, SSC, and posterior insula (PI). During a pain induction paradigm, minor activation of the contra-lateral SSC and increased activation in the ACC, AI, PI, and fronto-parietal operculum were reported. It is worthy of note that participants reported a significant decrease in pain intensity and unpleasantness (Zeidan et al., 2011). Later, the same authors performed a four-arm RCT comparing MBI vs. placebo vs. sham mindfulness using a pain induction paradigm with ASL MRI. Interestingly, all groups showed a significant reduction in pain intensity and unpleasantness, but the MBI demonstrated a unique brain mechanism including greater activation of the OFC, sg-ACC, and AI. In line with previous evidence, these studies highlight emotion reactivity (AI, ACC, VS) and implicit emotion regulation (OFC, vMPFC) systems as the main emotion regulation targets of MBIs, again notably without any major involvement of PFC-related systems (top-down emotion regulation).

Other researchers have explored the effects of MBIs in clinical populations. In one of the first such studies, Goldin and Gross conducted an MBSR longitudinal study with people suffering from social anxiety disorder (SAD). Comparing two emotion regulation strategies using an anxiogenic task with negative self-beliefs, the authors found that being breathing-focused (vs. distraction-focused) produced minor negative emotional experiences, decreases in amygdala activation, and increased activation of the PCC, SPL, and IPL (areas involved in top-down emotion regulation, but also in self-awareness and attention processing; Goldin and Gross, 2010). The same authors performed an RCT comparing MBSR with aerobic exercise (AE), also in SAD patients, in this case comparing mindful attention (metacognitive perspective of mental content) and reacting (thinking according to negative self-beliefs) as strategies for dealing with negative-self-belief-induced emotions. During the task, the MBSR group reported fewer negative emotions, and showed differential engagement of attention regulation areas, with increased activation of the right IPL and SPL, and decreased activation of the culmen and left lingual gyrus (Goldin et al., 2013), areas involved in the orienting-attention network, implicated in early spatial detection of stimuli (Posner et al., 2006). The authors interpreted this finding as suggesting that MBIs enhance approaching behavior/attention toward anxiogenic stimuli, a core deficit in SAD (Goldin et al., 2013). In the context of the same trial condition, both groups significantly



decreased social anxiety symptoms, disability and negative self-attribution, while also increasing positive self-views. Examining the neural correlate of self-views, the MBSR group displayed larger responses in the PCC, and dMPFC, which correlated with minor social anxiety, disability, and increased mindfulness (Goldin et al., 2012). Finally, Hölzel et al. ran an RCT with generalized anxiety disorder (GAD) patients, comparing MBSR and psychoeducation treatment groups performing an emotion labeling task during fMRI. The findings highlighted small increases in amygdala activation in both groups, and major increases of activity in the vLPFC, as well as increased functional connectivity between these regions (Hölzel et al., 2013). These studies point toward the idea that MBIs target basic cognitive processes broadly involved in attention regulation, including information updating, response inhibition, and goal maintenance (Malinowski, 2013). Interestingly, these are core functions for the CEN, and for the top-down emotion regulation system (Okon-Singer et al., 2015). In sum, these studies provide evidence that MBIs might exert their effects through top-down/cognitive-control emotion regulation mechanisms. Besides sample size, noteworthy limitations of these studies include the lack of control of basal cognitive deficits in patients, and of personality and comorbidity factors, which might influence basal neuroimaging results.

### ***Expert Meditators (EMs): Cross-Sectional Studies on Emotion, Pain, and Reward***

Lutz et al. used an annoying auditory task during fMRI, comparing Tibetan monks and controls during active compassion meditation. They found increased activity in the AI and ACC, which were proportional to first-person experience of compassion intensity (Lutz et al., 2008a). Using the same experimental task, but during focused-attention meditation, researchers also found a direct relationship between meditation expertise (total hours of practice) and amygdala deactivation (Brefczynski-Lewis et al., 2007). Taylor et al. compared Western EMs with novel meditators using emotional pictures during fMRI, and observed a decrease in activation levels of the PCC and MPFC (DMN) during active meditation in EMs. During passive observation, beginner meditators showed major amygdala activation increases for negative affective pictures (Taylor et al., 2011). These studies highlight a specific modulation of the emotion generation system in EMs during emotion tasks.

Other studies have explored the effects of EMs in pain processing. Gard et al. compared Western EMs with controls, contrasting active meditation, and resting state using a pain induction paradigm with fMRI. The authors found no differences between groups in pain intensity, but in active meditation during pain induction, EMs referred less unpleasantness and a major activation in the right AI and a deactivation in the right and left inferior PFC (Gard et al., 2012). Grant et al. also compared EMs with controls during a pain induction task in fMRI. EMs showed decreased activation of the PFC, amygdala and hippocampus, and increased activity in the AI, ACC, and thalamus. Interestingly, the decreased functional connectivity between PFC and AI and ACC predicted lower pain in EMs (Grant et al., 2011). In a similar study, EMs showed lower baseline activation in the AI, ACC, and amygdala, and during pain induction higher activation of AI and ACC regions than controls (Lutz A. et al., 2013). These studies indicate that EMs specifically increases activation of subcortical emotion generation regions, related to affective processing of pain, and deactivates top-down mechanisms, evidencing a unique emotion regulation bottom-up mechanism.

Other studies have used reward or economic behavioral paradigms for studying emotion processing in EMs. Grecucci et al. compared EMs with a control group contrasting a “cognitive” vs. an “experiential” emotion regulation strategy during two monetary distribution tasks. While receiving offers in the dictator game, EMs showed decreased emotion arousal and physiological reactivity, with no effect of the strategy observed. While receiving unfair offers in the ultimatum game (UG), EMs accepted more unfair offers and performed less punishment, particularly during the “experiential” emotion regulation strategy (Grecucci et al., 2015a). Another study used fMRI during the execution of the UG. Compared to controls, EMs accepted more unfair offers, and during that particular condition engaged a particular functional brain response with greater activation of the PI than the AI, and major activation in the SSC and posterior superior temporal cortex (Kirk et al., 2011). Note that the PI is preferentially involved in interoception and the AI in emotion reactivity/generation and emotional awareness (Craig, 2009; Gu et al., 2013). These studies show that during socially induced negative emotions, EMs showed stronger modulation of their interactive behavior (less punishment) and greater emotion regulation, which was mediated via increased activation of interoception and exteroception brain regions, modulating emotion generation regions.



Kirk et al. used the monetary incentive delay task in EMs during fMRI, looking to disentangle the neural differences between anticipation and receipt of monetary reward. Compared to controls, during the anticipation phase EMs displayed decreased activation of the bilateral caudate, and increased activation of the bilateral PI. During the encoding of gains of reward, a minor activation of the vMPFC was seen (Kirk et al., 2015), indicating a dampening of the reward system. The same authors used a passive conditioning task (pairing a yellow light to juice intake) to evaluate how changes in the predictability of reward, encoded by the prediction error (PR) neural signal, differ between EMs and matched controls. In this task, the delay of the reward decreases PE (negative PE), while the intake of unexpected reward generates an increase in PE signal (positive PE). EMs were found to be less prone to positive and negative PE signals in the putamen (part of the striatum and the reward system), which again was associated to major activation in the PI (Kirk and Montague, 2015). Interestingly, both studies show a specific modulation in value reward processing in the striatum and vMPFC, from interoceptive body awareness regions (PI) that correspond to bottom-up emotion regulation systems, in line with the bottom-up mechanism hypothesis of emotion regulation changes derived from mindfulness practice.

**Table 4:** Summary of neuroimaging studies using emotion-task experiments in different mindfulness conditions.

<b>Mindfulness condition</b> (different models) <b>vs control condition</b> (Waiting list, or active control).	<b>Study design.</b>	<b>Population.</b>	<b>Sample size:</b> mindfulness (M) vs control groups. (C).	<b>Experimental task and neuro-imaging method:</b> resting state functional magnetic resonance imaging (rs-fMRI), task based functional magnetic resonance imaging (fMRI), electroencephalography (EEG).	<b>Main finding:</b> summarized in terms of brain, and/or physiological response changes.  (* = finding indicates bottom-up mechanisms).	<b>References</b>
<i>Dispositional Mindfulness</i>						
Dispositional mindfulness	Cross sectional / Uncontrolled study	Healthy	M: 27	Affect labeling task during fMRI	Level of DM mediates the relationship between right vMPFC, right vLPFC activation and right amygdala deactivation	Creswell <i>et al.</i> , 2007.
Dispositional mindfulness	Cross sectional / Uncontrolled study	Healthy	M: 27	Viewing negative emotional faces during fMRI + rs-fMRI	Higher DM correlated with less amygdala reactivity. Also with less resting connectivity in midline brain regions (self-referential processing)	Way <i>et al.</i> , 2010.
Dispositional mindfulness	Cross sectional / Uncontrolled study	Healthy	M: 46	Viewing negative/positive pictures during EEG (LPP: late positive potential)	Higher DM correlated to lower LPP during high-arousal negative emotions	Brown <i>et al.</i> , 2013.

Dispositional mindfulness	Cross sectional / Uncontrolled study	Healthy	M: 290	rs-fMRI – local synchronization	Higher DM correlated to local synch in left OFC, left parahippocampal gyrus, right insula. Local synch in OFC-predicted positive affect, and in IFG-predicted purpose/meaningful life	Kong <i>et al.</i> , 2015.
<b>Mindfulness Induction</b>						
Mindfulness induction	Cross sectional / Uncontrolled study	Smokers looking for treatment to stop smoking	M: 47	Cue-induced craving during fMRI.	Reduced neural activity in sg-ACC [craving-related – emotion reactivity region] and a reduced functional connectivity between this same region with the bilateral insula and ventral striatum with no direct involvement of PFC regions (*)	Westbrook <i>et al.</i> , 2013
Mindfulness induction	Cross sectional / Nonrandomized controlled study	Healthy	M: 24 / C: 22	Cued expectation and perception of negative pictures during fMRI	During expectation major activations in prefrontal regions: left AI, right and left dMPFC and left dLPFC. During perception reduced activation in right amygdala & parahippocampal gyrus [emotion processing reactivity] (*)	Lutz J. <i>et al.</i> , 2013.
Mindfulness induction vs Reappraisal strategy	Cross sectional / Nonrandomized controlled study	Healthy	M: 24 / C: 23	Cued expectation and perception of negative pictures during fMRI	Both groups: similar activity of the m-PFC and the amygdala. Major activations in MI group, during expectation: vLPFC, vLPFC, Supramarginal gyrus and left insula. During perception: major activity in the caudate in the cognitive group	Opialla <i>et al.</i> , 2014.
<b>Mindfulness-based interventions</b>						
Mindfulness-based stress reduction	Cross sectional / Nonrandomized controlled study (novice vs those who attended the course)	Healthy	M: 20 / C: 16	Self-reference task during fMRI	Significant difference in the neural correlates of the self-reference task, during experiential focus an increased activation in right brain regions: lateral PFC, insula, second somatosensory area, and IPL	Farb <i>et al.</i> , 2007.
Mindfulness-based stress reduction vs Waiting list	Longitudinal / Nonrandomized controlled study	Healthy	M: 20 / C: 16	Sadness induction paradigm during fMRI	MBI group changed activation pattern in key emotion regulation regions: major activation in the right anterior insula, r-IPFC and sg – ACC.	Farb <i>et al.</i> , 2010.
Mindfulness-based stress reduction	Longitudinal / Non Controlled trial	Social Phobia	M: 16	Breath focus task during fMRI	Reduced amygdala activity, major activation in precuneus, SPL, IPL compared to distraction focus task	Goldin & Gross, 2010.
Mindfulness Training (4 days)	Longitudinal / Non Controlled trial	Healthy (pain)	M: 15	Breath focus meditation during noxious stimulation task in fMRI	MBI reduction in pain intensity: major activation in ACC, anterior insula. MBI reduction in pain unpleasantness: major activation in OFC and thalamus (*)	Zeidan <i>et al.</i> , 2011.
Mindfulness-based stress reduction vs Aerobic exercise	Longitudinal / Randomized controlled trial	Social Phobia	M: 31 / C: 25	Self-reference task during fMRI	MBIs during negative self-view: major activation in PCC, and dMPFC activity-associated less social anxiety disability and mindfulness level	Goldin <i>et al.</i> , 2012.
Mindfulness-based stress reduction vs Aerobic exercise	Longitudinal / Randomized controlled trial	Social Phobia	M: 31 / C: 25	Emotion regulation of negative self-beliefs task during fMRI	MBI regulating negative self-beliefs: fewer negative emotions, major activation in R-IPL, R-SPL	Goldin <i>et al.</i> , 2013.
Mindfulness-based stress reduction vs Stress management education	Longitudinal / Randomized controlled trial	Generalized Anxiety Disorder	M: 15 / C: 11	Affect labeling of emotional expressions during fMRI	Both groups less amygdala activation. MBI major activation in vLPFC. Increase functional connectivity between amygdala and PFC regions	Hölzel <i>et al.</i> , 2013.

Mindfulness Training (6 weeks) vs Shared reading and listening group	Longitudinal / Randomized controlled trial	Healthy	M: 30 / C: 31	Affective Stroop conflict resolution task during fMRI	Both groups improved significantly in a response inhibition task. MBI reduced emotional interference, in negative emotion processing: increased bilateral dLPFC, right anterior insula and m-PFC (*)	Allen <i>et al.</i> , 2012.
Mindfulness Training (8 weeks) vs Compassion training vs Health discussion group	Longitudinal / Randomized controlled trial	Healthy	M: 12 / C: 12 / Compassion Training: 12	Observation of emotional pictures during fMRI	In MBI: decrease in right amygdala activation (all valences). In Compassion Training: trend increase in right amygdala response in negative pictures (*)	Desbordes <i>et al.</i> , 2012.
Mindfulness Training (4 days) vs Sham mindfulness vs Placebo vs Control	Longitudinal / Randomized controlled trial (four-arm)	Healthy (pain)	M: 80	Pain regulation strategy during noxious stimulation task in fMRI	MBI reduction in pain intensity: major activation in sg - ACC, anterior insula, OFC. Placebo analgesia: major activation in DLPFC and secondary somatosensory cortex (*)	Zeidan <i>et al.</i> , 2015.
<i>Expert Meditators</i>						
Tibetan Buddhist monks	Cross sectional / Case-control study	Healthy	M: 14 / C: 16	Auditory stimuli during focus attention task in fMRI	EM: amygdala deactivation	Brefczynski-Lewis <i>et al.</i> , 2007.
Tibetan Buddhist monks	Cross sectional / Case-control study	Healthy	M: 15 / C: 15	Auditory stimuli during active compassion meditation in fMRI	EM: increased activation in the anterior insula and ACC, proportional to compassion experience intensity	Lutz A. <i>et al.</i> , 2008.
Zen Western vs novices meditators	Cross sectional / Case-control study	Healthy	M: 12 / C: 8	Observation of emotional pictures during active meditation in fMRI	EM during meditation: major deactivation of m-PFC and PCC. Relative deactivation of amygdala and insula vs novice meditators. Novice during meditation: downregulation of amygdala	Taylor <i>et al.</i> , 2011.
Zen Western	Cross sectional / Case-control study	Healthy	M: 13 / C: 13	Noxious stimulus during fMRI	EM during pain: reduced activation in PFC, amygdala, hippocampus. Major activations in ACC, insula, thalamus.	Grant <i>et al.</i> , 2011.
Vipassana	Cross sectional / Case-control study	Healthy	M: 17 / C: 17	Noxious stimulus during fMRI	EM during pain in meditation: reduced activation in lateral PFC, major activation in ACC, R-posterior insula	Gard <i>et al.</i> , 2012.
Tibetan tradition	Cross sectional / Case-control study	Healthy	M: 14 / C: 14	Noxious stimulus during fMRI	EM: equal pain, less unpleasantness. During pain: major AI, ACC. Minor baseline activation AI, ACC, amygdala	Lutz A. <i>et al.</i> , 2013.
Buddhist Western	Cross sectional / Case-control study	Healthy	M: 18 / C: 26	Dictator Game (DG) and Ultimatum Game (UG) during Skin Conductance Level (SCL)	EM: in DG reduced arousal, distress and SCL. In UG accept more unfair offers	Grecucci <i>et al.</i> , 2015b.
Buddhist Western	Cross sectional / Case-control study	Healthy	M: 26 / C: 40	Ultimatum game during fMRI	EM: in UG accept more unfair offers. Major activation of the posterior insula (interoception) versus anterior insula (emotion reactivity) in controls; major activation in somatosensory and posterior superior temporal cortex	Kirk <i>et al.</i> , 2011.
Zen Western	Cross sectional / Case-control study	Healthy	M: 34 / C: 44	Monetary incentive delay during fMRI	EM during reward anticipation: reduced activation in caudate nucleus, major activation in bilateral posterior insula. During reward receipt: reduced activation in vMPFC	Kirk <i>et al.</i> , 2011.



Buddhist Western	Cross sectional / Case-control study	Healthy	M: 28 / C: 30	Passive conditioning task during fMRI	EM during reward prediction: reduced positive and negative prediction error BOLD in putamen. Major activation in posterior insula	Kirk <i>et al.</i> , 2015.
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## INTEGRATING PSYCHOLOGICAL, CLINICAL AND NEUROSCIENCE EVIDENCE ON EMOTION REGULATION IN MINDFULNESS RESEARCH

The field of contemplative science, the scientific study of the effects of mindfulness, and contemplative practices in mental health and biological functions, is fairly new but growing quickly. In this article we have focused exclusively on the relationship between mindfulness practices, using diverse empirical models (dispositional mindfulness, mindfulness inductions, MBIs, and EMs), and emotion regulation functions from psychological and neurobiological perspectives. A range of MBIs have demonstrated utility in several clinical conditions (see Table 1), targeting a myriad of emotion dysregulation symptoms (Gotink *et al.*, 2015).

With the aim of understanding mechanisms underlying mindfulness health benefits, authors have proposed several psychological and neurocognitive models (see Table 2) that cover attention, emotion, and self-awareness systems as target mechanisms (Tang *et al.*, 2015). Here we focused particularly on emotion regulation mechanisms targeted by mindfulness meditation, reviewing different studies using psychological and neuroimaging measurements, ranging from correlational to randomized longitudinal designs.

In the field of mindfulness and emotion regulation, one main claim is that mindfulness might elicit a particular type of emotion regulation strategy often called “mindful emotion regulation” that relies on bottom-up mechanisms, in contrast to cognitive reappraisal, which relies on a top-down mechanism. Although there is no single definition, mindful emotion regulation is conceived as a unique emotion regulation strategy, that results from encountering diverse emotional states from a mindful mental state, which includes awareness and acceptance (Chambers *et al.*, 2009; Farb and Segal, 2012; Chiesa *et al.*, 2013; Grecucci *et al.*, 2015a). In particular, it is stated that bottom-up emotion regulation strategies (like those implied in mindfulness) don’t require PFC and top-down mechanisms (Chambers *et al.*, 2009; Farb and Segal, 2012; Chiesa *et al.*, 2013; Grecucci *et al.*, 2015a). In terms of neurobiological emotion regulation systems, these strategies

might rely on modification of implicit emotion regulation and emotion generation systems, but not on changes in the explicit emotion regulation system. In this section, in accordance with the reviewed studies, we will assess whether this claim and its assumptions are met.

Studies measuring structural brain changes in EMs highlight changes in the MPFC and diverse subcortical regions, including regions devoted to meta-awareness, memory consolidation, extero-interoception, and emotion regulation (Fox et al., 2014), with no exact matching to bottom-up systems, but with no involvement of typical LPFC. Longitudinal studies with MBIs have also implicated regions typically involved in the same functions described above (like the AI and amygdala), but no changes in the MPFC and LPFC have been found, regions known for top-down emotion regulation. Strikingly, only AI and brainstem regions overlap between EM and MBIs studies, suggesting neuroplasticity in key areas for emotion generation, interoception, mood, and viscerosomatic processing. As mentioned, no inference about causality (in EM studies), nor about brain functions, can be derived from these studies.

Studies measuring dispositional mindfulness have found negative correlations with negative affect and positive correlations with positive affect traits; factorial analysis has pointed out the distinct and interrelated nature of mindfulness and emotion regulation as constructs. Mental health outcomes of mindfulness might be mediated by emotion regulation capacities (Coffey et al., 2010). Similarly, dispositional mindfulness has been linked to a higher right PFC, minor amygdala activation and changes in rs-fMRI in regions from all the emotion regulation systems (see Table 4). These studies provide evidence of top-down regulation mechanisms. As stated early, several limitations preclude an unequivocal interpretation of these findings in the context of mindfulness and emotion regulation research.

Two studies using mindfulness inductions (mindfulness as emotion regulation strategy) have provided preliminary evidence of direct bottom-up regulation engagement, changing the emotion generation system, with no involvement of the PFC. However, these studies lack an alternative cognitive emotion regulation strategy for contrasting the specificity of the strategy (see Table 4). In addition to the noted methodological limitations, we argue that using a unique mindfulness induction session might be insufficient for eliciting a “mindful emotion regulation”

strategy and the recruitment of the bottom-up brain systems. Secondly, central to this discussion is the question of how mindfulness as an emotion regulation strategy is defined and operationalized. Is it a formal practice, identical or derived from mindfulness meditation? Or is it a particular state, related to the notion of mindfulness as a transient state? We will return to this discussion in the next section.

Longitudinal studies have yielded mixed results regarding the involvement of different emotion regulation systems (top- down vs. bottom-up). Studies with healthy populations using self-experiential focus recruit emotion-generation (AI, sg-ACC) and body-awareness (AI, SSC) systems. Well-designed RCTs with active control groups have mostly (but not exclusively) demonstrated changes in emotion generation (amygdala, AI, ACC) and implicit emotion regulation systems (v-MPFC, OFC), while being effective in regulating negative emotions. Clinical studies with anxiety disorder populations have shown major involvement of explicit emotion regulation systems (see Table 4). It is worth noting that these differences might be due to methodological limitations (e.g., sample size), but also to the specific cognitive demands of the experimental tasks (such as self-reference, regulation of self-beliefs or affect labeling tasks) that by nature require top-down regulation mechanisms. Overall, changes in bottom-up neural mechanisms are in line with the findings of psychological studies of MBIs, in which decreases in emotional cognitive reactivity, and rumination strategies, and increases in mindfulness skills, self-compassion, and meta- awareness emotion regulation strategies, appear to underlie the beneficial effects of MBIs (see Table 3).

Finally, studies with EMs using emotion and pain paradigms have consistently demonstrated changes in bottom-up emotion generation systems (amygdala, AI, sg-ACC), with reported deactivations in, or no involvement of, the PFC. In some studies involving social emotion or reward processing tasks, EMs displayed increased engagement of interoception brain system (mainly PI), modulating emotion generation, and implicit emotion regulation systems of reward-related areas (caudate, putamen, v-MPFC; see Table 4), providing evidence of the engagement of a bottom-up emotion regulation system in EMs.

From the reviewed studies, we argue that there is support for the claim that mindfulness practice changes the bottom-up emotion regulation systems (emotion generation and implicit emotion regulation systems), although this effect diverges

across different empirical models dispositional mindfulness, mindfulness inductions, MBIs and EM studies. In line with Chiesa et al. (2013), studies with EMs show a clearer engagement pattern of bottom-up systems, suggesting that these types of strategies are developed through long-term meditation training. However, intervention studies with a RCT design are better suited for providing evidence about a causal relationship between mindfulness training and bottom-up emotion regulation system changes.

## **The Problem of Mindful Emotion Regulation**

From psychological studies, including theoretical and evidence-based psychological models (Table 3), as well as neuroimaging studies (Table 4), it becomes evident that mindfulness (in MBIs and EMs) also engages and requires top-down emotion regulation. As Lutz et al. stated, mindfulness meditation can be conceived as “a family of complex emotional and attentional regulatory strategies developed for various ends” (Lutz et al., 2008b). From a traditional Buddhist psychology perspective, the development and refinement of attention (attention regulation; Grabovac et al., 2011), and the capacity for monitoring and labeling affective states (Analayo, 2003), are central for achieving the intended effects of mindfulness meditation. From this viewpoint, and taking into account models of different emotion regulation brain systems and different emotion regulation strategies, the notion of “mindful emotion regulation” (Chambers et al., 2009; Farb and Segal, 2012; Chiesa et al., 2013; Grecucci et al., 2015) seems to imply certain problematic aspects.

The notion of “mindful emotion regulation” entails two problematic aspects. The first refers to the nature and definition of the construct “mindful emotion regulation” itself, and the second refers to its brain correlates or engagement/functioning of emotion regulation systems, which we will address separately.

Although we have extensively shown that emotion regulation is (somehow) enhanced by mindfulness practice, we argue that the notion of “mindful emotion regulation” has not been accurately and properly defined. Is “mindful emotion regulation” a psychological trait, stable in time, that diverges across subjects? Or is it a particular mental practice derived from mindfulness? Or is it a mental state, like

a transient moment of mindfulness? Generally, the common view across authors is that “mindful emotion regulation” is a *somehow unique* emotion regulation strategy, the result of encountering diverse emotional states from a mindful mental state, including awareness and acceptance (Chambers et al., 2009; Farb and Segal, 2012; Chiesa et al., 2013; Grecucci et al., 2015). From a first-person perspective, this definition does not make explicit specifications regarding what the practitioner should do while engaging within the emotional state, only succinctly suggesting the gradual development of experiential qualities (attentiveness, acceptance, etc.). What should the focus of attention be (external or internal stimuli)? And, in terms of behavior, what exactly should be done to *perform* the regulation (approach, stop, or hold back)? From a psychological perspective, there is not a clear commitment regarding the unique (or common) involvement of attentional or emotional or body awareness processes. Thus, in line with clinical evidence (Table 3), it is not clear whether “mindful emotion regulation” is properly a unique emotion regulation strategy, with a unique neurocognitive underlying mechanism.

In light of this debate, we argue that “mindful emotion regulation” entails a variety of emotion regulation *processes*, including top-down processes which are cognitively based, involving attention and voluntary cognitive control, conscious monitoring, and explicit regulatory functions; and bottom-up processes, which are affect driven, based on emotion functions that modulates arousal, valence and the encoding of subjective value regarding the triggering stimuli. We argue that “mindful emotion regulation” entails as well a variety of emotion regulation *strategies*, in accordance with the different strategies taught within MBIs and EMs trainings. In this context, we propose a distinction between primarily *top-down* mindfulness-based emotion regulation strategies and *bottom-up* mindfulness-based emotion regulation strategies. Since emotions are multi-componential processes (Thompson, 1990), and like Gross’s classification of emotion regulation strategies, our distinction is based on the primary component of the *emotional response* that is targeted and drive the regulation of the emotional state (Koole, 2009).

Top-down mindfulness-based emotion regulation strategies correspond to affect labeling, mindful detachment, dereification, meta-awareness, and cognitive reappraisal, among others, for which *cognitions* and *thought process* are the primary targets of the strategy. Within this group we can find impulses control and



emotion dysregulation managing strategies, like those delivered in MBIs (like in DBT and ACT) in which subjects use intentional efforts to increase their attention and awareness capacities for better regulation and control of emotions (Linehan, 1993; Hayes et al., 1999). In this group, dereification and meta-awareness would correspond to more sophisticated strategies, since they involve the development of insight into the nature of the thought process itself (e.g., see thoughts not as facts; Dahl et al., 2015). Using the *process model* of emotion regulation by Gross, we can understand that increases of mindfulness can indeed modulate any of the five stages: selecting or modifying a situation, deployment of attention, changing cognition (cognitive reappraisal), modulating the experience, and behavior, or physiological response (Gross, 2001). This distinction is in line with findings in MBIs (Table 4), and by Chiesa et al. (2013), and is consistent with the claim that novel practitioners in MBIs use primarily top-down emotion regulation strategies.

In bottom-up mindfulness-based emotion regulation strategies, *sensory-perception* and *interoceptive-proprioception* are the primary aspects of the emotional response targeted by the strategies. The bottom-up strategies are characterized by the intentional stance to directly feel (instead of think) or to experience, thus targeting primarily the *feeling* processes (sensory-perception and interoceptive-proprioception). Bottom-up mindfulness-based emotion regulation strategies include concrete experiential explorations that focus for example on unimodal body sensations, like feeling the temperature of the skin, or exteroceptive sensations, feeling the peri-personal space around, to interoceptive sensations, like feeling the internal sensations of the body. Other strategies focus on the broad multi-modal sensory perception of the body, in which interoceptive, exteroceptive sensations, and basic sensory (auditory and visual) perceptions are used as *a whole* as the main focus of intentional experiential explorations (Kabat-Zinn, 2005).

From the above, the bottom-up mindfulness-based emotion regulation strategies range from the titrated exposure to negative sensations (e.g., physical pain), to different body and perception modalities conscious explorations, to the exposure to the complete range of negative and positive emotions without holding or avoiding/rejecting, which are thought within MBIs and EMs trainings. In sum, there is an explicit intention of experiential exploration of bodily sensations (e.g., the *felt sense*) underlying *all* type of emotion and mental content (Hölzel et al., 2011a). For example in the MBCT program, participants are instructed to use the

“opening the door of the body” strategy, which invites to be aware of the body sensations that accompany any intense emotions, stepping back from cognitive analysis and rumination and thus cultivating “intimacy” with the raw and usually rejected experience of emotions (Segal et al., 2002). As we have argued, these strategies are primarily the result of changes in bottom-up emotion regulation systems (e.g., exposure to painful feelings), and can be present in mindfulness inductions, MBIs and EMs.

We further noted that studies applying cognitive reappraisal to emotions generated via bottom-up stimulation can result in a paradoxical increase in amygdala reactivity (Herwig et al., 2010; McRae et al., 2012), which in turn can be related to ruminative or repetitive negative thinking as maladaptive cognitive emotion regulation strategies (see Table 3), characteristic of anxiety and depression disorders (Aldao et al., 2010). Dysfunctional top-down emotion regulation in psychiatric conditions such as MDD (Johnstone et al., 2007) might be related to dysfunctional forms of self-evaluative processes such as rumination and worry (Farb and Segal, 2012). In this sense, emotions can be generated from top-down and bottom-up systems (Ochsner et al., 2009; McRae et al., 2012), and the way/pathway emotions are generated seems to play a crucial role in the successfulness of emotion regulation strategies. Bottom-up-generated emotional states, as pain and reward in EM studies reveal, might be best targeted by bottom-up mindfulness emotion regulation strategies (see Table 4).

## **Embodied Emotions and Emotion Regulation**

Classical theories of emotions from Aristoteles, Spinoza, and Hume have highlighted the importance of the body and physiological aspects of emotions, conceiving them essentially as psychosomatics states (Colombetti and Thompson, 2008). Post Jamesian contemporary authors like Damasio and Prinz assert that emotions are basically the perception of the actual physiological condition, affirming in a broad sense the embodied nature of emotions (Damasio, 1999; Prinz, 2004). As Colombetti et al. noted, cognitivist theories of emotions have neglected the role of the body in the generation of emotional states (Colombetti and Thompson, 2008), and as we argue, as well in the regulation of emotional states.

In this context, one of the problematic aspects of Gross’s “process model” of

emotion regulation is the assumption of a linear fixed sequence through which emotions are generated, starting from attention to relevant external stimuli, cognitive appraisals, to emotional responses and behaviors as secondarily generated (Koole, 2009). Nevertheless, relevant stimuli can trigger emotions without cognitive reappraisal (e.g., Neumann et al., 2003) and emotions can be generated from the bottom-up systems (Ochsner et al., 2009; McRae et al., 2012). Using magneto-encephalography Rudrauf et al. showed that emotional stimuli elicited early brain activation in the visual cortex, spreading through the ventral visual stream, temporopolar regions, to OFC/vMPFC, ACC, and SSC. This early activation was correlated to arousal ratings and heart beats changes (Rudrauf et al., 2009). Also, it is known that bodily movements can actively influence emotions (Strack et al., 1988; Niedenthal et al., 2005), the manipulation of body posture can alter the regulation of mood (Veenstra et al., 2016), and intentional movement can regulate emotional states (Shafir et al., 2013). From this, even more relevant is the fact that *previous* emotional states can strongly influence cognitions and attention processes (Okon-Singer et al., 2015), which then will drive the emotion regulation process. We argue that this model is fairly reductionist (neurocentric), since it denies the constitutive interwoven nature of body and brain and that their widely known continuous bi-directional interactions are essential for adaptive behavior (Chiel and Beer, 1997).

We argue that the cognitivist “neurocentric” model also disregard the complex reciprocal influences between cortical (high-order) and subcortical (low-order) regions (Okon-Singer et al., 2015). This “cortico-centric” model of the brain, in which “high”-order regions dominate “low”-order regions (Parvizi, 2009), fits very well with the “process model” of emotion regulation, in which only the cortical top-down emotion regulation system has a privileged role for regulating emotional states. As we have shown in this article, bottom-up (mindfulness- based) emotion regulation strategies modulate *sensory-perception* and *interoceptive-proprioception* components of the emotional state, due to changes in bottom-up emotion regulation systems. These subcortical systems are central in the homeostatic regulation of neuro-vegetative and visceral functions which provide the *bodily* aspect of emotion experience (Bechara et al., 2000; Critchley et al., 2002).

The enactive approach to mind-brain considers cognition, emotion, and body

functions as parts of an integrated system at neurobiological, psychological, and phenomenological domains (Thompson and Stapleton, 2009). One of its central principles is the notion of embodiment, or embodied cognition, which in simple terms claims that the whole body (not only the brain) is involved in building up cognition (Varela et al., 1991; Kiverstein, 2012), and in this particular case the experience of emotions (Colombetti and Thompson, 2008; Slaby et al., 2013; Colombetti, 2014). From this perspective, the emotional or affective dimension is connatural and constitutive of organism's adaptation and agency in the world. Organisms have to be "sensible" to their environment in order to *make sense* and *adaptively respond* to new demands, in this account emotions are inseparable from cognitions (Colombetti, 2014). Central for the affective constitution of organisms, three interrelated activities characterize the embedded body-brain system: the capacity of *self-regulation* of internal states, *sensorimotor coupling* with the environment and *intersubjective interaction* with other agents (Thompson and Varela, 2001).

In this context, we argue that emotions are the *ensuing* and *guiding* state of the organism engagement with the environment (world), in which the regulation of its own internal homeostatic states (humoral, visceral, somatic-motor) is inseparable from the emotional state itself (that is targeted with the regulation). As an example, we cannot think that body temperature (the target of the regulation) is something separate and distinct from the homeostatic mechanisms that continuously regulate body functions to keep the temperature constant (regulation mechanism). In fact, the actual body temperature emerges as the result of the reciprocal interactions of diverse regulatory mechanisms. Derived from this, we propose a preliminary account of emotion regulation as an embodied process, basically rejecting the dualism between emotional states (and its somatic expressions, motor and autonomic systems), and the processes and mechanisms of emotion regulation. Emotions and its experience are the result of the continuous reciprocal interactions of top-down, bottom-up, sensory-perception and interoception processes, in which top-down and bottom-up systems can serve as generative and regulatory mechanisms. As we have reviewed in this paper, both emotion systems participate in the generation and expression of emotional states (Ochsner et al., 2009; McRae et al., 2012), at the same time, both are engaged in the regulation of internal homeostatic states (humoral, visceral) and expressive somatic-motor responses (Frank et al., 2014; Kohn et al., 2014; Etkin et al., 2015).

The embodied approach to emotion regulation regarding the problem of “mindful emotion regulation” allows us to conceive top-down and bottom-up mindfulness based strategies in a dimensional and continuous way. These strategies primarily target different aspects of the emotional state, *cognitions* and *thought process*, *sensory-perception*, and *interoceptive- proprioception*, and their corresponding neural substrates, in this way, at the same time regulating and *ensuing* the current emotional state. From this, it is possible to understand that even mindfulness induction and MBIs can deploy bottom-up regulation strategies, and also EMs can use top-down emotion regulation strategies as part of their repertoire. At the same time, different mindfulness related practices (as samatha, vipashyana and compassion, etc.), as taught within MBIs and EMs trainings might differentially engage the components of the emotional state (Dahl et al., 2015).

In sum, our approach to emotions and emotion regulation intends to overcome the “neurocentrism” and “corticocentrism” of current cognitivist model of emotion regulation. Our embodied account of emotion regulation considers emotional states and regulatory mechanisms as *inseparable*, relying in shared neural networks. It offers a preliminary new framework for integrating neurobiological, psychophysiological, and psychological systems perspectives on emotion regulation and clinical interventions. It aims to be a multilevel and non-reductive paradigm to advance the understanding of emotion dysregulation psychopathologies and their changes in the context of various biological and psychological treatments.

## **CLINICAL IMPLICATIONS: EMOTION REGULATION, MINDFULNESS, AND PSYCHOTHERAPY**

As we have seen, MBIs have shown efficacy in a myriad of psychological disorders, characterized by emotion dysregulation psychopathology (see Table 1). From the perspective of longitudinal, clinical, and affective neuroscience studies, we hypothesize that changes in bottom-up emotion regulation systems might be a key differential feature of MBIs vs. the usual Western psychotherapeutic approaches—more specifically, not in the sense that only MBIs elicit changes in these systems (which is not the case), but in the sense that MBIs explicitly involve the engagement of bottom-up mindfulness emotion regulation strategies, using the *sensory* and *interoceptive* components of emotions as targets and *vehicles* for emotion regulation (according to embodied emotion regulation account).

From a clinical psychotherapeutic perspective, this means that the therapist (or MBI instructor) will be able to guide the patient/client into the application of different top-down and bottom-up mindfulness based strategies. In the case of bottom-up strategies, the clinician encourages the participants to focus on the “bodily” components of different emotional state, always conveying the attitudinal stance of acceptance and openness. In this way, discouraging the intend to control and subjugate negative emotional states, but more importantly, discouraging the use of maladaptive top-down emotion regulation strategies like *avoidance*, *rumination*, and *suppression* among others.

In this sense, there is a constant incentive to shift from a *self-narrative* perspective (ruminative), based on past or future stories, to a *self-experiential* present-centered perspective, so the experience of emotion is decoupled from maladaptive evaluative cognitions. As stated by Chambers, one main difference between psychotherapeutic interventions like psychoanalysis and CBT, and MBIs, is that the former aim to change the content of emotional states (*self-narratives* and cognitions), while MBIs focus on changing the relationship (and not the content) with the emotional (painful) states (Chambers et al., 2009); changing the perspective from which it is experienced, encouraging acceptance and curiosity about the experience itself (*self-experiential focus*). From an emotional learning perspective, this process can be seen as an exercise of *exposure* (to certain emotions or experiences), *extinction* of maladaptive cognitions or reactive responses, and *reconsolidation* as a new relationship pattern regarding own experiences or daily life problems (Hölzel et al., 2011a).

## **Mindfulness and Mentalization in the Context of Psychotherapy**

Mindfulness and mentalization can be conceived as different heuristics and approaches to understand mental health, clinical interventions, and psychopathological developments. The notion of mentalization has a heterogeneous origin, starting from the construct of *theory of mind* developed in the field of etiology/cognitive science (Premack and Woodruff, 1978), the concept of *symbolization* from psychoanalysis (Choi-Kain and Gunderson, 2008) and the notion of *meta-cognition* from novel developments in the empirical study of attachment (Main, 1991). In clinical terms mentalization is defined as the capacity to understand one’s own actions and those of others in terms of intentional



mental states like desires, needs, and feelings (Choi-Kain and Gunderson, 2008). According to psychodynamic theories, mentalization is a developmental capacity that depends on the quality of the early mother–infant relationship, the development of secure attachment in the infant and a mother’s capacities for mentalization (Fonagy et al., 2002). Originally developed to understand BPD psychopathology, actually its deficit has been implicated in a wide range of conditions including autism and schizophrenia, among others (Roffman et al., 2012). Enhancing mentalization is viewed as a common factor responsible for psychotherapeutic change processes, not only in psychodynamic approaches, but also in other clinical perspectives (Björgvinsson and Hart, 2006 for CBT; Lewis, 2006 for DBT). Moreover, in patients with BPD, increased capacity for mentalization is considered the central mechanism of change in all effective treatments (Fonagy and Bateman, 2006).

Exploring the common ground between mindfulness and mentalization, Goodman (2014) uses four aspects of mentalization: (1) observing mental phenomena, (2) describing or labeling mental phenomena, (3) describing the meaning and motivation of one’s own and others’ behavior as the product of mental states, and (4) understanding the intrinsic linkage and mutual influence of mental states in oneself and others. Taking into account Baer et al.’s models (see Table 2), Goodman suggests that mentalization and mindfulness overlap in two key areas: observing mental phenomena, and labeling/describing mental phenomena. From the perspective of emotion regulation systems, both mental processes correspond to top-down emotion regulation strategies, such as metacognitive awareness and affect labeling. However, the capacity for attributing intentionality to mental states and for understanding the interpersonal influences of mental states, are distinctive factors of mentalization (Goodman, 2014). Given the interpersonal nature of psychotherapy, mentalization capacities constitute central skills for the therapist (to work with patients) and for the patients (to be developed within the treatment; Fonagy and Bateman, 2006). Another important difference between mindfulness and mentalization, is the type of relationship intended with mental contents and temporality of life events. As we stated, MBIs don’t intend to change mental contents, neither explore life events from the past or future possibilities, its main focus is the present- centered non-evaluative awareness of the self-experience. Unlike mentalization interventions, in which the focus is to explore, cognitively understand and change mental contents, which may be referred to future or past

life events, but also to emotions and dysregulated emotional states (Allen, 2006). In line with this, mentalization as an emotion regulation strategy has been considered a top-down strategy, relying in the explicit emotion regulation and in the theory of mind brain systems (Fonagy and Luyten, 2009; Vrticka and Vuilleumier, 2012). As we have stated, MBIs engages bottom-up emotion regulation strategies, which constitutes the distinctive ingredient from other forms of psychotherapies. From our perspective, mindfulness and mentalization have common and different psychobiological functions, which are complementary in the context of treatments for diverse psychopathologies related to emotion dysregulation and mentalization deficits. Nevertheless, further research needs to be done with a view to achieving a better understanding of the biological and psychological differences between these constructs, as well as integrating them properly in psychotherapeutic treatments.

## **CONCLUSIONS AND FUTURE DIRECTIONS**

Over the last few years, research on contemplative and affective sciences has grown considerably. In this article we have shown how mindfulness is related to emotion regulation using different theoretically and empirically derived models. The main hypothesis explored is that emotion regulation changes are a core mechanism underlying the salutary effects of mindfulness and MBIs. Nevertheless, many of the psychological and neurocognitive theoretical models of mindfulness's mechanisms are not properly and empirically validated. At the same time, empirical studies face many methodological limitations as well.

One important problem is the notion of mindfulness itself. As was mentioned, it has been used for referring to a wide range of psychological phenomena, like a trait (or dispositional mindfulness), a proper meditation practice or a mental state (Davidson, 2010). Even the concept of mindfulness lacks a unique operationalization, since many authors have proposed different definitions, understanding it as an attention capacity, an attitude, a characteristic type of awareness, or even a combination of these (Quaglia et al., 2015). As Grossman states, the complexity of the concept seems more related to a lack of consensus between experts, among other critical issues that constructors of inventories might disregard (Grossman, 2008).



On one side, studies measuring dispositional mindfulness using self-report scales have demonstrated good reliability and convergent validity (Quaglia et al., 2015) and a preliminary coherent putative neural correlate (see Table 4). Coffey et al. have demonstrated that mindfulness and emotion regulation correspond to related but different constructs (Coffey et al., 2010). Nevertheless, the construct of dispositional mindfulness entails several problematic aspects, starting from the assumption that self-report mindfulness scales (basically the self-perception of a person) actually tap into the proper practices of mindfulness (Grossman, 2011). For instance, the specificity of the instruments to MBIs is unknown, e.g., other interventions not based on mindfulness might change the mindfulness level (Lutz et al., 2015). Finally, using these instruments in the context of MBIs might induce biased responses because of the verbal exposure to the word and concept of mindfulness itself, and not because of any actual acquired capacity (Van Dam et al., 2012). Another problematic issue with dispositional mindfulness is the wide range of confounders or variables that actually impact the dispositional “mindfulness level,” including other overlapping and related psychological traits that also vary within normative and clinical populations, like: attention and emotional functions, attitudinal and biased dispositions, prior socialization with the construct and experience with related practices (like yoga or psychotherapy; Quaglia et al., 2015). Future studies will have to control for these factors to better disentangle the nature of dispositional mindfulness as a construct itself.

For longitudinal clinical studies, RCTs with active control groups and multi-arm designs seems to be methodologically the “gold standard” for unraveling the efficacy and effectiveness of a given therapeutic intervention, either for inferiority or superiority studies. As in Zeidan et al. (2015), comparing mindfulness, sham mindfulness, placebo, and control could demonstrate the efficacy of all interventions for pain relief, but noting a differential brain mechanism in emotion regulation of pain (Zeidan et al., 2015). For further understanding the differential engagement of the emotion regulation systems in MBIs, future neuroimaging longitudinal studies will have to explicitly compare different mindfulness instructions within the experimental manipulations (i.e., top-down—attention based vs. bottom-up bodily-based). Then they can explore the acquisition and development of the strategies and their neural correlates. For avoiding problematic aspects of self-report scales, clinical studies should try to include behavioral outcome measures of mindfulness. For better understanding putative mechanisms,

longitudinal studies should use several prospective measurements of variables of interest to better disentangle how changes in independent variables and mediators affect dependent variables (Kazdin, 2009).

Using neurobiologically based emotion regulation systems as a framework, we have described how top-down strategies (explicit emotion regulation system) and bottom-up strategies (emotion generation and implicit emotion-regulation systems) can be present within novice and expert meditators. In order to deal with the controversy of emotion regulation mechanisms underlying mindfulness in MBIs and EMs, we have proposed the distinction between mindfulness-based top-down emotion regulation strategies based on attention and acceptance, vs. mindfulness-based bottom-up strategies, which target bodily representations of emotional states. We proposed an *embodied* perspective on emotion regulation as a preliminary framework as a means for understanding different emotion regulation systems, rejecting the dualism between *somatic* emotional states and the processes and mechanisms of emotion regulation. From this, the experience of emotional states is build up from the continuous reciprocal interactions of regulatory mechanisms. This perspective offers an integrative view of cognitive and emotion processes within homeostatic regulatory mechanisms, as well as a non-hierarchical view for conceiving cortical and subcortical systems, as well as brain and body interactions. Further developments might complement this framework integrating first-person phenomenological accounts of emotions and emotion regulation, looking for further integrate experiential and subjective reports with psychophysiological and neurobiological measurements (see Colombetti, 2014, for affective neuro-physiophenomenology).

In line with these recommendations and limitations, from the perspective of methodological and measurement techniques, we suggest that research on mindfulness and emotion regulation should take advantage of mobile device technologies, for example using experience sampling methods, or biological measurements including mobile EEGs or galvanic response devices, thereby increasing the ecological validity of measurements, variables and constructs of interest. Serum biological markers of inflammatory response and neuroplasticity (BDNF, for example) are also of relevance as putative biological mechanisms of MBIs. As regards neuroimaging technologies, future studies might integrate different methods, taking advantage of the specificity of each, for example

combining the spatial resolution of MRIs with positron emission tomography (PET), which might help to disentangle differences in neurotransmitters or neuro-radiological markers of neuro-inflammation. Within MRI techniques, the use of computational modeling might help to build and test more precise and sophisticated theoretical models for understanding cognitive emotional systems underlying mindfulness and emotion regulation. Finally, multivariate pattern analysis is situated at a privileged level for decoding mental states (certain emotion regulation strategies or mindfulness states) from brain signatures using trained classifiers.

Clinical applications of MBIs will require a very good understanding of what's better for whom, and distinguishing what types of psychological treatments, regular psychotherapy (of different types) or MBIs (of different types) are better for different types of depression or anxiety disorder. This leads to another question regarding how to combine different forms of psychotherapy with MBIs in the context of a wider and more comprehensive model of healthcare, even including psychopharmacological treatments. A better understanding of emotion regulation mechanisms underlying mindfulness and psychotherapy, from biological and clinical perspectives, will foster new insights into emotional life and its disturbances, with the purpose of refining and developing better therapeutic interventions for the widespread mental health disorders characterized by emotion dysregulation.

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## **Self-compassion mediates the relationship between mindfulness and borderline personality disorder symptoms**

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Individuals suffering from borderline personality disorder (BPD) experience difficulties with mindfulness. How mindfulness influences BPD symptoms, however, is still unknown. We hypothesized that the relationship between mindfulness and BPD symptoms would be mediated by self-compassion. In study 1, we recruited 29 individuals with BPD and 30 group matched healthy controls. In study 2, we complemented our results with findings from a larger, nonclinical sample of 89 participants that were recruited during an open-house event at the local university. All participants completed questionnaires assessing self-compassion, mindfulness, BPD symptom severity, and emotion dysregulation. In both studies, self-compassion mediated the relationship between mindfulness and BPD symptom severity as well as between mindfulness and emotion dysregulation. Self-compassion seems to be one psychological process that could explain the relationship between mindfulness and BPD symptoms. One promising approach in therapy could be to target self-compassion more directly during mindfulness trainings and interventions.

Borderline personality disorder (BPD) is a complex, severe mental illness characterized by pervasive patterns of instability in emotion regulation, impulse control, interpersonal relationships, and self-image (Leichsenring, Leibing, Kruse, New, & Leweke, 2011; Lieb, Zanarini, Schmahl, Linehan, & Bohus, 2004; Skodol et al., 2002). Recent studies showed that BPD symptom severity was associated with self-reported difficulties in mindfulness (Baer, Smith, & Allen, 2004; Scheibner, Spengler, Kanske, Roepke, & Bermpohl, 2016; Wupperman, Neumann, & Axelrod, 2008). Mindfulness is a concept derived from Buddhist tradition and has been defined in modern Western psychology as nonjudgmental attention to and awareness of the present moment (Kabat-Zinn, 1994). Mindfulness stands in contrast to several key symptoms of individuals with BPD, for example, their difficulty to pay attention to and be aware of their own feelings and emotions

(Bijttebier & Vertommen, 1999; Leible & Snell, 2004; Levine, Marziali, & Hood, 1997; Yen, Zlotnik, & Costello, 2002). Consequently, mindfulness exercises are a central mean in the treatment of BPD (Miller, Wyman, Huppert, Glassman, & Rathus, 2000; Stepp, Epler, Jahng, & Trull, 2008), especially in Dialectical Behavioral Therapy (DBT; Linehan, 1993). Some first evidence suggests that mindfulness exercises improve BPD symptoms, in particular emotion regulation (Perroud, Nicastro, Jermann, & Huguelet, 2012; Sauer & Baer, 2012). However, the psychological processes through which mindfulness is associated with reduced BPD symptoms are still largely unknown. Here, we argue that the relationship between mindfulness and BPD symptoms is mediated by self-compassion.

Self-compassion is defined as an attitude of kindness toward oneself in face of crisis, that acknowledges one's own emotions without overly identifying with them and sees imperfection as part of being human (Neff, 2003a). Self-compassion consistently displayed positive relationships with psychological well-being and negative relationships with psychopathology in past research (MacBeth & Gumley, 2012; Zessin, Dickhäuser, & Garbade, 2015). In Buddhist tradition, mindfulness has beneficial effects only if it improves some form of acceptance and compassion (Gilpin, 2008; Rosch, 2007; Salzberg, 2003). Similarly, in Western psychology, self-compassion has been conceptualized as an outcome of mindfulness practice (e.g., Bishop et al., 2004; Brown, Ryan, & Creswell, 2007). A state of mindful awareness when suffering allows oneself to acknowledge one's pain in the first place without judgment. Then, feelings of self-kindness and common humanity can arise to actively soothe the self (Neff & Dahm, 2015). These views are supported by studies showing that increases in mindfulness predict increases in self-compassion (Birnie, Speca, & Carlson, 2010; Shapiro, Brown, & Biegel, 2007). Further, in a longitudinal study with non-clinical samples, mindfulness precipitated self-compassion, but not vice versa (Bergen-Cico & Cheon, 2014). Moreover, a growing number of studies on the effects of mindfulness-based training programs demonstrated increases in self-compassion (Bergen-Cico & Cheon, 2014; Birnie et al., 2010; Rimes & Wingrove, 2012; Robins, Keng, Ekblad, & Brantley, 2012; Shapiro, Astin, Bishop, & Cordova, 2005). Further studies showed that mindfulness-induced changes in self-compassion mediated decreases in stress (Shapiro et al., 2007), depressive symptoms (Kuyken et al., 2010), worry, and fear of emotion (Keng, Smoski, Robins, Ekblad, & Brantley, 2012), as well as increases in well-being (Baer, Lykins, & Peters, 2012). In their review on mechanisms of mindfulness meditation, Hölzel et al. (2011) argue

that self-compassion works as an emotion regulation strategy, as it teaches how to cope in instances of pain and suffering. At the same time, individuals with BPD commonly experience severe self-criticism and difficulties in emotion regulation, contrary to mindful and self-compassionate attitudes, that likely lead to anger and self-harm (Krawitz, 2012; Linehan, 1993; Warren, 2015). In sum, self-compassion has been proposed to mediate the relationship between mindfulness and well-being, and seems to target symptoms central to BPD.

To the best of our knowledge, no study to date has examined the role of self-compassion in the relationship between mindfulness and BPD symptoms in samples of individuals with BPD as well as healthy controls. Preliminary evidence stems from a study by Perroud et al. (2012) that assessed BPD patients' mindfulness skills during and after DBT therapy. Patients only significantly improved on one of four discrete mindfulness dimensions: acceptance without judgment. Acceptance without judgment in turn predicted treatment success. These results suggest that a kind, accepting attitude similar to self-compassion had a major impact on the treatment success of BPD. Further preliminary support of an inverse relationship between BPD and self-compassion stems from a study which investigated mindfulness, self-compassion, and BPD in a nonclinical sample (Rivera, 2013). Not only were self-compassion deficits related to increased BPD symptoms, but self-compassion also fully accounted for the relationship between mindfulness and BPD symptom characteristics. However, as the researchers in the above mentioned studies either did not assess self-compassion directly (Perroud et al., 2012) or did not compare its effects between clinical and nonclinical samples (Rivera, 2013), further evidence is needed.

We here argue that self-compassion explains the relationship between mindfulness and BPD, because self-compassion is a result of mindfulness training and helps individuals with BPD to build a kind attitude towards their emotions and towards themselves. We tested a model in which mindfulness predicts BPD symptoms, and this relationship is mediated through self-compassion. This model was based on previous literature that demonstrated beneficial effects of mindfulness on BPD symptoms (Perroud et al., 2012; Sauer & Baer, 2012), and the mediating role of self-compassion in mindfulness training (Baer et al., 2012; Keng et al., 2012; Kuyken et al., 2010; Shapiro et al., 2007). Since our study was cross-sectional, we cannot draw conclusions about the directionality of the relationship between



mindfulness and BPD, and BPD symptoms could equally predict mindfulness, mediated through self-compassion. In study 1 we collected data from a BPD patient group and a healthy control group. In study 2 we aimed to complement our results with findings from a larger, more heterogeneous sample of participants from the general population. Based on previous research with these variables in patients with BPD (Feliu-Soler et al., 2017) or healthy controls (Rivera, 2013), we included a sample of healthy participants to investigate whether the relationship between self-compassion, mindfulness, and emotion regulation holds true at different (i.e., healthy, subclinical, and clinical) levels of emotional distress. For this purpose, we operationalized BPD as a continuous measure (Widiger, 1992). General severity of present BPD symptoms as measured by the Borderline Symptom List (BSL-23; Bohus et al., 2009) and current levels of emotion dysregulation as measured by the Difficulties in Emotion Regulation Scale (DERS; Gratz & Roemer, 2004) were assessed as indicators of BPD symptoms. We also chose emotion dysregulation as an indicator of BPD in line with Linehan's biosocial theory of BPD, which postulates emotion dysregulation to be the core symptom of this disorder (Linehan, 1993; Linehan, Bohus, & Lynch, 2007).

The hypotheses were as follows:

*Hypothesis 1:* In individuals with BPD and a healthy control group, self-compassion mediates the effect of mindfulness on BPD symptom severity (model 1) and emotion dysregulation (model 2).

*Hypothesis 2:* In a representative sample from the general population, self-compassion mediates the effect of mindfulness on BPD symptom severity (model 1) and emotion dysregulation (model 2).

### **Study 1: self-compassion as a mediator in individuals with BPD and healthy controls**

#### **Method**

Study 1 was embedded in a larger behavioral study (Scheibner et al., 2016) that aimed at identifying mindfulness deficits in BPD using a behavioral task. The study design was reviewed by the local ethical committee and the investigation was carried out in accordance with the latest version of the declaration of Helsinki. Informed

consent of the participants was obtained prior to participation and after the nature of the procedures had been fully explained.

### *Participants*

Twenty-nine individuals with BPD and 30 healthy controls participated in the current study. Group membership was established using the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (First, Gibbon, Spitzer, Williams, & Benjamin, 1997; Wittchen, Zaudig, & Fydrich, 1997) module for BPD. Participants were screened for comorbidity using the Structured Clinical Interview for DSM-IV Axis I and II (First, Gibbon et al., 1997; First, Spitzer, Gibbon, & Williams, 1997; Wittchen et al., 1997) and the Mini-International Neuropsychiatric Interview (Ackenheil, Stotz, Dietz- Bauer, & Vossen, 1999; Sheehan & Lecrubier, 1998). Three trained clinical psychologists administered all clinical interviews. To ensure reliability of the diagnosis, two psychologists were present during the diagnostic interview and afterwards compared their diagnosis.

Participants in the group of individuals with BPD had to meet five or more criteria for BPD. To prevent confounding effects of psychiatric comorbidity, psychotic symptoms and diagnosis of bipolar disorder were exclusion criteria. Further exclusion criteria for this group were current high suicidal tendency, organic brain damage, and very low intellectual ability ( $IQ < 70$ ). One BPD patient was excluded from the data analysis because the patient did not adhere to the instructions given in the questionnaires ( $n = 1$ ). The remaining 28 individuals with BPD (23 females, 82.1%) ranged in age from 23 to 59 years with a mean age of 35.82 years ( $SD = 9.65$ ). The majority of individuals with BPD (53.6%) had acquired a general certificate of secondary education (German *Abitur*). Ten participants with BPD reported that they were taking antidepressant medication ( $n = 4$  SSRI,  $n = 2$  SSNRI, and  $n = 4$  not specified), one quetiapine, and one pregabalin. One participant occasionally used promethazine and two hypnotic medications; those on-demand medications were not taken during the last 24 hours prior to testing.

Participants in the group of healthy controls had no current mental or personality disorder and no history of depression or post-traumatic stress disorder. This group consisted of 30 participants who were recruited by on- line advertisement and group-matched for sex (22 females, 73.3%), age ( $M = 34.43$ ,  $SD = 12.08$ ), and highest level of scholarly education (53.3% of the healthy controls had *Abitur*) with



the respective characteristics of the individuals with BPD. Individuals with BPD and healthy controls did not differ significantly on sex ratio, age, or education level (see Table 1). Participants in both groups reported little to no previous history with mindfulness training or meditation, and individuals with BPD reported little to no experience with DBT.

**Table 1.** Sample Characteristics (Study 1 and Study 2)

	BPD ( <i>n</i> = 28)	HC 1 ( <i>n</i> = 30)	HC 2 ( <i>n</i> = 86)
Sex: female (% [ <i>n</i> ]) <sup>a</sup>	82.1 (23)▲	73.3 (22)	40.7 (35)▲
Age (years): <i>M</i> ( <i>SD</i> ) <sup>a</sup>	35.82 (9.65)	34.43 (12.08)	32.71 (12.58)
Education (German, % [ <i>n</i> ]) <sup>a</sup>			
Hauptschulabschluss	7.1 (2)▲	3.3 (1)	1.2 (1)▲
Mittlere Reife	28.6 (8)▲	30.0 (9)	1.2 (1)▲
Fachhochschulreife	10.7 (3)▲	13.3 (4)	20.9 (18)▲
Abitur	53.6 (15)▲	53.3 (16)	75.6 (65)▲
Number of BPD criteria: <i>Mdn</i> ( <i>R</i> )	7.00 (4.00)	0.00 (3.00)	NA
Self-compassion: <i>M</i> ( <i>SD</i> )	11.34 (3.80) ▲	20.87 (3.48)	19.03 (4.47)▲
Reliability	.91	.90	.93
Mindfulness: <i>M</i> ( <i>SD</i> )	1.73 (0.39) ▲	2.76 (0.42)	2.67 (0.43)▲
Reliability	.77	.82	.79
BPD symptom severity: <i>Mdn</i> ( <i>R</i> ) <sup>b</sup>	2.02 (2.87) ▲	0.11 (0.65)	0.43 (3.00)▲
Reliability	.91	.65	.88
Emotion dysregulation: <i>M</i> ( <i>SD</i> )	3.64 (0.59) ▲	2.11 (0.51)	2.33 (0.65)▲
Reliability	.91	.90	.94

*Note.* BPD = group of individuals with BPD; HC 1 = group of healthy controls in study 1; HC 2 = group of healthy controls in study 2; *M* = mean; *SD* = standard deviation; *Mdn* = median; *R* = range; NA = not applicable as variable was not measured in respective group. Reliability values correspond to Cronbach's  $\alpha$ . <sup>a</sup>Group differences were tested two-sidedly; <sup>b</sup>Medians and the corresponding ranges are reported because data were not normally distributed for the BSL-23 in both groups of healthy controls, and thus these parameters are representative for the data distribution (Field, 2009).

Significant group differences between BPD and HC 1. ▲ Significant group differences between BPD and HC 2. Significant group differences between HC 1 and HC 2.

## Measures

Self-compassion was measured using the widely employed 26-item Self Compassion Scale (SCS; Neff, 2003b) in its German version (Hupfeld & Ruffieux, 2011). The SCS consists of three bipolar subscales. These represent Neff's (2003a, 2003b) postulated three components of self-compassion: self-kindness (e.g., I'm tolerant of my own flaws and inadequacies) versus self-judgment (e.g., When times are really difficult, I tend to be tough on myself), common humanity (e.g., I try to see my failings as part of the human condition) versus isolation (e.g., When I'm feeling

down I tend to feel like most other people are probably happier than I am), and mindfulness (e.g., When I fail at something important to me I try to keep things in perspective) versus over-identification (e.g., When something upsets me I get carried away with my feelings). Respondents self-report their behaviors on a five-point Likert scale from 1 (almost never) to 5 (almost always).

Please note that the definition of mindfulness used in the SCS differs from the conceptualization of mindfulness by Kabat-Zinn (1994), which is adopted in the present study. Mindfulness in the sense of self-compassion specifically refers to maintaining perspective in challenging circumstances in order to soothe the self (Neff & Dahm, 2015).

Mindfulness was assessed using the 14-item short form of the Freiburger Fragebogen zur Achtsamkeit (Freiburg mindfulness inventory) in its German version (FFA; Buchheld, Grossmann, & Walach, 2001; Walach et al., 2004). Participants self-rate their subjective experience of mindfulness in everyday life (e.g., When I notice an absence of mind, I gently return to the experience of the here and now) on a four-point Likert scale from 1 (rarely) to 4 (almost always). The short version was shown to be a robust and valid instrument in general and clinical populations. The administration of the short version of the FFA is suitable in samples without any knowledge of Buddhist psychology (Walach et al., 2004).

In order to assess BPD-typical symptoms, the short form of the Borderline Symptom List was utilized in its German version (BSL-23; Bohus et al., 2009). The BSL-23 consists of 23 items (e.g., I wanted to punish myself or My mood rapidly cycled in terms of anxiety, anger and depression). Participants self-rate how much they suffered from each problem in the course of the previous week on a five-point Likert scale from 0 (not at all) to 4 (very strong).

Emotion dysregulation was operationalized through the 36-item Difficulties in Emotion Regulation Scale (DERS; Gratz & Roemer, 2004) in its German translation (Ehring, Tuschen-Caffier, Griepenstroh, & Berking, 2010). The DERS assesses individuals' typical levels of emotion dysregulation. Sample items include: "When I'm upset, I feel guilty for feeling that way" or "I know exactly how I am feeling." Items are self-rated on a five-point Likert scale from 1 (almost never) to 5 (almost always).

### *Procedure*

After successful recruitment, a questionnaire packet (containing the SCS and the DERS) was sent to the participants' homes in order to reduce assessment time. Participants were instructed to fill out the questionnaire by them selves and in a non-distracting environment. The remaining measures (i.e., the FFA and the BSL-23) were completed on the day of the study. Participants were continuously encouraged to ask questions if anything was not clear. At study completion, participants received monetary reimbursement for their effort.

### *Statistical Analyses*

All analyses were conducted using SPSS statistics 21.0 software package for Windows and all hypotheses were tested at a one-sided significance level of  $\alpha = .05$ , unless otherwise specified. Mediation analyses were performed using bootstrapping methods in the PROCESS SPSS macro (Hayes, 2013). This macro represents the state of the art in mediation analysis, which is to formally test the significance of the indirect effect of the independent variable on the dependent variable by the mediating variable (Hayes, 2009; Zhao, Lynch, & Chen, 2010). For the analysis at hand, non-parametric bootstrapping with bias-corrected bootstrap 95% confidence intervals based on 5,000 bootstrap samples was utilized. If zero was not contained within the bounds of the confidence interval, there existed an indirect effect unequal zero in the population with a probability of 95%. This category of mediation analysis makes no assumptions about the sampling distribution of the indirect effect and is appropriate for small samples (Hayes, 2009; Preacher & Hayes, 2004).

In order to examine the hypothesized interplay between mindfulness, BPD symptoms, and self-compassion, mindfulness was entered as the independent variable, the respective indicators of BPD symptoms as the dependent variables, and self-compassion as the mediating variable (see Figure 1). In other words, this model tested the hypothesis that the association between mindfulness and BPD was mediated by self-compassion. Effect size was estimated with  $k^2$ , which is the ratio of the obtained indirect effect to the maximum possible indirect effect given the present study design and data. This effect size was chosen, as it is standardized and bounded, facilitating interpretation. Further, it is insensitive to sample size and allows for the construction of bootstrap confidence intervals (Preacher &

Kelley, 2011).

**Table 2.** Inter-correlations for Main Variables in Each Group (Study 1 and Study 2)

	BPD ( <i>n</i> = 28)			HC 1 ( <i>n</i> = 30)			HC 2 ( <i>n</i> = 86)		
	2	3	4	2	3	4	2	3	4
1 SCS	.72**	-.56**	-.49**	.55**	-.47**a	-.60**	.69**	-.57**a	-.76**
2 FFA		-.50**	-.37*		-.32*a	-.44**		-.54**a	-.72**
3 BSL-23			.34*			.33*a			.72**a
4 DERS			1			1			1

*Note.* SCS = Self-Compassion Scale; FFA = Freiburger Fragebogen zur Achtsamkeit (Freiburg mindfulness inventory); BSL-23 = Borderline Symptom List 23; DERS = Difficulties in Emotion Regulation Scale. BPD = group of individuals with BPD; HC 1 = group of healthy controls in study 1; HC 2 = group of healthy controls in study 2. The significance was tested one-sidedly. \*Spearman's  $r_s$  is reported as data were not normally distributed for the BSL-23 in both groups of healthy controls and thus assumptions of Pearson's  $r$  were violated (Field, 2009). \* $p < .05$ . \*\* $p < .01$ .

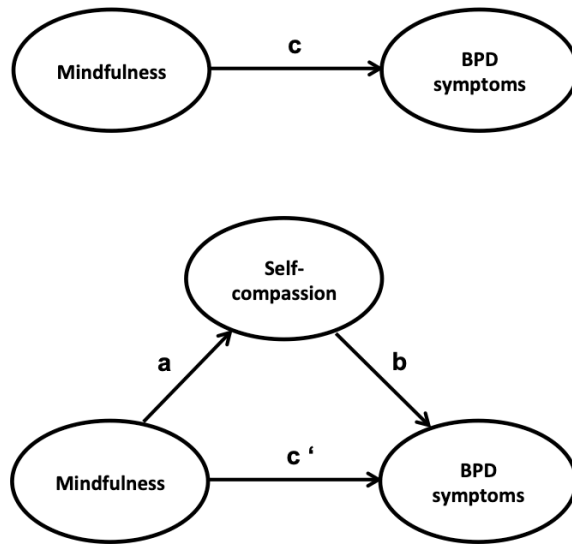
## Results

Zero-order correlations for the variables used in the main analyses in both groups are shown in Table 2. Results of all conducted mediation analyses are summarized in Tables 3 and 4. As correlations were high between the SCS and the FFA in both groups, multicollinearity measures, namely, the tolerance factor (TOL) and the variance inflation factor (VIF) were checked (BPD: TOL = 0.49, VIF = 2.05; HC 1: TOL = 0.70, VIF = 1.43) and did not exceed critical values (TOL < 0.1, VIF > 10; Eid, Gollwitzer, & Schmitt, 2013; Field, 2009).

*BPD Symptom Severity as Dependent Variable (Model 1).* The first model tested whether the effect of mindfulness on reduced BPD symptom severity functions through high levels of self-compassion. There was a significant total effect of mindfulness on BPD symptom severity in the group of individuals with BPD, but not in the group of healthy controls.

When self-compassion was added to the model, the direct effect of mindfulness on BPD symptom severity no longer reached a level of statistical significance in the group of individuals with BPD and was also non significant in the group of healthy controls. There was a significant indirect effect  $a \times b$  of mindfulness on BPD symptom severity through self-compassion in each group. The effect sizes  $k^2 = .24$  (bootstrap 95% CI [.04, .45]) and  $k^2 = .22$  (bootstrap 95% CI [.07, .42]), respectively. They denote that 24% (22%, respectively) of the maximum possible indirect effect was obtained.

*Emotion Dysregulation as Dependent Variable (Model 2).* The second model tested whether the association between mindfulness and reduced emotion dysregulation is mediated by self-compassion. The total effect of mindfulness on emotion dysregulation was not significant in the group of individuals with BPD, but reached significance in the group of healthy controls.



**Figure 1.** Simple mediation analyses where the effect of mindfulness on BPD symptoms is not versus is mediated by self-compassion (ellipses represent variables and single-headed arrows represent regression coefficients).

When self-compassion was entered into the model, the direct effect of mindfulness on emotion dysregulation was neither significant in the group of individuals with BPD nor in the group of healthy controls. Again, there was a significant indirect effect  $a \times b$  of mindfulness on emotion dysregulation through self-compassion in each group. The effect sizes were  $k^2 = .26$  (bootstrap 95% CI [.04, .57]) and  $k^2 = .27$  (bootstrap 95% CI [.10, .47]), respectively.

**Table 3.** Mediation Analyses in the Group of  $n = 28$  Individuals With BPD (Study 1)

	$k^2$	Path	Total and direct effects				Indirect effects			
			Coeff.	SE	<i>p</i>		Bootstrap coeff.	SE	95% CI	Stand. coeff.
(1) FFA – SCS – BSL-23	.24	a	6.97	1.34	<.0001	$a \times b$	–0.51	0.27	–1.08, –0.04	–.29
		b	–0.07	0.04	.09					
		c	–0.86	0.29	<.01					
		c'	–0.35	0.40	.39					
(2) FFA – SCS – DERS	.26	a	6.97	1.34	<.0001	$a \times b$	–0.51	0.31	–1.28, –0.04	–.34
		b	–0.07	0.04	.07					
		c	–0.55	0.28	.06					
		c'	–0.04	0.38	.92					

Note. FFA = Freiburger Fragebogen zur Achtsamkeit; SCS = Self-Compassion Scale; BSL-23 Borderline Symptom List short form, DERS = Difficulties in Emotion Regulation Scale.

**Table 4.** Mediation Analyses in the Group of  $n = 30$  Healthy Controls (Study 1)

	$\hat{R}^2$	Path	Total and direct effects				Indirect effects			
			Coeff.	SE	$p$		Bootstrap coeff.	SE	95% CI	Stand. coeff.
(1) FFA – SCS – BSL-23	.22	a	4.52	1.30	< .01	$a \times b$	-0.10	0.05	-0.22, -0.02	-.25
		b	-0.02	0.01	< .05					
		c	-0.12	0.07	.12					
		c'	-0.02	0.08	.85					
(2) FFA – SCS – DERS	.27	a	4.52	1.30	< .01	$a \times b$	-0.34	0.14	-0.71, -0.13	-.28
		b	-0.08	0.03	< .01					
		c	-0.53	0.21	< .05					
		c'	-0.19	0.22	.41					

Note. FFA = Freiburger Fragebogen zur Achtsamkeit; SCS = Self-Compassion Scale; BSL-23 = Borderline Symptom List short form; DERS = Difficulties in Emotion Regulation Scale.

## Discussion

In both models, these combinations of significant and nonsignificant effects are labeled “indirect-only mediation” by Zhao et al. (2010, p. 201). The total effect of mindfulness on indicators of BPD symptoms is reduced by including self-compassion as a mediator. Moreover, this pattern of effects shows that omitted mediators are unlikely. Ergo, the indirect path from mindfulness to indicators of BPD symptoms via self-compassion is consistent with the hypothesized theoretical framework in which mindfulness is associated with higher levels of self-compassion, which in turn is associated with lower levels of indicators of BPD symptoms. We further conducted post hoc power analyses with the program G\*Power 3.1 (Faul, Erdfelder, Buchner, & Lang, 2009) to assure that the insignificant direct effect could not be attributed to a lack of statistical power. Power analyses were calculated with  $\alpha = .05$ , the respective sample sizes, and the effect sizes which were estimated from the respective squared multiple correlation (model 1: estimated  $\eta^2 = .33$  in group of BPD patients, estimated  $\eta^2 = .25$  in group of healthy controls; model 2: estimated  $\eta^2 = .24$  in group of BPD patients, estimated  $\eta^2 = .38$  in group of healthy controls). The power was greater than .70 in all four analyses (model 1:  $1-\beta = .89$  in group of BPD patients,  $1-\beta = .71$  in group of healthy controls; model 2:  $1-\beta = .72$  in group of BPD patients,  $1-\beta = .96$  in group of healthy controls).

In sum, the models with mindfulness as the independent variable, self-compassion as the mediating variable, and BPD symptom severity or emotion dysregulation as the dependent variable fitted the data in both groups. We can conclude that self-compassion plays a role in the relationship between mindfulness and the severity of BPD-typical symptoms, and this effect can be detected in individuals with BPD as

well as healthy participants, controlling for sex, age, and education. Although this study is the first to examine the interplay between mindfulness, self-compassion, and BPD symptoms, the most important limitation is the small size of the samples.

## **Study 2: self-compassion as a mediator in a representative sample**

In study 2 we tested whether self-compassion mediates the relationship between mindfulness and reduced BPD symptom severity and emotion dysregulation in the general population. For this purpose, we analyzed the mediation models in a larger sample of participants. The study design was reviewed by the local ethical committee and the investigation was carried out in accordance with the latest version of the declaration of Helsinki. Informed consent of the participants was obtained prior to participation and after the nature of the procedures had been fully explained.

## **Method**

### *Participants*

Eighty-nine participants were part of the second study. To achieve a wide range of symptoms and traits, participants were only required to be 18 years or older and to exhibit sufficient German language skills. Three participants were excluded from analysis, as they failed to fill out the SCS ( $n = 1$ ) or the BSL-23 ( $n = 2$ ). The remaining 86 participants ranged in age from 18 to 65, with a mean age of  $M = 32.71$  ( $SD = 12.58$ ). Data on the sex item was missing for  $n = 19$ . For reported gender, the proportion was almost equal (35 females, 40.7%, and 32 males, 37.2%). The majority of participants (75.6%) had acquired a general certificate of secondary education (German *Abitur*). Participants reported how much previous experience they had with mindfulness and mindfulness-related practices on a scale from 1 (not at all) to 4 (advanced). Participants reported most experience with general relaxation techniques ( $M = 2.2$ ,  $SD = 0.86$ ), followed by yoga ( $M = 1.93$ ,  $SD = 0.94$ ), meditation ( $M = 1.82$ ,  $SD = 0.98$ ), muscle relaxation ( $M = 1.8$ ,  $SD = 0.89$ ), and mindfulness ( $M = 1.42$ ,  $SD = 0.56$ ). For more demographic data and group comparisons with the samples from study 1, see Table 1.

*Measures* (See Study 1.)



## *Procedure*

The study took place during an open house event at the local university. Visitors of the event were asked to participate in the study in return for sweets. Participants filled out the demographics questionnaire, the SCS, the FFA, the BSL-23, and the DERS. On the last page we asked participants: “Have you answered all questions honestly? If your answer is ‘no’ we will still send you an evaluation of your results. You would however greatly help our scientific interpretation of the data if you answered this last question.” All participants answered the last question with “yes” and were thus included in the study. Since the purpose of the open house event was to educate visitors about psychology, they received a feedback on their results. The feedback was carefully phrased, for example, high BSL-23 scores were described as “You often experience strong emotions. This can be overwhelming sometimes.”, and it was explicitly mentioned that the evaluation should not be considered a clinical diagnosis.

*Statistical Analyses* (See Study 1.)

## **Results**

Means, standard deviations, zero-order correlations, and reliabilities for all main variables are displayed in Tables 1 and 2. The results of the mediation analyses are summarized in Table 5. Again, as correlations were high between the SCS and the FFA, multi collinearity measures were checked ( $TOL = 0.53$ ,  $VIF = 1.89$ ) and did not exceed critical values ( $TOL < 0.1$ ,  $VIF > 10$ ; Eid et al., 2013; Field, 2009).

*BPD Symptom Severity as Dependent Variable (Model 1).* The first model tested whether the effect of mindfulness on reduced BPD symptom severity functions through high levels of self-compassion. There was a significant total effect of mindfulness on BPD symptom severity. When self-compassion was included into the model, the direct effect was reduced, but maintained significance. The indirect effect  $a \times b$  of mindfulness on BPD symptom severity via self-compassion was also significant. The effect size was  $k^2 = .20$  (bootstrap 95% CI [.10, .31]).

*Emotion Dysregulation as Dependent Variable (Model 2).* The second model tested whether the effect of mindfulness on reduced emotion dysregulation functions through high levels of self-compassion. There was a significant total effect of mindfulness on emotion dysregulation. When controlling for self-compassion, the direct effect was reduced, but maintained significance. There was

a significant indirect effect  $a \times b$  of mindfulness on emotion dysregulation through self-compassion. The effect size was  $k^2 = .36$  (bootstrap 95%CI [.23, .48]).

**Table 5.** Mediation Analyses in the Representative Sample of  $n = 86$  From the General Population (Study 2)

	$\hat{k}^2$	Path	Total and direct effects				Indirect effects			
			Coeff.	SE	$p$		Bootstrap coeff.	SE	95% CI	Stand. coeff.
(1) FFA – SCS – BSL-23	.20	a	7.21	0.83	< .0001	$a \times b$	-0.28	0.09	-0.47, -0.14	-.24
		b	-0.04	0.01	< .01					
		c	-0.59	0.11	< .0001					
		c'	-0.31	0.15	< .05					
(2) FFA – SCS – DERS	.36	a	7.21	0.83	< .0001	$a \times b$	-0.52	0.11	-0.73, -0.32	-.34
		b	-0.07	0.01	< .0001					
		c	-1.10	0.11	< .0001					
		c'	-0.58	0.13	< .0001					

Note. FFA = Freiburger Fragebogen zur Achtsamkeit; SCS = Self-Compassion Scale; BSL-23 = Borderline Symptom List short form; DERS = Difficulties in Emotion Regulation Scale.

## Discussion

In both models, this combination of significant effects is labeled “complementary mediation” by Zhao et al. (2010, p. 201). This indicates a significant indirect effect; yet it is accompanied by a reduced, but still significant direct effect. We find corroborating evidence that self-compassion is a mediator of the relationship between mindfulness and indicators of BPD symptoms, but there remains the likelihood of an omitted mediator in the direct path.

## General discussion

The purpose of the present studies was to investigate the role of self-compassion in the relationship between mindfulness and reduced BPD symptoms. We hypothesized that self-compassion mediates the effect of mindfulness on BPD symptom severity and emotion dysregulation in individuals with BPD, a healthy control group, and a representative sample from the general population. Our results suggest that self-compassion mediates the effect of mindfulness on reduced BPD symptoms measured as BPD symptom severity as well as emotion dysregulation. In line with our hypotheses, we were able to find evidence for these mediation effects in a group of individuals with BPD, a group of healthy controls (study 1) as well as in a representative sample from the general population (study 2).

In study 1, we found an indirect-only mediation of the relationship between mindfulness and BPD symptoms through self-compassion. One interpretation of

this result is that individuals suffering from BPD may benefit from mindfulness largely through enhancement of self-compassion. While indirect-only mediation implies that no other mediators are likely, another possible explanation could be that the sample size was too small to find a direct effect. On the other hand, post hoc power analyses revealed that statistical power to detect a direct effect was good. In the more diverse sample examined in study 2, which differed significantly on the BSL-23 and the SCS from the healthy controls as well as the individuals with BPD in study 1 (see Table 1), self-compassion partially mediated the effect of mindfulness on reduced BPD symptoms (complementary mediation). Our finding of complementary mediation suggests that further mediators of the effect may exist. While we here focused on self-compassion as a potential mediator of the relationship between mindfulness and BPD, other studies have investigated other mediators, for example rumination (Selby, Fehling, Panza, & Kranzler, 2016). At the same time, studies that investigated the effect of mindfulness and self-compassion as well as other variables on well-being found that mindfulness and self-compassion were significant mediators even if other variables were taken into account (Gu, Strauss, Bond, & Cavanagh, 2015; Svendsen, Kvernenes, Wiker, & Dundas, 2017; van der Velden et al., 2015). However, especially in heterogeneous nonclinical populations, there may exist additional pathways through which mindfulness exerts its beneficial effects (see Hill & Updegraff, 2012).

Our results contribute to a growing body of evidence that mindfulness is a precondition of self-compassion and that self-compassion is one of the mechanisms through which mindfulness affects well-being and mental health (Baer et al., 2012; Bergen-Cico & Cheon, 2014; Birnie et al., 2010; Hollis-Walker & Colosimo, 2011; Keng et al., 2012; Kuyken et al., 2010; Rimes & Wingrove, 2011; Robins et al., 2012; Shapiro et al., 2005; Shapiro et al., 2007). Moreover, Hölzel et al. (2011) hypothesized that self-compassion is a mediator of mindfulness because it works as an emotion regulation strategy. Results of our study support this idea, as we show that self-compassion mediates the relationship between mindfulness and emotion dysregulation.

Among the strengths of the present studies are the assessment of BPD in the first study by structured clinical interviews, the implementation of validated measures to operationalize self-compassion, mindfulness, BPD symptom severity, and emotion dysregulation, as well as the investigation of the mediation models in three

different samples. Nevertheless, several limitations of both studies must be acknowledged. First, both studies are cross-sectional studies. Thus, one must also consider the possibility that the relationships between self-compassion, mindfulness, and BPD symptoms are bidirectional or even reversed. We cannot statistically verify whether mindfulness and self-compassion improve BPD symptoms, or whether BPD symptoms cause difficulties with mindfulness and self-compassion. It has been argued that cross-sectional analyses cannot determine mediation, since they do not measure the variables on different time points and thus do not fulfill a basic requirement of mediation analysis (Maxwell & Cole, 2007). Clearly, this calls for the replication of the findings at hand in large-scale studies with longitudinal designs. The variables should be assessed at least at three separate time points to establish mediation (MacKinnon, 2008).

Second, we did not apply a clinical control group. The especially adaptive path from mindfulness over self-compassion to decreased indicators of BPD symptoms in the group of individuals with BPD could merely reflect an effect of general psychopathology. Future studies may include clinical control groups in order to further clarify the role of self-compassion in the relationship between mindfulness and BPD symptoms in different clinical populations.

Further, some methodological issues should be addressed in future studies. For example, due to procedural constraints in study 1, the DERS and the SCS were assessed at participants' homes and the BSL-23 and the FFA were assessed when participants arrived at the laboratory. Future studies should pay more attention to controlling the timing and setting of the questionnaire assessment. In addition, in study 2, recruitment took place at an open house event. This recruitment method is biased towards participants who are interested in science and who are more educated than the average population. Future studies could use stratified sampling techniques to ensure participants from more diverse backgrounds.

As we found self-compassion to influence the relationship between mindfulness and BPD symptoms, one possible implication for clinical practice is the implementation of self-compassion into mindfulness trainings and interventions for BPD. While mindfulness was positively associated with self-compassion in this study, direct trainings may show even stronger effects. Hildebrandt, MacCall, and Singer (2017) have recently shown that interventions that explicitly focused on improving care, benevolence, and acceptance had greater effects on these qualities

than interventions that focused solely on mindful attention and body awareness. Clinicians working with individuals with BPD could teach self-compassion as an additional emotion regulation strategy for dealing with commonly experienced emotions, such as shame and feelings of self-worthlessness, which likely result in anger and self-harm (Warren, 2015). Krawitz (2012) suggests several specific psychotherapeutic techniques to encourage a self-compassionate attitude in individuals suffering from BPD and chronic self-loathing. For instance, positive biographical imagery or guided writing exercises from the perspective of an imaginary compassionate friend are thought to draw on the self-soothing system related to self-compassion (Gilbert, 2009; Gilbert & Procter, 2006). First empirical evidence for incorporating self-compassion into interventions for BPD was presented in a recent randomized pilot study with patients with a primary diagnosis of BPD (Feliu-Soler et al., 2017). Here, a three-week training program of loving-kindness compassion training was superior to continuing mindfulness practice alone in decreasing BPD severity and self-criticism.

In conclusion, the present research provides initial empirical evidence of self-compassion mediating the association between mindfulness and core BPD symptoms (emotion dysregulation) and their general severity in different samples of healthy controls as well as individuals with BPD. Future research could attempt to replicate the present findings in longitudinal studies with adequately large samples of individuals with BPD next to clinical and healthy control groups and investigating multiple mediator models. The training of mindfulness and self-compassion may be able to reduce BPD symptoms, providing effective emotion regulation strategies.

*Paper submitted for publication.*

## **Regulating negative emotions of others reduces own stress: Neurobiological correlates and the role of individual differences in empathy.**

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While witnessing the suffering of other people results in personal distress, it is not clear whether regulating others' emotions in such situations also comes at an emotional cost for the observer. The present study included 62 subjects and used a novel functional Magnetic Resonance Imaging (fMRI) paradigm to investigate mechanisms of self and other emotion regulation via reappraisal and their relationship with individual differences in compassion and cognitive empathy. We found that individuals exhibited especially high levels of personal distress when an interaction partner -vs. themselves- was exposed to aversive photographs and that especially highly compassionate individuals were prone to such personal distress. When engaging in social emotion regulation, however, personal distress was reduced in the observer at a similar rate as in self emotion regulation. FMRI analyses showed increased activation for other vs. self emotion regulation in the precuneus and the left temporo-parietal junction, which are commonly engaged in social cognition. This activation was associated with lower self-reported stress and decreased sympathetic autonomic activity. Moreover, precuneus activation during other regulation showed a specific functional connectivity profile with parietal emotion regulation regions. This study demonstrates benefits of actively regulating another person's emotions for reducing one's own distress and identifies the precuneus as an important node for social emotion regulation.

## **Introduction**

Many of us have had the experience of seeing another person suffering, and being so overwhelmed by our own emotional reaction to that suffering, that helping the other person becomes virtually impossible. In fact, several behavioral and neuroscientific studies over the past years have shown that being exposed to other's suffering can elicit personal distress in the observer (Batson et al., 1987; Hein & Singer, 2008; Saarela et al., 2007), which engages the activation of a brain network including the anterior insula (AI) and the anterior cingulate cortex (ACC), among

others (for meta-analysis Bzdok et al. 2012). When the feeling of personal distress is strong, this leads to a need to direct attention to the self in order to alleviate own discomfort, thus preventing prosocial behavior or even the feeling of sympathy for the sufferer (Buruck, Wendsche, Melzer, Strobel, & Dörfel, 2014).

One means of reducing personal distress is through regulation of one's own emotions. Modifying emotional states, e.g. through controlling one's facial expressions or changing the cognitive perspective on the situation, that is, cognitive reappraisal (Gross, 1998; Gross & Muñoz, 1995), allows coping with and managing stress in diverse contexts. Scholars have suggested that high emotion regulation capacities do not only reduce personal distress but also facilitate helping and altruistic behavior (De Waal & Preston, 2017; Decety & Jackson, 2004; Lebowitz & Dovidio, 2015).

Previous research has shown that especially those individuals with high trait levels of emotional empathy, i.e., the sharing of others' emotions and sympathy, are prone to showing higher levels of personal distress (Powell, 2018). Interestingly, this relationship between empathy and personal distress seems to be mediated by low capacities to control own emotions (Buruck et al., 2014; Powell, 2018). Taken together, these studies suggest that empathy comes at an "emotional cost" for the observer, i.e., higher distress levels, which can be overcome by the use of emotion regulation strategies.

Interestingly, when confronted with another person who is in an emotionally aversive situation, people frequently and readily regulate this *other* person's emotional state, for example by calming or comforting them. This process has been referred to as social, interpersonal or other emotion regulation (Niven et al., 2009; Zaki & Williams, 2013) and has only relatively recently received attention in social cognitive neuroscience (Reeck et al., 2016; Zaki & Williams, 2013). In the context of the aforementioned reaction of personal distress and the need for self emotion regulation when seeing somebody in despair, it seems in fact surprising that so many individuals would engage in regulating others as this represents a further confrontation with the other person's intense emotional state, which might increase the burden for the self, i.e., personal distress. One study in medical students indeed seems to suggest just that: Regulating another person depleted emotional resources in the regulator, which was shown to increase emotional exhaustion (Martínez-Íñigo et al., 2015). Interestingly though, there is conflicting



evidence reporting that regulating other's emotions can actually increase the regulator's well-being (Niven et al., 2012). Thus, it is an open question how social emotion regulation is related to own emotional wellbeing. Given the pervasiveness of regulating others in social interactions (Ham & Tronick, 2009), however, we propose here that regulating other's emotions might have beneficial effects on the regulation of one's own emotional state.

Neuroimaging studies of recent years have sought to contribute to an understanding of social emotion regulation and its relationship to self emotion regulation. These initial studies, which utilized paradigms where people inside a Magnetic Resonance Imaging (MRI) scanner regulated a person outside of it, have shown that other emotion regulation identified overlaps in brain areas mediating self emotion regulation, including activity in prefrontal cortex (Hallam et al., 2014; Jensen et al., 2014). Moreover, social emotion regulation was shown to involve temporal and parietal (including TPJ) cortices, which have been taken to indicate social cognition processes (Hallam et al., 2014). However, studies to date seem limited by small sample sizes (Jensen et al., 2014) and did not directly assess the emotional state (i.e., distress levels) of the regulator while regulating the other person.

Thus, in the current study we sought to further elucidate the relationship between self and other emotion regulation on a behavior and brain level, and more specifically set out to test the hypothesis that regulating others' adverse emotional states contributes and leads to regulating personal distress. Furthermore, we sought to explore whether levels of trait emotional empathy moderate self and social regulation capacities, hypothesizing that subjects with higher empathy (compassion level) will display higher personal distress when regulating self and others. To evaluate these questions, we developed a new self and other emotion regulation task, in which subjects had to alternate between regulating their own emotions and regulating the emotions of another person (an unfamiliar confederate) outside of the MRI scanner, while being exposed to aversive pictures. To investigate the success of emotion regulation, i.e., cognitive reappraisal, we used self-report stress ratings and electrodermal activity as a measure of sympathetic activation.

## Methods

### *Participants*

Sixty-two healthy individuals (52 female, mean age = 38.5 years,  $sd=10$ ) were recruited from the general population in the city of Berlin in the context of a longitudinal intervention study on the effects of a Mindfulness-based Stress Reduction (MBSR) program, pre-registered at [clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03035669) NCT03035669. Only data that were collected before randomization into the longitudinal study will be reported here and longitudinal data will be reported on elsewhere (Guendelman et al., in preparation). Subjects underwent an online and in-person screening procedure, and reported no history of neurological or psychiatric disorders, no current use of psychoactive drugs, native German fluency, normal or corrected-to-normal vision and no contra-indication for performing an fMRI experiment. All participants provided written informed consent prior to the investigation. The study was approved by the ethics committee of Humboldt-Universität zu Berlin and was carried out in accordance with the guidelines of the declaration of Helsinki.

### *Procedure*

Subjects underwent the Self-Other Emotion Regulation paradigm (SORT) in the context of an fMRI experiment on day one and completed various socio-emotional measures on day two. On the day of the fMRI experiment, participants were asked to arrive 1 hour early to the neuroimaging center and to wait for approx. 15 minutes in the waiting room with a confederate of the investigator, who was unknown to the participant and introduced to them as another subject and their partner for the upcoming session. Both persons were treated as experimental subjects by the experimenter team and were told that they were going to do the same task together, one in the scanner and one outside of it. Both subjects were given the experimental instructions and took a trial version of the paradigm before completing the actual task.

### *Empathy*

Subjects completed the Multifaceted Empathy Test (MET) (Dziobek et al., 2008; Foell, Brislin, Drislane, Dziobek, & Patrick, 2018), a validated behavioral task that dissociates cognitive and emotional empathy components. The MET is built upon

naturalistic stimuli and demands subjects to deploy different functional facets of empathy, outperforming the limitations of standard self-assessment questionnaires. The MET is composed of 40 pictures showing one or more persons in emotional scenes (e.g., a child in a war scene), half of them correspond to positive and half to negative emotions. For the emotional empathy part, which was adapted to focus on sympathy/compassion, subjects answered the question “How much compassion do you feel for this person?” for negative pictures and “How happy are you for the person?” for positively valenced pictures. For the cognitive empathy part, participants were asked to select the correct emotional state of the depicted person out of a set of four possible answers.

### *Self-Other Emotion Regulation Task (SORT)*

In the SORT, participants are required to alternate between ER\_self (regulating themselves in the scanner) and ER\_other (regulating the confederate outside of the scanner) while being exposed to aversive pictures. The strategies subjects are asked to engage include reappraisal and mindful-acceptance as emotion regulation methods, and permitting of any emotional state as a baseline condition. For this study, only the reappraisal (from here on ER\_self and ER\_other) and the permit conditions will be focused on; mindful-acceptance strategies will be reported on in a separate publication on the longitudinal effects of an MBSR intervention (Guendelman et al., in preparation). The strategies were applied via verbalization of specific sentences that were displayed on the photos for both self and other conditions (as for the regulation conditions with reappraisal: “This is just a photo!”; as for the non-regulation conditions with permit: “Permit the reaction!”). Subjects were told to not only read the sentences, but to really engage and actively apply the respective strategies to down-regulate (or permit) their own and their partner’s current negative emotional states. Participants communicated with the subject outside the scanner through a microphone, conveying explicitly the sentences and instructing the different strategies for regulation and non-regulation. Subjects had to verbalize the strategy during the first two seconds of the picture, in order to standardize implementation across subjects and conditions. For the ER\_self condition, subjects self-instructed aloud the strategy (reappraisal) as means for reducing own distress. For the ER\_other condition, participants used the strategy (reappraisal) as means for reducing the other’s current distress. Subjects were told to “have the other person in mind” while regulating them. During the permit

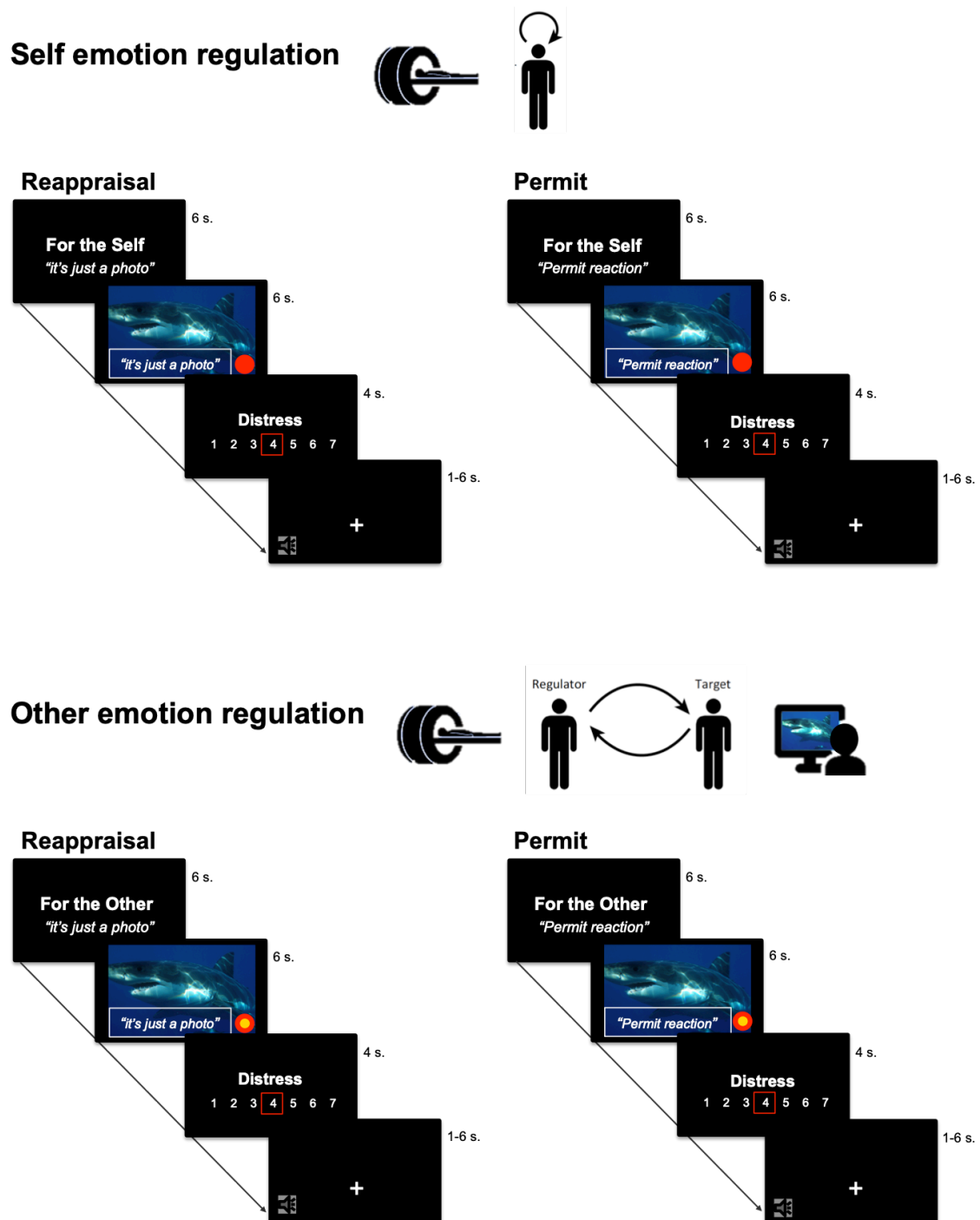
conditions subjects were asked to also verbalize to themselves and the partner to permit the respective emotions. They were instructed to not try to either regulate (decrease) or to worsen distress (increase) for themselves or the confederate. Since these are non-regulation conditions we expect higher distress levels.

Subjects were told that their physiological arousal state was constantly monitored during the experiment and that if they failed to regulate themselves, there would be the possibility of an aversive sound appearing at the end of the block, which was intended to motivate volitional effort and decreasing habituation throughout the task. A pumping red dot, which was displayed on the photographs (see figure 1), allegedly represented the arousal state of the subject in the scanner during ER\_self trials.

A pumping red-yellow dot allegedly corresponded to the arousal state of the subject outside of the scanner during ER\_other trials, offering to the regulator live and dynamic information regarding the other's autonomic state. Subjects were told that during the ER\_other trials, if they failed to regulate the other (as quantified by the physiological arousal), the aversive sound would appear for both subjects. They were explicitly told that no aversive sound would occur during the permit conditions (neither for the self nor the confederate), and that self reported stress ratings had no effect on the likelihood of getting the aversive sound throughout the whole experiment. The aversive sound was customized for every subject at the beginning of the scanner session, never overpassing the individual's accepted intensity threshold. For standardization purposes every subject was randomly assigned to receive a fixed number of 3 to 5 aversive sounds during the whole experiment (See table S1).

The aversive pictures of the SORT were taken from the international affective picture system (IAPS)(Lang, P.J., Bradley, M.M., & Cuthbert, 2008), and included neutral and negatively valenced pictures of high and low arousal (cf. for a list of pictures used see table S2). (Supplemental material is available on a pdf file in the memory stick device).

Stimuli were presented in a blocked event-related design with 4 blocks for each condition (*self emotion regulation-reappraisal*, *self emotion permitting*, *other emotion regulation-reappraisal*, *other emotion permitting*). Every block started with a 6 s introductory screen indicating the block type e.g. "For the other: it's just



**Figure 1:** Schematic representation of the SORT experimental set-up in the fMRI scanner. In the experiment, the subject in the scanner (the regulator), alternates between two strategies (reappraisal vs. permit) and foci (self vs. other person), resulting in four conditions: *self emotion regulation via reappraisal* ("it's just a photo"), *self emotion permitting* ("permit the reaction"), *other emotion regulation via reappraisal* ("it's just a photo"), *other emotion permitting* ("permit the reaction"). (Manikin figures are adapted from Reeck et al., 2016)

a photo", corresponded to regulate the other with reappraisal, followed by the interleaved presentation of 6 pictures (2 neutral, 2 negative high arousal, 2 negative low arousal) for 6 s each. Participants had 4 s to rate their own distress level after every picture. At the end of each block a fixation cross was presented,

during this period the aversive sound could appear (See figure 1). The fixation cross was jittered (mean 2000 ms, SD 1635 ms; with an in house MatLab script) using an exponential distribution of random numbers, accounting for the repetition time and stimulus presentation, optimizing power and efficiency for sampling the hemodynamic response in our experimental design (cf. (Henson, 2007)).

### *Data acquisition and preprocessing*

#### *Skin conductance*

During the experiment, electrodermal activity was collected with a biopac MP-150 system with a sampling rate of 1000 Hz. Two skin conductance electrodes were placed on the index finger and thumb of the left hand. A pulse oxymeter for measuring heart rate and oxygen levels was placed on the left middle finger. Skin conductance was processed using Ledalab version 3.4.9 (Benedek & Kaernbach, 2010) using continuous decomposition analyses. Data were low-pass filtered with 1 Hz, downsampled to 100Hz, and smoothed with a moving average with a window size of 1 s.

#### *fMRI*

Brain images were collected with a Siemens 3 Tesla Trio scanner, with a 32-channel head coil. Structural brain images were acquired with a Magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence (1×1×1mm<sup>3</sup> resolution), with TE=2.52 ms, TR=1900 ms, flip angle = 90° and 100% field of view. During the experimental task, whole brain T2\*-weighted functional images were acquired with a standard EPI (Echo-Planar Imaging) sequence for fMRI, with TE=30 ms, TR=2000 ms, flip angle = 90°, field of view 100%, with an acquisition matrix= 64 x 64 x 33 slices, slice thickness of 3.75 mm, with descending slice acquisition; a total of 1050 volumes were acquired per subject.

Data pre-processing and analysis were carried out with FSL 6.0 (FMRIB's Software Library, [www.fmrib.ox.ac.uk/fsl](http://www.fmrib.ox.ac.uk/fsl)). Images were spatially smoothed with a Gaussian kernel of 5mm (FWHM) and high-pass filtered with a cutoff of 100 s. Functional EPI images were registered to the high-resolution structural MPRAGE images using boundary-based registration (BBR) and to standard space images (MNI\_152, 2 mm resolution) using affine linear transformation with 12 degrees of freedom using FLIRT (Jenkinson & Smith, 2001).

Correction of head motion was performed using rigid-body transformations based on a linear registration tool (Jenkinson, Bannister, Brady, & Smith, 2002). Finally, a quality control of the mean frame displacement, signal to noise ratio and standard deviation of signal over voxels was performed for each subject. Based on these, two participants were discarded due to excessive movement (mean absolute displacement >1.5 mm).

### *Data analyses*

#### *Behavioral data*

To estimate the effects of emotion regulation strategies on stress levels during the SORT, a 2 (Focus: Self vs. Other) by 2 (Strategy: Regulate vs. Permit) repeated measures analysis of variance (ANOVA) was performed. In posthoc comparisons, p-values were Bonferroni corrected

Behavioral responses in the MET including intensity of compassion/sympathy and accuracy of cognitive empathy were analyzed as the mean of ratings and the sum of correct answers, respectively. To estimate the relationship between compassion, cognitive empathy and emotion regulation, behavioral responses from the MET and the SORT were correlated using linear regression models. Behavioral data were analyzed using IBM SPSS Statistics software, version 21.

Skin conductance responses (SCR) were analyzed in the 6 s following stimulus onset, using a minimum amplitude criterion of 0.01  $\mu$ S. SCR data was used as a regressor of interest in fMRI analyses, using a within-subjects approach, which accounts for potential inter-individual effects (i.e. daytime, state anxiety).

#### *fMRI*

Preprocessed images were entered into a general linear model (GLM) for statistical analysis. A first level analysis at the individual level included regressors for each experimental condition (4 conditions) convolved with the canonical hemodynamic response function. Complementary first level analyses additionally included parametric regressors derived from de-meaned distress ratings and SCRs (in separate analyses), in order to investigate covariations of these parameters with the BOLD signal.

Higher-level group statistics were performed with FLAME-1, using mixed effects



modeling for all first-level analyses (as fixed effects). Contrasts of interests consisted of: ER\_other > ER\_self; ER\_self > ER\_other; ER\_other \* distress > ER\_self \* distress; ER\_other \* SCR > ER\_self \* SCR; ER\_other \* SCR; ER\_self \* SCR. All statistic images were thresholded with a cluster-defining threshold of  $p < 0.001$ , and corrected for multiple comparisons (FWE) with cluster threshold of  $p < 0.05$  (Worsley, 2001).

### *fMRI conjunction analysis*

Brain activation common to both ER\_self and ER\_other was identified using a conjunctive analysis, according to the minimum statistic compared to the conjunction null (Nichols, Brett, Andersson, Wager, & Poline, 2005). Each contrast was individually thresholded at  $p < 0.0005$ , and the conjunction image (ER\_other  $\cap$  ER\_self) was cluster thresholded at  $p < 0.001$  and corrected for multiple comparisons with a cluster threshold of  $p < 0.05$ .

### *fMRI psycho-physiological interaction*

To further elucidate the neuronal correlates of ER\_other, a psycho-physiological interaction (PPI) functional connectivity analysis was conducted. The precuneus was used as a functional seed region of interest (ROI) given its functional activation pattern in the GLM contrast ER\_other over ER\_self (ER\_other > ER\_self). Analyses were performed on the covariation parameter estimates for ER\_other from the first-level analyses including negative variation of stress ratings as parametric regressors (ER\_other \* -distress). Starting from the centroid of the ROI (2 / -68 / 40, in MNI 152 coordinates), we created a 5mm diameter sphere and extracted the time-course of the seed ROI for each subject. In the first level analysis, the psychological component corresponded to the basic task regressor (ER\_other), the physiological component to the time-course of the precuneus, and the interaction of both (PPI). The higher-level group statistics show brain regions with increased or decreased functional connectivity with the precuneus, during ER\_other, involved in distress regulation. All statistic images were thresholded using a cluster threshold of  $p < 0.001$  and corrected for multiple comparisons (FWE) with a cluster threshold of  $p < 0.05$  (Worsley, 2001).

## Results

### *Manipulation check*

Individual interviews after the study confirmed that all subjects believed that the second person (the confederate) outside the scanner was indeed performing the experiment with them, and that they were all actively trying to regulate the second person during the experiment.

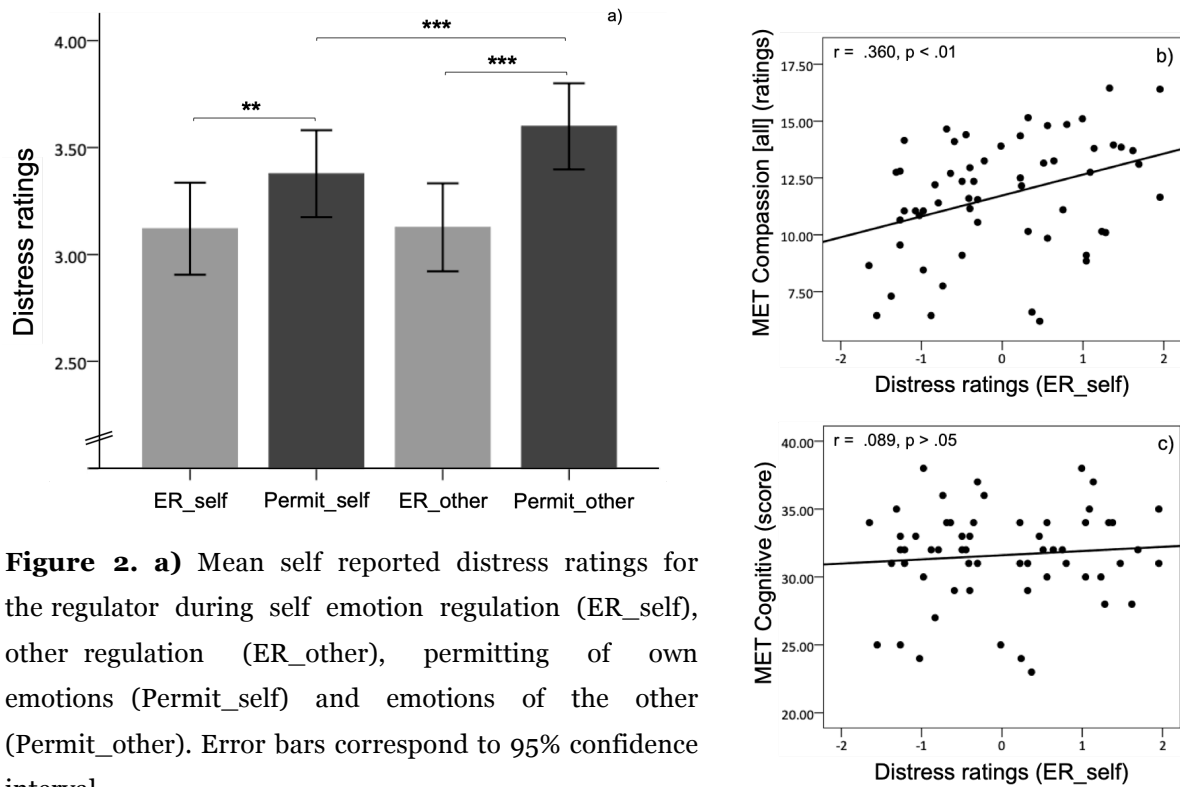
### **Behaviour**

#### *Effects of self and other emotion regulation on self reported distress ratings:*

Analyses yielded a main effect of Focus ( $F_{1,62} = 8.55, p = .005, \eta^2_p = .121$ ), indicating that focusing on the other resulted in higher distress than focusing on the self ( $p = .005$ ). A main effect of Strategy ( $F_{1,62} = 38.75, p < .001, \eta^2_p = .385$ ) showed that emotion regulation via reappraisal significantly reduced distress ratings compared to the permit condition ( $p < .001$ ). A significant interaction effect of Focus x Strategy ( $F_{1,62} = 11.28, p = .001, \eta^2_p = .154$ ) shows that Permit\_other was associated with higher distress ratings compared to Permit\_self ( $p < .001$ ), and ER\_self and ER\_other had similar distress reducing effects ( $p > .05$ ). (Figure 2a).

#### *Association between compassion, cognitive empathy and distress ratings after emotion regulation*

To evaluate the relationship between compassion, cognitive empathy and self emotion regulation, linear regression analyses yielded that higher compassion was associated with higher distress ratings in ER\_self ( $R^2 = .130, F_{1,56} = 8.36, p = .005$ ), (Figure 2b & see figure S1), whereas cognitive empathy was not associated with distress ratings in ER\_self ( $R^2 = .008, F_{1,56} = .446, p > .05$ ) (Figure 2c). The same pattern of associations was found between distress ratings for ER\_other and compassion ( $R^2 = .131, F_{1,56} = 8.44, p = .005$ ), but not with cognitive empathy ( $R^2 = .017, F_{1,56} = .976, p > .05$ ) (See Figure S2. iii, iv).



**Figure 2. a)** Mean self reported distress ratings for the regulator during self emotion regulation (ER\_self), other regulation (ER\_other), permitting of own emotions (Permit\_self) and emotions of the other (Permit\_other). Error bars correspond to 95% confidence interval.

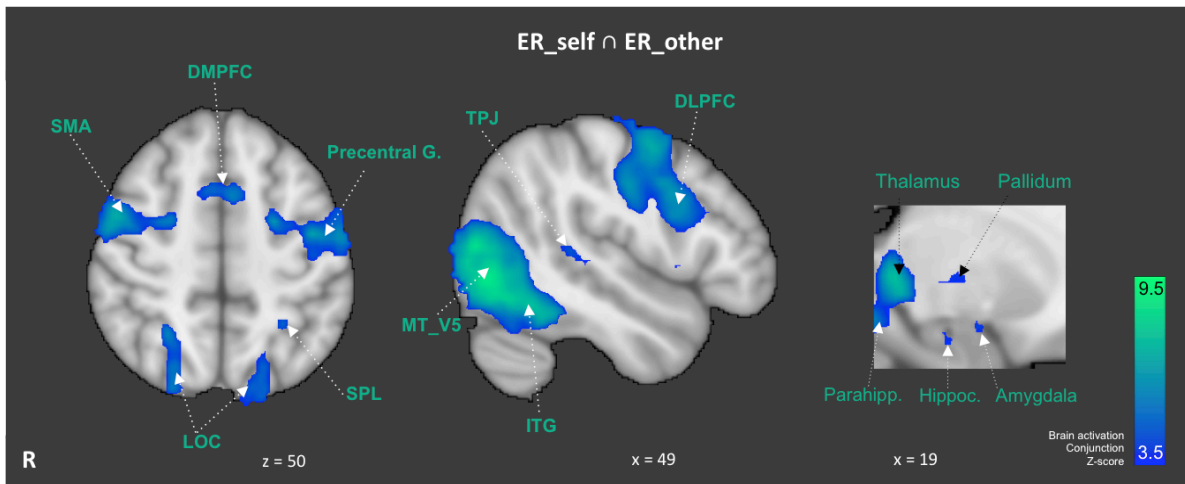
Pairwise comparisons with Bonferroni corrections (\*\*  $p < .005$ ; \*\*\*  $p < .001$ ) confirmed a main effect of Strategy: ER conditions (self and other) are perceived as less distressing than Permit conditions (for self and other), and a main effect of Focus: focusing on the other is perceived as more distressing than focusing on the self. A significant Focus  $\times$  Strategy interaction revealed that although Permit\_other was perceived as more distressing than Permit\_self, ER\_other compared to ER\_self led to similar distress reduction for the regulator. (Note: for y axis –distress rating- scale was cut from 0 to 2). Associations between compassion **(b)** and cognitive empathy **(c)** in the MET and distress ratings in the SORT self condition.

## fMRI

### *Common neuronal correlates of ER\_self and ER\_other*

Analyses of common neuronal correlates of regulating self and other (conjunction analysis of ER\_self and ER\_other contrasts;  $ER\_self \cap ER\_other$ , Figure 3) showed a significant overlap in several cortical brain regions including the bilateral dorso-lateral prefrontal cortex right inferior frontal gyrus (R IFG), bilateral supplementary motor area (SMA), bilateral motor cortex (precentral gyrus), dorsomedial prefrontal cortex (DMPFC), anterior mid-cingulate cortex (aMCC), superior temporal gyrus (STG), right temporo-parietal junction (TPJ), all areas previously associated with ER mechanisms. Other cortical and subcortical regions linked to perceptual, memory, motor and arousal representations of emotion

processing showed a significant overlap (Figure 3 & Table S3).



**Figure 3.** Common neuronal correlates of self and other emotion regulation (ER\_self and ER\_other conjunction, cluster-wise thresholded at  $p < 0.001$ , FWE at  $p < 0.05$ ) revealed overlapping brain activation in regions associated with emotion regulation & generation as well as motor and social cognition.

#### *Self emotion regulation: Specific neuronal correlates of ER\_self versus ER\_other*

To investigate the specific neuronal correlates of ER\_self compared to ER\_other, we contrasted the two conditions, which resulted in a differential brain activation in a cluster in the R middle temporal gyrus (MTG), extending into MT\_V5 (See Figure S3 & Table S4.).

#### *Associations between brain activation during ER\_self and SCR*

A covariation analysis between ER\_self (whole brain BOLD signal changes) and the SCR signal showed that higher activation in the precuneus, posterior cingulate cortex (PCC), superior parietal lobule (SPL), bilateral MTG and MT\_V5 was associated with lower SCR (See Table S5.), suggesting a role of these cortical regions in emotion and arousal regulation (Alcalá-López et al., 2017; Riedel, et al., 2018).

#### *Other emotion regulation: Specific neuronal correlates of ER\_other versus ER\_self*

To investigate the specific neuronal correlates of ER\_other compared to ER\_self,

we contrasted the conditions. Results showed increased brain activation for ER\_other in the precuneus, PCC, and left TPJ (Figure 4 in light blue, Table 1). Those regions have been associated with social cognition, self-other differentiation, and mentalizing before (Bzdok et al., 2012; Kanske et al., 2015; S. Valk et al., 2016), suggesting that the respective social processes might play a role in ER\_other. Meta-analytic maps from Neurosynth (reverse inference) for the terms “social cognition” (from 220 studies; in light blue) and “emotion regulation” (from 247 studies; in green) (z thresholded at  $p < 0.001$ ) (Yarkoni et al., 2011), support the notion that the ER\_other brain regions identified here overlap with both social cognition and emotion regulation areas.

#### *Associations between brain activation during ER\_other and SCR*

The covariation analysis between the ER\_other (whole brain BOLD signal changes) and the SCR signal showed that higher activation in the left precentral gyrus and SMA, bilateral supramarginal gyrus (SMG), R MTG, MT\_V5, was associated with lower SCR (Table 2), which is indicative of a role of these cortical regions in decreasing own stress during ER\_other.

#### *Associations between neuronal correlates of ER\_other versus ER\_self with stress ratings*

To further characterize the role of ER\_other brain activation in emotion regulation, a covariation analysis of the contrast ER\_other > ER\_self and distress ratings showed that activation in precuneus (peak at [2, -64, 38]; CS 238; z score 3.88; FWE  $p < 0.001$ ), left TPJ (peak at [-52, -58, 26]; CS 155; z score 4.29; FWE  $p < 0.01$ ) and intracalcarine cortex (peak at [12, -74, 12]; CS 213; z score 4.41; FWE  $p = 0.001$ ) was associated negatively with distress levels (Figure 4 in green).

#### *Associations between neuronal correlates of ER\_other versus ER\_self with SCR*

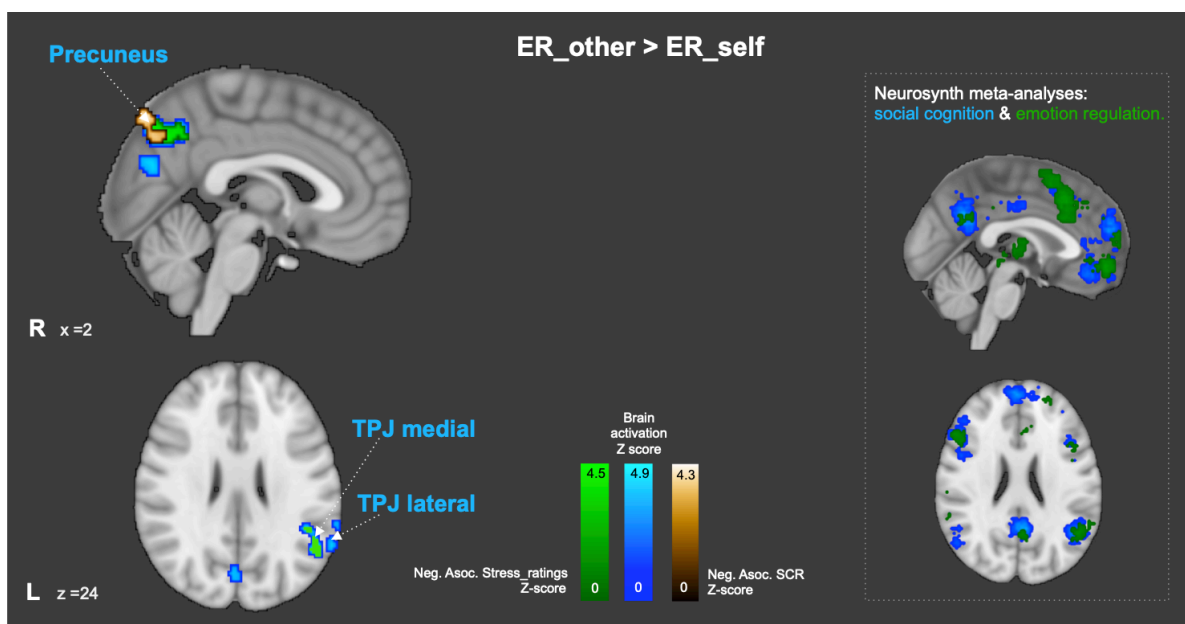
Furthermore, a covariation analysis of the same contrast ER\_other > ER\_self and SCR signal showed that activation in precuneus (peak at [0, -74, 48]; CS 247; z score 4.3; FWE  $p < 0.001$ ) and left occipital pole (peak at [-8, -94, 14]; CS 105; z score 3.75; FWE  $p < 0.05$ ) was associated negatively with SCR level (Figure 4 in gold). This suggests that during ER\_other, regions such as the precuneus and left TPJ, which have traditionally been associated with social cognition, are involved in regulating emotions in the regulator as well.

**Table 1.** ER\_other > ER\_self brain activation.

Brain region	H	CS	MNI Coordinates			Z max
			X	Y	Z	
Precuneus	R	509	2	-68	40	4.89
Precuneus/PCC	L		-12	-50	36	3.7
PCC	L		-6	-54	32	3.4
Intracalcarine cortex	R	450	12	-74	12	4.62
Lingual gyrus	R		8	-66	2	4.22
Cuneal cortex	R		2	-72	22	4.16
Posterior TPJ (medial)	L	139	-52	-58	26	4.19
Parietal operculum	L		-46	-44	26	3.9
Posterior TPJ (lateral)	L	118	-62	-56	24	4.38
Supramarginal gyrus	L		-64	-50	22	4.09

Note: All results are cluster-wise thresholded at  $p < 0.001$  and  $FWE < 0.05$ . TPJ located according to Mars TPJ connectivity-based parcellation atlas, implemented in FSL.

Abbreviations: H, hemisphere; CS, cluster size in the number of activated voxels; L, left; R, right; Z max, z score maximum value for the cluster; PCC, posterior cingulate cortex; TPJ, temporo parietal junction.



**Figure 4.** In light blue: Neuronal correlates of other vs. self emotion regulation (ER\_other > ER\_self) revealed brain activation in right precuneus and left TPJ, which were associated with social cognition. In green: Covariation map of ER\_other > ER\_self with distress ratings, showing brain areas that were negatively associated with distress ratings. In gold: Covariation map of ER\_other > ER\_self with SCR signal (negative association). All statistical z maps scores are cluster-wise thresholded at  $p < 0.001$  and  $FWE < 0.05$ . Neurosynth meta-analytic maps (reverse inference), for the terms social cognition (light blue) and emotion regulation (green), thresholded at  $p < 0.001$  (Yarkoni et al., 2011).

**Table 2.** Covariation of ER\_other brain activation negatively associated with SCR signal.

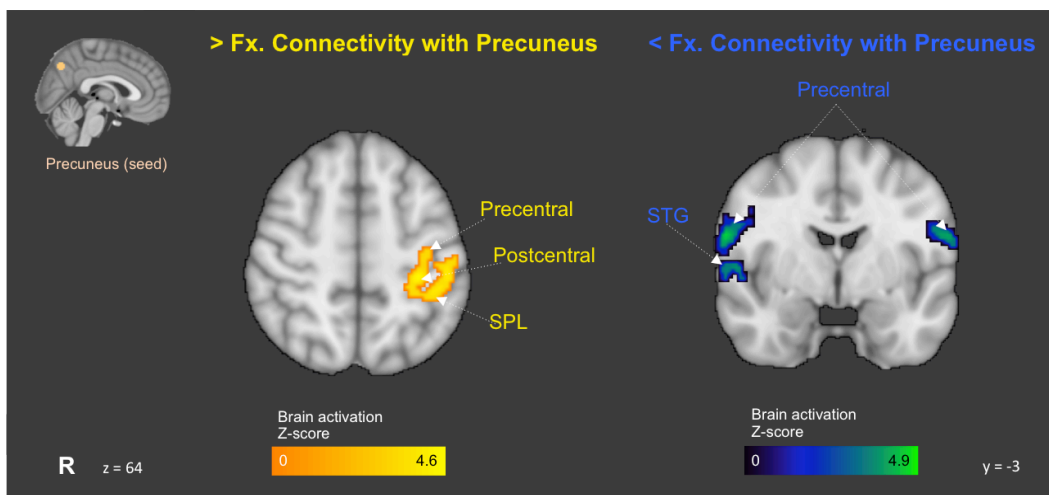
Brain region	H	CS	MNI Coordinates			Z max
			X	Y	Z	
MT_V5 (into MTG)	R	2677	48	-66	0	6.81
SMG (into I somato-sensory cortex, and SPL)	R	1744	58	-24	38	5.25
ITG (fusiform gyrus)	L	1696	-42	-48	-14	6.01
SMG (II somato-sensory cortex, IPL)	L	1629	-58	-26	38	5.95
Precentral Gyrus (into SMA)	L	97	-30	-8	52	4.04

Note: All results are cluster-wise thresholded at  $p < 0.001$  and FWE  $< 0.05$ .

Abbreviations: H, hemisphere; CS, cluster size in the number of activated voxels; L, left; R, right; Z max, z score maximum value for the cluster; MTG, middle temporal gyrus; MT\_V5, middle-temporal - visual area 5; SMG, supramarginal gyrus; ITG, inferior temporal gyrus; SMA, supplementary motor area.

### *Psycho-physiological interactions (PPI) during ER\_other*

To further investigate the role of the precuneus in downregulating own emotions during ER\_other, we conducted a PPI analysis using the precuneus activation peak that covaried with distress ratings as a seed ROI. Results showed an increased functional connectivity with the left postcentral gyrus – primary somatosensory cortex (peak at  $[-32, -30, 52]$ ; CS 838; z score 4.56; FWE  $p < 0.0001$ ) spanning into the SPL and IPL (SMG) and motor cortex, and right SPL (peak at  $[20, -62, 64]$ ; CS 124; z score 4.24; FWE  $p < 0.01$ ) (Figure 5).



**Figure 5.** Psycho-physiological interactions (PPI) during ER\_other. Using the precuneus as a functional seed, the analysis revealed increase and decrease of functional connectivity with regions associated with emotion regulation and social cognition (cluster-wise thresholded at  $p < 0.001$  and FWE at  $p < 0.05$ ). SPL, superior parietal lobule; STG, superior temporal gyrus.



Moreover, the PPI showed decreased functional connectivity of the precuneus with the bilateral STG, bilateral precentral gyrus and L lingual (Figure 5, table 3), regions associated with social cognition, motor mirroring and empathic distress (Ashar, Andrews-Hanna, Dimidjian, & Wager, 2017; Kanske et al., 2015; Molenberghs, Cunnington, & Mattingley, 2012; Oliver et al., 2018).

**Table 3.** PPI, brain areas with decreased functional connectivity with precuneus during ER\_other.

Brain region	H	CS	MNI Coordinates			Z max
			X	Y	Z	
STG	R	285	60	6	- 6	4.47
Precentral gyrus (motor cortex)	R	243	64	0	20	4.89
Precentral gyrus (motor cortex)	L	146	-52	-6	24	4.00
STG, opercular cortex.	L	114	-58	-18	10	3.86
Lingual gyrus	L	91	-24	-44	-12	4.02

Note: Results are derived from the PPI functional connectivity analysis using precuneus as seed-ROI during ER\_other which covaried with stress ratings. All results are cluster-wise thresholded at  $p < 0.001$  and  $FWE < 0.05$ . Abbreviations: H, hemisphere; CS, cluster size in the number of activated voxels; L, left; R, right; Z max, z score maximum value for the cluster. STG, superior temporal gyrus.

## Discussion

The present study used a novel fMRI paradigm to investigate mechanisms of self and other emotion regulation and their relationship with individual differences in compassion and cognitive empathy. We found that individuals exhibited high levels of personal distress when an interaction partner was experiencing negative emotions in response to aversive photographic stimuli and that especially highly compassionate individuals were prone to personal distress. Interestingly, when engaging in social emotion regulation, the benefits in terms of reducing personal distress were similar as when regulating the self. Brain imaging and skin conductance results identified the precuneus, typically involved in social cognition, as important nodes for reducing own distress in the context of active alleviation of another person's stress.

### *Linking personal distress, compassion, and self & other emotion regulation*

Our experimental manipulation yielded that being exposed to another person's emotional stress and telling them to permit their emotional reactions caused higher levels of personal distress than when participants had to permit their own

emotional reactions. Moreover, personal distress in the context of other's suffering was especially high in individuals who scored high on compassion in the external task MET (Dziobek et al., 2008). Concomitantly, our results also show that subjects with higher compassionate feelings have lower emotion regulation performance in general (i.e., higher distress ratings). Taken together the findings indicate that being a compassionate person comes at the cost of higher personal distress when being exposed to and when regulating other's suffering. Our results are in line with findings linking empathetic feelings, personal distress, and emotion regulation (Buruck et al., 2014; Powell, 2018), supporting models that assign an important role for emotion regulation in prosociality (De Waal & Preston, 2017; Decety & Jackson, 2004).

Interestingly, regulating the other person in distress resulted in a similar reduction of own distress as in self emotion regulation. This finding corroborates a study by Niven and colleagues (Niven et al., 2012), in which regulating the emotions of another person did also increase the regulator's well-being. Thus, regulating another person can have considerable benefit for the self. An interesting additional observation was made by Martínez-Íñigo and colleagues (Martínez-Íñigo et al., 2015), who compared subjects regulating others' emotions while receiving positive and negative feedback about their performance. Decreasing other's suffering was here associated with *higher* personal distress (emotional exhaustion) in the regulator after negative feedback compared to positive feedback, suggesting that a benefit for the regulator is facilitated only if the act of regulation is seen as being effective for the other person.

Intriguingly, although the literature and our own findings highlight the costs of compassionate feelings for personal distress, changing the role from a passive observer to an active regulator/helper seems to counteract these "costs", benefiting both the target and the regulator. This resembles other characteristic mammalian altruistic behaviors (such as targeted helping, consolation or reassurance behaviours) where while helping the target the carer also benefits (De Waal & Preston, 2017). We speculate that those benefits for own stress reduction represent an adaptive mechanism of social emotion regulation beyond the more obvious mechanisms of prosociality and social cooperation.

*Neuro-physiological mechanisms of self & other emotion regulation*

FMRI analyses yielded common activation for self and other emotion regulation in a widespread brain network including dorso-lateral and dorso-medial prefrontal cortex, inferior frontal gyrus, supplementary motor area, as well as basal ganglia and other temporal and occipital cortex regions (see table 1), which is in line with recent quantitative meta-analyses of emotion regulation (Frank et al., 2014; Kohn et al., 2014; Morawetz et al., 2017). These findings are compatible with the view of emotion regulation as a large scale distributed process, emerging from the global interaction of different network modules (Brandl et al., 2018; Kohn et al., 2014).

While regulating one's own versus another person's emotions specifically activated the right MTG, regulating another person versus the self was associated with higher activation in the precuneus and left TPJ, brain regions widely associated with social cognition, i.e., the differentiating between self and other and the understanding of other persons' mental states (Kanske et al., 2016, 2015; Schilbach et al., 2012; Valk et al., 2016). Thus, the specific contribution of those brain areas in social emotion regulation might hint towards those operations during the task. In fact, the same brain regions, i.e., precuneus and TPJ, have been found in previous studies contrasting other versus self regulation (Hallam et al., 2014; Xie et al., 2016), in line with the notion of social regulation as a combination of socio-cognitive and emotion regulation processes (Reeck et al., 2016). The overlap of neurosynth meta-analytic maps for both processes further lends support for this notion (Figure 4).

Interestingly, a covariation analysis showed that for this specific activation of other versus self emotion regulation, the precuneus and left TPJ activation were associated with lower emotional distress as indicated by associations with both distress ratings and skin conductance responses, pointing towards a role beyond social cognition, i.e., in regulation of emotions of others. In support of that interpretation, a PPI analysis found that during the regulation of others the precuneus showed increased functional connectivity with several parietal brain areas that have shown to be involved in regulating own and others' emotions such as the primary somatosensory cortex, including the left superior parietal lobule and supra-marginal gyrus (Frank et al., 2014; Hallam et al., 2014; Kohn et al., 2014; Morawetz et al., 2017; Reeck et al., 2016; Xie et al., 2016). Our additional brain-SCR covariation analyses provide further support for the role of parietal cortices in emotion regulation, especially in social regulation (Table 2). Interestingly,

decreased functional connectivity was shown for the precuneus with various social cognition regions such as the bilateral STG and left lingual gyrus, which seems to speak for a specific role of the precuneus in emotion regulation rather than understanding mental states when regulating others. Interestingly, very recent evidence seems to support this notion: a behavioral-fMRI study demonstrated that precuneus activation and connectivity with parietal regions are associated with self emotion regulation (Loeffler et al., 2018), and several studies have shown its involvement in self-related emotion appraisal (Alcalá-López et al., 2017; Riedel et al., 2018), besides its known role in social cognition (Kanske et al., 2016, 2015; Schilbach et al., 2012; Valk et al., 2016). In fact, precuneus' emotion regulation effects could be explained by its privileged afferent anatomical connections with the parietal lobule, anterior cingulate cortex, supplementary motor area, as well as basal ganglia (Cavanna & Trimble, 2006; Buckner & DiNicola, 2019), all known regions involved in emotion regulation (Frank et al., 2014; Kohn et al., 2014; Morawetz et al., 2017). In sum, during social regulation, the precuneus' functional connectivity profile might favor emotion regulation through engaging somatosensory/parietal mechanisms, in this way enabling self regulation in the context of regulating another person. At the brain level, our findings could speak in favor of shared neural representations for regulating the self and others, as it has been shown for many other socio-emotional capacities, like empathy and mentalizing (Lamm et al., 2011; Lombardo et al., 2010).

### *Implications for clinical psychology and medicine*

The finding that engaging in social emotion regulation can help to alleviate personal distress may have implications for the understanding and treatment of disorders involving dysfunctions in emotion regulation as well as empathy and compassion, respectively. For example, individuals with borderline personality disorder (BPD) have been characterized by a dysfunction in empathy and misinterpretation of social signals (Dziobek et al., 2011; Roepke, Vater, Preißler, Heekeren, & Dziobek, 2012), which adds to the well-known emotion dysregulation (Ruocco, Amirthavasagam, Choi-Kain, & McMain, 2013), and in turn leads to high personal distress in the context of social interactions. A paradigmatic case occurs in romantic relationships. Here it has been shown that when facing their partners' intense emotions, a person with BPD reacts with high personal distress and dysfunctional interactive behaviors, such as higher hostility, lower attentive-

listening to and decreased closeness to their partner (Miano, Grosselli, Roepke, & Dziobek, 2017). One potential way of reducing stress in those situations may lie in directing attention to alleviating the partner's stress rather than just focusing on the self. Current therapeutic approaches, like dialectical behavioral therapy, are teaching interpersonal effectiveness and distress tolerance as skills for dealing with interpersonal distress (Linehan, 1993), although they do not explicitly consider training in social emotion regulation for these patients.

Our data showed that especially high compassionate individuals show personal distress when witnessing and regulating others in suffering. Thus, the findings might be relevant for individuals of certain professions, which involve the exposure to others in emotional need and which involve, as part of their daily routine, engagement of compassion and sympathy such as health care providers (e.g. nurses, doctors) or social workers (Sinclair et al., 2016). Interestingly those professionals have been shown to frequently suffer from so called compassion or empathic distress fatigue (Sinclair, Raffin-Bouchal, Venturato, Mijovic-Kondejewski, & Smith-MacDonald, 2017). Concordantly, a large study found that doctors with higher trait compassion also reported higher personal distress (Gleichgerricht & Decety, 2014), thus confirming our results regarding the “costs of compassion”. This finding might seem counterintuitive given that their professions seem to involve the alleviating of others' suffering too and according to our results this could be one means of *reducing* personal distress. That being said, it is possible that taking action to alleviating other's suffering is confined to instrumental methods and physical factors, not necessarily involving and targeting the negative emotions of those individuals (e.g. a doctor performing a routinary medical interview rather than trying to alleviate emotional pain by direct personal interaction). Teaching means as to how to engage in the latter might allow health care providers to benefit from the effects shown in our study: reducing personal distress, which in part is a “cost” of compassion, through the regulation of other's negative emotions.

### *Limitations*

There are several strengths and limitations of our study. The study of social emotion regulation and its neuronal underpinnings has only relatively recently started (Hallam et al., 2014; Xie et al., 2016) and to the best of our knowledge our study to date includes the largest group of subjects, thus increasing its explanatory

power. However, among the 62 subjects, 52 were female, which might have influenced the results and reduces their generalizability given also that gender differences have been reported for empathy and emotion regulation (McRae, Ochsner, Mauss, Gabrieli, & Gross, 2008). Other contextual factors including age, race and gender of the dyad (regulators and confederates) could have potentially influenced our findings.

While our newly developed SORT paradigm was experienced as a believable interaction scenario in which participants committed to regulating their own and another person's emotions, it is a cognitively and affectively complex task. Moreover we cannot disentangle whether during social regulation subjects were indeed merely regulating their partner's emotions or also focusing on their own distress. However, differential brain activation for social versus self emotion regulation conditions and results of the disclosure interview speak in favor of the manipulation having worked. Compared to the self condition the social regulation condition could have been experienced as more stressful, given the risk of both (regulators and confederate) receiving aversive sounds. Notwithstanding, the behavioral results showed that both conditions were perceived as similarly stressful. For the future, an experimental setup allowing to concomitantly measure the distress and its reduction through social regulation of the target partner (e.g. collecting self-reported and physiological stress responses), respectively, which was not possible in the current design, would be of interest. Finally, new studies could take advantage of the SORT exploring how social emotion regulation varies accordingly in different types of social relationships (e.g. between peers, mother-infant dyads, couples) and across diverse clinical populations of known social dysfunction (e.g. borderline personality disorder, autism spectrum conditions).

## **Conclusions**

The current study sheds light on the psychological mechanisms and neural correlates of regulating own versus other's emotions. In line with previous research it showed that high levels of compassion are associated with especially high levels of personal distress in the observer/regulator. Our findings expand the current literature by showing that social emotion regulation has beneficial effects on personal distress and that the precuneus and left TPJ, areas mainly associated with the understanding of others mental states, are important mediators of reduced

distress in the observer. Thus, we provide evidence for a new approach of investigating emotion regulation linking socio-cognitive and emotional processes in real social interactions.



*Paper submitted for publication.*

## **Towards a mechanistic understanding of mindfulness-based stress reduction (MBSR) using an RCT neuro-imaging approach: Effects on self and other emotion regulation.**

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Although much research has shown that mindfulness-based interventions (MBIs) can reduce psychological stress, it is not clear if effects generalize to everyday social situations, which range among the largest stress triggers. Furthermore, mechanisms of MBIs have not been fully established. Emotion regulation (ER) has been suggested as one key mechanism, yet it is debated if cognitive reappraisal or acceptance strategies are targeted primarily. To address these questions, a neuroimaging-based randomized controlled trial (RCT) was performed, comparing mindfulness-based stress reduction (MBSR) with a reading/listening intervention (READ), using established empathy measures and a novel dyadic paradigm for self and other emotion regulation under stress as primary outcome on behavior and brain levels (clinicaltrials.gov NCT03035669). Compared to READ, MBSR led to self-reported stress reduction through cognitive reappraisal when regulating self and other and through acceptance only when regulating own stress. Concomitantly, MBSR led to increased brain activation over time for regulating own (temporal-, parietal-, insular cortices) and others' (precuneus, TPJ) emotions through acceptance and reappraisal, albeit this effect was also seen for the reading intervention for regulating own stress via reappraisal. Brain changes scaled positively with subjective stress reduction and amount of meditation practice. Interestingly, more distant generalization effects of MBSR on socio-emotional functioning (cognitive empathy and compassion) could not be shown. This study identified both cognitive reappraisal and acceptance as two ER mechanisms of MBSR and showed that effects extend in a graded manner from self to social settings.

## **Introduction**

Mindfulness based interventions (MBIs), have shown benefits in mental health outcomes, including reductions in psychological distress (such as depressive and stress symptoms) and an increase in well-being, in healthy and clinical populations (Goldberg et al., 2018; Madhav Goyal et al., 2014). MBIs are time-limited (8 weeks) systematized group interventions teaching mindfulness, i.e., the non-judgmental

awareness of the present-moment experience (Kabat-Zinn, 2005), through different meditation practices, body awareness, yoga and psycho-education elements (Shonin et al., 2013). Despite their widespread use, underlying mechanisms have not been fully established. Scholars have proposed that MBIs exert their effects through self-awareness, attention, and emotion regulation (Tang et al., 2015). Although primarily effecting self-related processes, it has recently been suggested that MBIs might also influence social functioning, such as increasing empathy, i.e., the concern for others in distress (Luberto et al., 2018), for example through targeting individual level processes crucial for social interactions, like emotion regulation.

Emotion regulation (ER), the capacity to modulate own emotional states (Gross, 1998), is thought to be one of the key active ingredients underlying the effects of MBIs. In fact, behavioral and brain imaging studies have shown preliminary evidence that MBIs can increase self ER and induce neuroplastic changes in respective neuronal circuits (for reviews cf., Guendelman et al., 2017; Chiesa et al., 2013). ER capacity might be especially important in social situations (Dimitroff et al., 2017; Engert, Linz, & Grant, 2018), because when facing other people in distress, individuals do not only have to manage their own stress, but also often engage in regulating others' negative emotional states, which has been referred to as social or other emotion regulation (Niven et al., 2009; Zaki & Williams, 2013).

From the perspective of mental training and therapeutic interventions there is an imperative need to define MBIs' active mechanisms in order to establish functional targets, i.e., specific psychological constructs, to further generalize and adapt their applicability to specific populations (Katz, Shah, & Meyer, 2018; Schnell & Herpertz, 2018). For the case of ER mechanisms, learned capacity needs to be translated into the acquisition of specific ER strategies such as cognitive reappraisal or acceptance. Identifying respective putative brain correlates of these mechanisms can assist this endeavor of identification (Morawetz et al., 2017; Zilverstand, Parvaz, & Goldstein, 2017). Study results on specific ER strategies, however, have been heterogeneous. While some recent studies have shown that MBIs enhance ER through the acquisition of *cognitive reappraisal*, i.e., the capacity to change the cognitive frame of a stressful stimuli (Garland et al., 2011, 2015, 2017), others have provided evidence that *acceptance*, i.e., the capacity to tolerate the experience of emotional stress without reacting on it, is the main

targeted ER mechanism (Britton et al., 2017; Lindsay, 2018; Lindsay & Creswell, 2017, 2019).

Furthermore, regarding social functioning, there is contradictory evidence whether MBIs actually increase empathy and prosociality (Luberto et al., 2018), or not (Hildebrandt et al., 2017; Kreplin et al., 2018; Trautwein, Kanske, Böckler, & Singer, 2020). To date, longitudinal studies investigating different ER strategies and considering ER in social contexts, which allow causal inferences to be drawn, are lacking.

Previous longitudinal functional brain studies have shown across different emotion-processing tasks that MBIs increase activation in areas like the prefrontal and cingulate cortex, anterior insula and hippocampus (Gotink et al., 2016; Guendelman et al., 2017; Young et al., 2017) – regions that have been linked to self ER (Kohn et al., 2014; Morawetz et al., 2017). Interestingly, other studies have highlighted activation gains in parietal cortex regions (i.e. including precuneus) (Goldin & Gross, 2010; Goldin et al., 2013), a node that appears to be sensitive for other ER (Hallam et al., 2014; Reeck et al., 2016). Nevertheless, none of these brain studies have directly compared cognitive reappraisal and acceptance as ER strategies, or its generalization to stressful social interactions. While neuroimaging studies can help in elucidating active and efficacious mechanisms of MBIs, no randomized controlled trial (RCT) exists as of yet that has investigated if brain changes through MBIs are induced in a dose-dependent manner by meditation practice and how neuroplasticity and subjective stress reduction are related, both of which would serve as evidence for the usefulness of brain read-outs as endpoints in MBIs. Finally, regarding further application of MBIs in the context of precision medicine, it remains unclear if brain activation pre- intervention can assist in the prediction of individuals' treatment outcomes. Thus, in the current study we sought to address those questions with an RCT including pre/post intervention functional neuroimaging focusing on the effects on stress reduction through emotion regulation.

Although the immediate stress-reducing effects of MBIs are well documented and subjective questionnaire reports seem to support that stress reduction generalizes into everyday life, evidence is lacking for this effect in actual distressing encounters with other individuals. In the current study, using a novel ecologically valid interactive task, we sought to ascertain whether MBIs can i) increase the capacity of

regulating emotions in self and others while experiencing a stressful interaction, and ii) induce functional neuroplastic changes in respective neuronal correlates.

More specifically, in the present study we investigated the effects of mindfulness based stress reduction (MBSR) on self ER and brain functioning using acceptance and cognitive reappraisal strategies. To ascertain if MBSR effects on ER extend to social contexts, we furthermore investigated its effects on other ER. Finally, in an effort to elucidate distant generalization effects of MBSR on socio-emotional functioning, we investigated the effects of the intervention on cognitive and emotional empathy. We hypothesized that MBSR, compared to an active control intervention, would: 1) increase the capacity for self ER and other ER as manifested in lower stress levels, using cognitive reappraisal and acceptance and 2) lead to higher brain activation in crucial regions for self ER (e.g. pre-frontal and parietal areas) and other ER (e.g. parietal and temporal areas) (primary outcome measures). 3) We furthermore sought to ascertain if at more distant socio-emotional levels, MBSR increases cognitive and emotional empathy (secondary outcome measures).

## **Materials and Methods**

### *Participants:*

Healthy subjects were recruited from the general population in the city of Berlin, Germany. Of 550 subjects assessed for eligibility, 484 were excluded (293 did not meet inclusion criteria, 189 declined to participate upon getting full study information). The remaining 68 were randomly assigned to either experimental (MBSR, n=34) or control group (READ, n=34; figure 1 CONSORT flow). Groups did not differ in gender, age or education (table S0). fMRI assessments were acquired at baseline (T1; MBSR (n=30), READ (n=29)) and post intervention (T2; MBSR (n=29), READ (n=26)).

### *Procedure:*

The study was advertised as a trial comparing the effects of two mental health interventions, through different procedures (e.g. posters, flyers, emails, etc.). Recruitment included online and in-person screening, exclusion criteria were history of neurological or psychiatric disorders, non controlled medical condition,

current use of psychoactive drugs, non-fluent German level, previous experience with meditation or yoga. Inclusion criteria included: commitment and capacity for performing daily homework (30 to 45 minutes) assignments during 8 weeks, normal or corrected-to-normal vision and absence of any contra-indication criteria for performing an fMRI experiment (list of inclusion/exclusion criteria in supplementary materials 1). Subjects received the interventions free of cost, and received a monetary reimbursement for study participation. People initially allocated to the READ group received the MBSR after the last assessment. Subjects were randomly assigned using a stratified procedure (with an in house Excel script), first allocating equal number of male subjects to each group, in order to secure gender proportion in both arms of the trial. A higher rate of female participants is a well-known selection bias in MBI trials (Macinko & Upchurch, 2019).

*Sample size, power, and outcomes:*

The study was preregistered at clinicaltrials.gov (id# NCT03035669). Given that the intention of the study was to establish mechanisms behind MBSR, the primary outcome measure of the trial was defined as functional brain changes in emotion regulation regions, as measured by significant longitudinal changes in the BOLD (blood oxygenated level dependent) signal. Based on MBSR functional brain correlates and the differential neuro-cognitive mechanisms involved in self and other ER, for MBSR compared to READ, we expected higher brain activation over time in pre-frontal, parietal and insular brain regions for self ER, and higher brain activation over time in parietal and temporal brain regions for other ER. Effect sizes for brain activations using emotion induction paradigms have been reported ranging from small to medium, contrasting emotion elicitation and baseline-resting conditions (e.g. Cohen's  $d=0.6$  for amygdala activation, Chang et al., 2015). Using G\*Power 3.1 we estimated a sample of 52 subjects (26 per intervention) would be able to detect an intermediate effect size (Cohen's  $d=0.4$ , power > 0.80,  $\alpha = 0.05$ ) using a repeated-measures ANOVA with within-between interactions. Given reported attrition rates (Carmody & Baer, 2008) and expected potential incompatibilities with scanner procedures (assuming a 20% attrition rate per group), a total of 64 subjects were enrolled in order to ensure 52 completers (see power analysis protocol in supplementary materials 2).

All participants provided written informed consent; the study was approved by the

ethics committee of the Humboldt-Universität zu Berlin and was carried out in accordance with the guidelines of the declaration of Helsinki.

### *Interventions:*

The MBSR consisted of a course with eight weekly group meetings of 2.5 hours, a 1-day meditation retreat, and daily home practice of approx. 45 minutes (meditation or yoga practices with audio-guided recordings). Subjects received training in different formal meditation techniques (body scan, mindful-awareness, etc.), informal meditation practices (e.g. mindful eating), yoga exercises, and psycho-education (e.g. how to approach emotional stress with mindfulness techniques). Audio-meditations were stored in a secure web-platform, daily entrance was registered and individual home meditation practice measured. The MBSR was led by an instructor with more than 10 years of experience in teaching meditation courses.

The READ group was specifically designed to match the non-specific factors of the MBSR (e.g. expectation, guidance by instructor, group support, daily assignments). It consisted of a course with eight weekly group meetings of 2.5 hours, a 1-day intensive reading and sharing session, and daily home assignment of approx. 45 minutes (audiobook listening). Subjects received instruction in different literature styles (fiction, myth, poetry, etc.), and performed different reading and sharing exercises during the meetings (e.g. reading load, dyadic exchange, commenting and discussion), and psycho-education regarding the benefits of reading and sharing groups. Audio books were retrieved directly at Audiobooks web, daily entrance were registered and individual time listening measured. The READ group was lead by an instructor with more than 10 years of experience teaching language and literature courses.

Concerning adherence, the overall mean practice was 30.2 hours (8.86 SD) for the MBSR group, resulting in 32 minutes of practice per day, and 34.1 hours (9.46 SD) for the READ group, resulting in 36 minutes of practice per day after excluding four outliers, which exceeded 3 standard deviations. There was no difference in mean groups practice (T-test  $t_{1-49} = 1.50$ ,  $p = .140$ ).

### *Assessments:*

As part of the overall trial, subjects underwent several psychological



questionnaires, behavioral tasks and brain imaging measurements before and after the intervention. In this publication we report the results from the neuroimaging experiment and the empathy task, corresponding to the pre-registered primary and secondary outcomes of the RCT.

Participants performed the Self-Other Emotion Regulation Task (SORT) in the MRI scanner on day one and subsequently completed the Multifaceted Empathy Test (MET) during the coming days. On the days of the fMRI experiments (before and after the intervention), subjects were required to arrive at the neuroimaging center 1 hour before the start of the session. Before the scanning session started, subjects were required to stay in a waiting room, where for 15 minutes they met and talked to an unknown confederate, who was introduced to them as their partner for the experiment. Both subjects were treated as real participants by the scientific team and were told that they were going to do the same task together, one in the scanner and one outside of it. Both were given the instructions of the experiment and completed a trial version of the paradigm before performing the actual task in the scanner. Given that randomization of subjects occurred after the pre-intervention measurements, experimenters and operators were blind to a subject's group.

#### *Emotional and Cognitive Empathy:*

Subjects completed the Multifaceted Empathy Test (MET), a validated behavioral task that dissociates cognitive and emotional empathy components by showing pictures of people in emotionally laden situations and asking subjects to answer sets of questions on these pictures (For details about the task, see: Dziobek et al., 2008; Foell, Brislin, Drislane, Dziobek, & Patrick, 2018). For this study we used a modified version of the emotional empathy part, assessing compassion and sympathy, respectively, for the depicted individuals by asking the subjects “How much compassion do you have for this person?” for negative pictures and “How happy are you for the person?” for positively valenced pictures. For the cognitive empathy part, participants were asked to select the corresponding emotional state of the depicted person out of a set of four possible answers.

#### *Self-Other Emotion Regulation Task (SORT):*

In the SORT subjects were requested to alternate between self ER (regulating themselves in the scanner) and other ER (regulating the emotions of the



confederate outside of the scanner) while both looked simultaneously at aversive pictures. Participants had to apply ‘reappraisal’ and ‘acceptance’ as emotion regulation methods and ‘permitting’ of any emotional state as a baseline condition. The strategies were implemented through the verbalization of unique sentences that appeared on the photos for both self ER and other ER conditions (reappraisal: “This is just a photo!”; acceptance: “Gently accept!”; permit: “Permit the reaction!”). Subjects were demanded to not only read the sentences, but to actively apply and engage with the strategies to down-regulate or permit, respectively, their and their partner’s current negative emotional states. Participants were required to communicate the strategy through a microphone during the first 2 seconds of the picture presentation, in order to standardize the strategy implementation across subjects and conditions. For self ER conditions, subjects self-instructed aloud the strategies as means for reducing own distress. For other ER conditions, participants used the strategies as means for reducing the other’s current distress; subjects were told to “have the other in mind” while regulating them. During the permit conditions subjects were asked to allow any emotional reaction and to refrain from regulating, i.e., decreasing or increasing stress for them self or the confederate.

Participants were instructed that their autonomic activation (measured via heart rate) was constantly monitored along the experiment and that if they were unsuccessful to regulate their stress, an aversive sound could appear at the end of each block. A pumping red dot, which was displayed on the bottom of the screen (see figure 2), allegedly indexed the arousal state of the participant in the scanner during self ER trials.

A pumping red-yellow dot allegedly indexed the arousal state of the person outside of the scanner during trials for other regulation (other ER), offering online information regarding the other’s autonomic state to the regulator. Participants were informed that during these trials, if they were unsuccessful in regulating the other (quantified by autonomic activation), the aversive sound would appear for both subjects. They were told that no aversive sound would appear during the permit conditions, and that self reported stress ratings had no effect on the likelihood of getting the aversive sound. At the beginning of the scanner session, the volume of the aversive sound was adjusted for each participant to a tolerable level. For standardization purposes every subject was randomly assigned to receive

a fixed number of 3 to 5 aversive sounds during the whole experiment (see supplementary materials table S1 for more details). From the participant's perspective, the aversive sound was delivered in a performance dependent way and operated as a negative feedback to the regulators, adding volitional effort to regulate and decreasing habituation to negative events throughout the task.

The pictures of the SORT were taken from the international affective picture system (IAPS; Lang et al., 2008), and included negatively valenced pictures (of high and low arousal) and neutral pictures (cf. supplementary materials table S2, for a list of pictures). The experiment had a block event-related design with 4 blocks for each condition (a total of 24 blocks). Every block started with a 6 second initial screen indicative of the block type e.g. "Regulate the other using Reappraisal", followed by the interspersed presentation of 6 pictures (2 neutral, 2 negative high arousal, 2 negative low arousal) for 6 seconds each. After every picture participants had 4 seconds to rate their own stress level. At the end of each block a fixation cross (with a jittered duration of 12-5900 ms, these values were generated with an in house MatLab script) was presented, during this period the aversive sound could appear (See figure 2). Overall, the experiment attempted to mimic real life situations in which one person regulates another person's emotional state, actively adapting her performance through both the dynamic information from the other (arousal index, i.e., red/yellow pumping dot) and the tailored aversive sounds. In line with Schilbach et al., 2013 experimental accounts for second-person neuroscience, our experiment entails a structured interaction (beyond a passive stimulus exposure), an emotional engagement of the participant (regulators have to actively modify other's and own distress), while only one individual is being measured (instead of two).

#### *Data acquisition and preprocessing:*

Brain images were acquired with a Siemens 3 Tesla Trio scanner, with a 32-channel head coil. Structural brain images were obtained with an MPRAGE (Magnetization-prepared rapid acquisition gradient echo) sequence (1×1×1 mm resolution), with TE=2.52 ms, TR=1900 ms, flip angle=9° and 100% field of view. During the experimental task, whole brain T2\*-weighted functional images were collected with the standard EPI (Echo-Planar Imaging) sequence for fMRI, with TE=30 ms, TR=2000 ms, flip angle=90°, field of view 100%, using an acquisition matrix=64 x 64 x 33 slices, slice thickness of 3.75 mm, with descending slice acquisition, a total

of 1050 volumes were acquired per subject for every session.

Data pre-processing and analysis were implemented with FSL 6.0 version (FMRIB's Software Library, [www.fmrib.ox.ac.uk/fsl](http://www.fmrib.ox.ac.uk/fsl)). A Gaussian kernel of 5mm (FWHM) for spatial smoothing and high-pass filter with a cutoff of 100 s was applied for every image. FLIRT was used for registration of functional EPI images to high-resolution structural MPAGE images (using boundary-based registration -BBR) and to standard space images (MNI\_152, 2 mm resolution) using affine linear transformation with 12 degrees of freedom (Jenkinson & Smith, 2001).

Head motion correction was performed using rigid-body transformations based on a linear registration tool (Jenkinson et al., 2002). A quality control of the mean frame displacement, signal to noise ratio and standard deviation of signal over voxels was performed for each subject. From these, two participants (one per group) were discarded due to excessive movement (mean absolute displacement >1.5 mm).

#### *Data analyses:*

#### *Inferential statistics:*

Behavioral data analyses and null hypothesis significance testing (NHST) using standard cutoff *p-values* of 0.05 was performed using IBM SPSS Statistics software, version 25. Additionally, as suggested somewhere else, to complement the classical NHST, we implemented a Bayesian inferential approach, calculating a Bayes factor concordantly for every NHST alongside the results (Quintana & Williams, 2018). In brief, the Bayes factor ( $BF_{10}$ ) is the ratio between the marginal likelihoods of the null model and the alternative model, representing the degree of confidence that both distributions are indeed different. In the same value it assess, in a dimensional way, if data conveys evidence (and its degree) in favors of the alternative or the null model (Quintana & Williams, 2018). For interpretation purposes, a  $BF_{10}$  over 3 index positive/moderate evidence in support of alternative model;  $BF_{10} > 10$  implies strong evidence for the alternative, and  $BF_{10} > 30$  very strong evidence. A  $BF_{10} < 0.33$  index positive/moderate evidence in support of the null model (Jarosz & Wiley, 2014). (Corresponding marks:  $BF_{10} > 100 = ^{^^}$ ;  $BF_{10} > 10 = ^{\wedge}$ ;  $BF_{10} < .33 = \#$ ). These analyses were performed with JASP, version 0.9.1, University of Amsterdam.

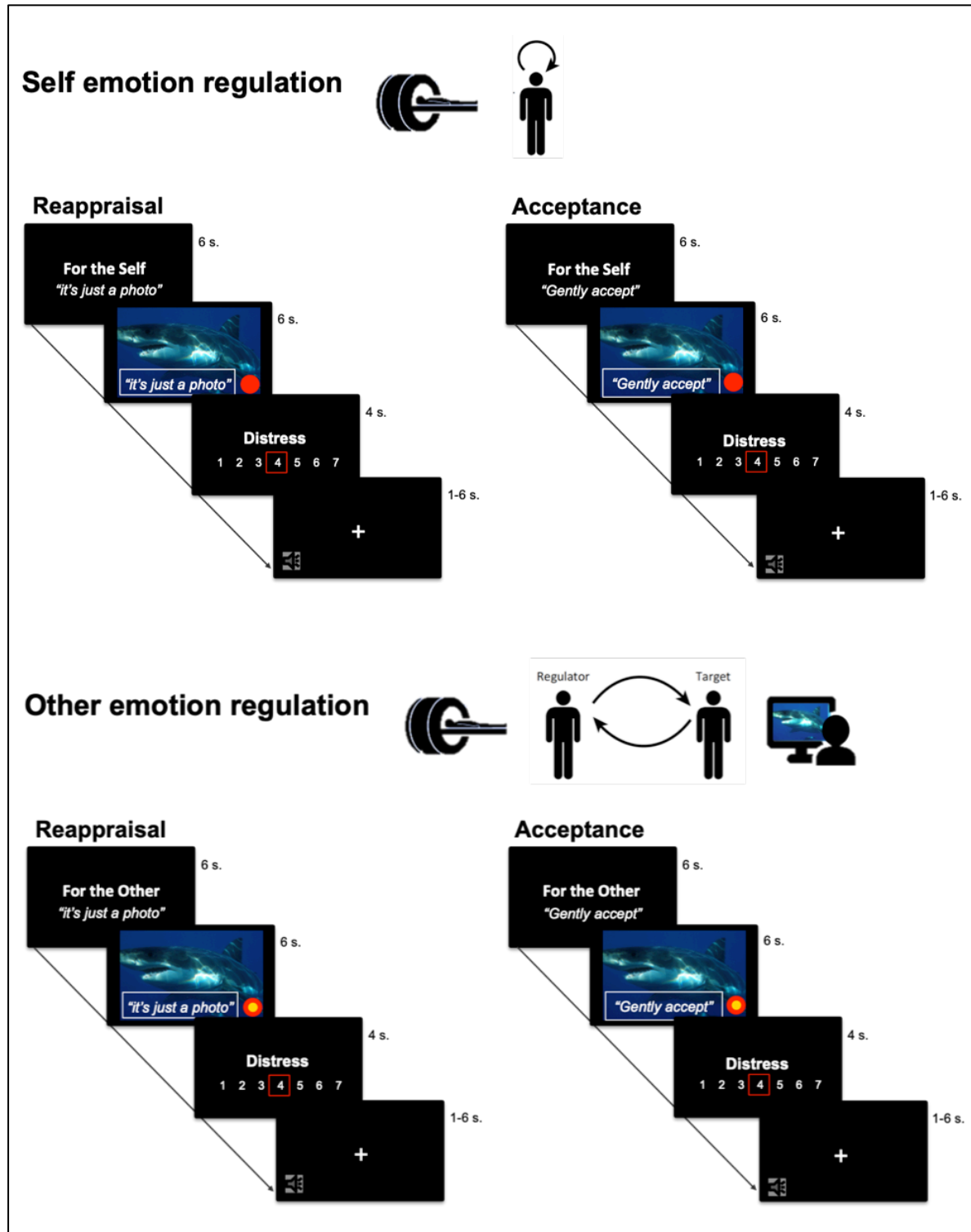


Figure 2: Schematic representation of the SORT experimental set-up in the fMRI scanner. In the experiment, the subject in the scanner (the regulator), alternates between two strategies (cognitive reappraisal vs. acceptance) and foci (self vs. other person), resulting in four conditions: *self emotion regulation via cognitive reappraisal* ("it's just a photo"), *self emotion regulation via acceptance* ("gently accept"), *other emotion regulation via cognitive reappraisal* ("it's just a photo"), *other emotion regulation via acceptance* ("gently accept"). (Manikin figures are adapted from Reeck et al., 2016)

*Behavioral data:*

To estimate the effects of the MBSR compared to the READ group on emotion regulation skills, measured as stress levels during the SORT, a 2 (pre vs. post intervention) x 2 (group: MBSR vs. READ) repeated measures ANOVA, followed by posthoc pairwise comparisons with Holm's corrections was performed. This procedure was performed for all 4 conditions of the experiment (self ER using reappraisal and acceptance, other ER using reappraisal and acceptance), and for the baseline conditions (permit for the self and the other condition); these results are reported in the supplementary material (fig. S1).

Regarding the MET, behavioral responses including intensity of prosocial feelings (compassion and sympathy) and accuracy of cognitive empathy were analyzed as of means of score ratings and the sum of correct answers, respectively. To compare the effect of both groups, a repeated measures ANOVA with a within factor, 2 x Times (T1 vs T2), and a between factor, 2 x Groups (MBSR vs READ) was performed with every component of the MET.

Alongside every standard ANOVA, a Bayesian repeated measures ANOVA was performed, using default options for Prior, of  $r$  scale fixed effects of 0.5,  $r$  scale random effects of 0.5,  $r$  scale covariates of 0.354 (Quintana & Williams, 2018).

*fMRI:*

Preprocessed images from T1 and T2 assessments were entered into a general linear model (GLM) for statistical analysis. A first level analysis at the individual level included regressors for each experimental condition (4 conditions of interest, self ER with reappraisal and acceptance, other ER with reappraisal and acceptance) convolved with the canonical hemodynamic response function.

Second level statistics with a two factors (group and time) GLM were performed with FLAME-1, using mixed effects modeling for all first-level analyses (as fixed effects), in this way accounting for within subjects correlations (Worsley, 2001). Contrasts of interest included the effects of each experimental condition. Whole-brain analyses were thresholded using permutation tests (with 5000 CIs) and corrected for multiple comparisons with threshold-free cluster enhancement (TFCE) thresholded at  $1 - \alpha (0.05) * 100 (0.95 - 1)$ , equivalent to a Family-wise Error correction (FWE) of  $< .05$ .

This method uses permutations for estimating 5000 confidence intervals based on observed data, this approach is meant to be an unbiased way to define cluster-like structures, while maintaining voxel-wise information. For every experimental condition, parameter estimates (PE) were extracted for brain regions showing group by time interactions (TFCE-clusters) with a voxel volume size larger than 10  $k$ . Finally, to disentangle the directionality of the effect, planned post-hoc two-sided T test comparing within group changes in PE over time were performed, using false-discovery rate (FDR) adjusted  $p$  values accordingly for every analysis. Cohen's  $d$  and Bayesian paired samples T test with a default prior Cauchy distribution of 0.707 were also calculated. Obtained  $p$  values, effect sizes, and Bayes factors are informed in the supplementary materials tables S3, S4, S5, S6. .

*Covariation analyses of home practice and brain activation changes:*

In order to elucidate the relationship between home practices adherence and brain activation changes over time and how it differs between groups, a covariation analysis (ANCOVA) using group as the predictor, home practices (in hours) as covariate, and change score ( $T_2 - T_1$ ) of the PE as the dependent variable was performed. PE's were taken from main brain region (larger cluster size) showing group by time interaction effects, for each condition. A Bayesian ANCOVA, comparing the models *group + hours of practice* versus only *group*, complemented the overall analyses.

*Covariation analyses of brain activation changes and gains in emotion regulation:*

To further identify the relationship between brain training effects and gains in ER skills over time, and how it differs between groups, a covariation analysis (ANCOVA) using group as the predictor, PE change score ( $T_2 - T_1$ ) as covariate, and change score ( $T_2 - T_1$  stress ratings) of the SORT as the dependent variable was performed. PEs were extracted from the brain regions with largest cluster sizes showing group by time interaction effects, for each condition. A Bayesian ANCOVA, comparing the models *group + brain gains* versus only *group*, complemented the overall analyses.

*Association of functional brain activation at baseline and gains in other emotion regulation:*

To estimate the diagnostic relevance of pre-intervention functional brain activation in predicting gains in other ER skills after MBSR, PE's of targeted brain regions (showing group by time interaction effects for other ER) at T1 and the change score of the stress ratings ( $T2 - T1$ ) of the SORT were associated using linear regression models. A Bayesian linear regression, comparing the alternative versus the null models complement the analyses. (Supplemental material is available on a *pdf file* in the memory stick device).

## Results

### *Manipulation check:*

After completing the experiment and assessments at T2, individual interviews for debriefing of the cover story and manipulation check were performed, confirming that all participants believed that the second person (the confederate) outside the scanner was indeed performing the experiment with them, and that they actively tried to regulate the second person during the experiment.

### *Behavior:*

#### *Effects of MBSR versus READ on self-reported stress levels during self and other emotion regulation in the SORT:*

For self ER using reappraisal, the repeated measures ANOVA resulted in a significant group by time interaction ( $F_{1,53} = 6.84$ ,  $p = .012$ ,  $\eta^2_p = .114$ ). Post-hoc planned comparisons showed decreased stress ratings over time only within the MBSR group (corrected  $p < .001$ ) but not in the READ group (corrected  $p = 1$ ), Bayes factor confirmed positive moderate evidence for the alternative model ( $BF_{10} = 4.78$ ; figure 3a).

For self ER with acceptance, the repeated measures ANOVA yielded a significant group by time interaction ( $F_{1,53} = 5.26$ ,  $p = .026$ ,  $\eta^2_p = .090$ ), post-hoc planned comparisons revealed increased stress ratings over time within the READ group (corrected  $p < .05$ ) but not in the MBSR group (corrected  $p = 1$ ), Bayes factor confirmed positive weak evidence for the alternative model ( $BF_{10} = 2.75$ ; figure 3b).

For other ER with reappraisal, the repeated measures ANOVA resulted in a significant group by time interaction ( $F_{1,53} = 4.07$ ,  $p = .049$ ,  $\eta^2_p = .071$ ), post-hoc planned comparisons showed decreases in stress ratings over time only within the



MBSR group (corrected  $p = .05$ ) and not in the READ group (corrected  $p = 1$ ), Bayes factor confirmed weak evidence for the alternative model ( $BF_{10} = 1.38$ ; figure 3c).

For other ER with acceptance, the repeated measures ANOVA yielded no group by time interaction ( $F_{1,53} = 2.66$ ,  $p = .109$ ,  $\eta^2_p = .048$ ), Bayes factor confirmed no evidence for the alternative model ( $BF_{10} = 0.68$ ; figure 3d).

As for the baseline conditions, for both permit in the self and other condition the repeated measures ANOVA yielded no group by time interaction, but a main effect of time (see supplementary materials fig. S1), suggesting higher stress ratings for both groups during the T2 assessment.

*Effects of MBSR versus READ on emotional and cognitive empathy using the MET:*

The repeated measures ANOVA yielded no group x time interactions for cognitive empathy ( $F_{1,56} = .542$ ,  $p = .465$ ,  $BF_{10} = 0.36$ ), nor for sympathy – emotional empathy for positive scenes ( $F_{1,56} = .304$ ,  $p = .558$ ,  $BF_{10} = 0.38$ ), or for compassion – emotional empathy for negative scenes ( $F_{1,56} = .092$ ,  $p = .762$ ,  $BF_{10} = 0.27$ ). Bayes factor confirmed no evidence for the alternative model (group x time interaction effects).

## ***fMRI***

*Effects of MBSR versus READ on functional brain correlates for self and other emotion regulation:*

For self ER with reappraisal, the two factors GLM (on single contrast Self ER REAP) did not reveal a group by time interaction, but a significant main effect of time in the left superior parietal lobule (SPL), left superior lateral occipital cortex (LOC-sup), and intracalcarine cortex (table 1). Follow up comparisons evidenced increased brain activation over time for the MBSR and READ groups (table 1).

For self ER with acceptance, the two factors GLM (on single contrast Self ER ACCEPT) yielded a significant group by time interaction in the left middle temporal gyrus (MTG), right SPL, right opercular cortex-anterior insula (OC-AI), among others (fig. 4). Planned follow up comparisons revealed significant increased brain activation over time in these regions in the MBSR group, with intermediate to large effect sizes, and strong to extreme evidence for the alternative model (fig. 4, table

2). In the READ group, only one region (PCC) showed significant reduction in brain activity over time, remaining regions mostly showed moderate evidence for the null model (table 2).

For other ER with reappraisal, the two factors GLM (on single contrast Other ER REAP) resulted in a significant group by time interaction including the left precuneus, right temporo-parietal junction (TPJ), right angular gyrus among others (fig. 5). Planned post hoc comparisons showed significantly increased brain activation over time in these regions in the MBSR group (with FDR-p values), with intermediate to large effect sizes, and moderate to extreme evidence for the alternative model (fig. 5, table 3). The READ group did not show brain changes over time (table 3).

For other ER with acceptance, the two factors GLM (on single contrast Other ER ACCEPT) yielded a significant group by time interaction in the right supra-marginal gyrus (SMG), right TPJ and the right precuneus (fig. 5). Planned follow up comparisons revealed a significant increase in brain activation over time in the right precuneus in the MBSR group (with FDR-p values), with small effect size and weak evidence for the alternative model (fig. 5, table 4). The READ group showed a significant decrease in brain activation over time in the right SMG and precuneus (with FDR-p values), with intermediate to large effect sizes, and moderate to extreme evidence for the alternative model (fig. 5, table 4).

*Dose effects of MBSR: Amount of home practice and brain activation changes:*

#### *Self ER with Acceptance*

The analysis of covariance comparing groups on the relationship between home practice and brain activation changes (during Self ER ACCEPT) revealed a significant effect of group (MBSR vs. READ) on left MTG activation gains when accounting for home practice ( $F_{1,45} = 14.64$ ,  $p < .0005$ ,  $\eta^2_p = .245$ ). Bayes ANCOVA showed that when controlling for group variance, home practice does not predict increased brain activation ( $BF_{10} = 0.62$ ), supporting the interaction of group and home practice on brain training effects (fig. 6).

#### *Other ER with Reappraisal*

The analysis of covariance comparing groups on the relationship between home practice and brain activation changes (during Other ER REAP) showed a

significant effect of group (MBSR vs. READ) on left precuneus activation gains when accounting for home practice ( $F_{1,45} = 7.76$ ,  $p = .008$ ,  $\eta^2_p = .147$ ). Bayes ANCOVA evidenced that when controlling for group variance, home practice does not predicts increase brain activation ( $BF_{10} = 0.35$ ), supporting the interaction of group and home practice on brain training effects (fig. 6). Bayes ANCOVA showed that when controlling for group variance, home practice does not predict increase brain activation ( $BF_{10} = 0.62$ ), supporting the interaction of group and home practice on brain training effects (fig. 6).

#### *Other ER with Acceptance*

The analysis of covariance comparing groups on the relationship between home practice and brain activation changes (during Other ER ACCEPT) showed a significant effect of group (MBSR vs. READ) on right SMG activation gains when accounting for home practice ( $F_{1,45} = 16.66$ ,  $p < .001$ ,  $\eta^2_p = .270$ ). Bayes ANCOVA showed that when controlling for group variance, home practice does not predict increased brain activation ( $BF_{10} = 0.37$ ), supporting the interaction of group and home practice on brain training effects.

#### *Effects of brain activation changes on gains in emotion regulation:*

##### *Self ER with Acceptance*

The analysis of covariance comparing groups on the relationship between brain activation changes (during self ER ACCEPT) and gains in self ER (stress level) revealed a significant effect of group (MBSR vs. READ) on changes in stress ratings when accounting for brain training effects of left MTG ( $F_{1,51} = 7.85$ ,  $p = .007$ ,  $\eta^2_p = .133$ ) (fig. 7). Bayes ANCOVA showed that when controlling for group variance, left MTG activation gains (PEs change) do not predict performance improvement in ER (stress ratings) ( $BF_{10} = 0.66$ ), supporting the interaction of group and brain changes on behavioral training effects (fig. 7a).

##### *Other ER with Reappraisal*

The analysis of covariance comparing groups on the relationship between brain activation changes (during Other ER REAP) and gains in social emotion regulation (stress level) showed a significant effect of group (MBSR vs. READ) on changes in stress ratings when accounting for brain training effects of the left precuneus ( $F_{1,51} = 4.39$ ,  $p = .041$ ,  $\eta^2_p = .079$ ) (fig. 7). Bayes ANCOVA revealed that when controlling

for group variance, left precuneus activation gains (PEs change) do not predict performance improvements in other ER (stress ratings) ( $BF_{10} = 0.33$ ), supporting the interaction of group and brain changes on behavioral training effects (fig. 7c).

#### *Other ER with Acceptance*

The analysis of covariance comparing groups on the relationship between brain activation changes (during Other ER ACCEPT) and gains in social emotion regulation (stress level) revealed a significant effect of group (MBSR vs. READ) on changes in stress ratings when accounting for brain training effects of the right SMG ( $F_{1,51} = 4.56$ ,  $p = .037$ ,  $\eta^2_p = .082$ ) (fig. 7). Bayes ANCOVA evidenced that when controlling for group variance, right SMG activation gains (PEs change) do not predict performance improvement in ER (stress ratings) ( $BF_{10} = 0.60$ ), supporting the interaction of group and brain changes on behavioral training effects (fig. 7b).

#### *Functional brain predictors of emotion regulation training effects:*

To explore functional brain markers for predicting emotion regulation gains specific for other ER, the linear regression analysis evidenced that pre-intervention right TPJ activation (during Other ER REAP) predicted lower stress levels during social regulation  $R^2 = .069$ ,  $F_{(1,52)} = 3.84$ ,  $p = .055$ , (fig. 8), i.e., the lower the activation at T1 the higher the benefits on social emotion regulation. Bayesian linear regression resulted in weak evidence for the alternative model ( $BF_{10} = 1.31$ ), offering weak support for predicting emotion regulation gains from baseline right TPJ activation.

## **Discussion**

Although mindfulness-based interventions (MBIs) have shown to be effective in numerous studies, it is not clear what mechanisms exactly underlie their stress-reducing effects and if they generalize to social situations. To address these questions, we conducted a neuroimaging-based RCT, comparing the effects of a two months mindfulness-based stress reduction (MBSR) with a reading/listening intervention (READ) on self and other emotion regulation and their neuronal correlates (as primary outcome) and empathy (as secondary outcome). We found that MBSR led to improved emotion regulation through both cognitive reappraisal

and acceptance in both self and other conditions. Complementing those results, MBSR led to increased brain activation for regulating the self (temporal-, parietal-, insular cortices) and others' (precuneus, TPJ), especially when regulating own and other's stress via acceptance. More distant social generalization effects of MBSR on cognitive empathy and compassion could not be shown. Taken together, this study identifies both cognitive reappraisal and acceptance as active ER mechanisms of MBSR and shows that effects extend in a graded manner from self to social settings.

*Effects of MBSR on socio-emotional functioning:*

The study yielded strong and specific effects of MBSR on perceived stress in situations where subjects engaged in regulating themselves, which is in line with previous research (for reviews cf. Guendelman et al., 2017). More importantly for the specific aims of this study, we also found stress-reducing effects of MBSR for situations where subjects regulated the partner. However, this was only the case when subjects used reappraisal as strategy to regulate the other. The MBSR group did not experience stress reduction when regulating the other person via acceptance, i.e., when they told the partner to gently accept the distress they were experiencing in response to the aversive pictures. We believe that this advantage of reappraisal might be due to the somewhat counterintuitive and in western cultures socially ill-accepted nature of acceptance strategies. Telling the other person to accept distress seems to indicate that the other should endure and hold that aversive emotion, which *prima facie* seems to make matters worse for that other person. It would be interesting to investigate if for individuals from cultures that embrace acceptance as a cultural norm such as Buddhist cultures (Eckman et al., 2005; Panaïoti et al., 2015), acceptance leads to a stronger stress reduction when regulating others than in individuals from western cultures.

Interestingly the MBSR group did not improve in the emotional and cognitive empathy behavioral test relative to READ, thus not supporting our secondary outcome hypothesis. This is in line with recent large empirical and meta-analytical studies (Hildebrandt et al., 2017; Trautwein et al., 2020; for a meta-analysis: Kreplin et al., 2018) that show that MBIs have no effects on empathy and mindreading. Accordingly, some studies using specifically the MBSR training have found no effect on empathy using standard self-reported measurements (Lamothe et al., 2018; van Dijk et al., 2017; for a review: Lamothe, Rondeau, Malboeuf-

Hurtubise, Duval, & Sultan, 2016). Nevertheless, meditation interventions that explicitly train compassion or perspective taking have shown to increase empathy and mindreading capacities (Hildebrandt et al., 2017; Trautwein et al., 2020).

In sum, our study provides evidence that eight weeks of MBSR can increase emotion regulation not only for oneself but also in situations where one regulates another person. This hints at some generalization of the stress-reducing effects of MBSR to social settings. Nevertheless, it remains to be shown if more distant generalization effects to socio-emotional domains can be achieved by longer application of MBSR, or with adapted programs such as compassion or communication based MBI interventions.

*Emotion Regulation as a mechanism mediating stress-reduction of MBSR: Behavior*

In an effort to elucidate stress-reducing mechanisms of MBSR, the study at hand focused on two prominent emotion regulation strategies, cognitive reappraisal and acceptance of aversive emotional states. The results showed that especially cognitive reappraisal emerged as a potent strategy to reduce stress through MBSR compared to READ, as it was effective in self ER and other ER. The MBSR program encompasses the training of cognitive reappraisal strategies (like detachment and cognitive reframing) and related processes (such as affect labeling and meta-awareness) (Dahl, Lutz, & Davidson, 2015; Vago & Silbersweig, 2012). Our positive behavioral effects are in line with previous research that has shown cognitive reappraisal gains after MBIs (18,19,20). Thus those cognitive reappraisal elements inherent in MBSR seem to be especially potent and beneficial for emotion regulation.

Acceptance as ER strategy proved to be effective only in the self condition after MBSR compared to READ, i.e., stress stayed constant over time in the MBSR group, while it increased in the READ group. We tend to interpret this as a relative benefit due to the MBSR training, as the re-exposure to the aversive experimental setting at T2 was perceived as more stressful in the non-regulation condition when subject simply permitted emotions that arose (Figure S9). Thus, this baseline increase in stress over time needs to be taken into account when interpreting directionality in the regulation conditions.

Based on self-rated stress, it seems that subjects benefited from both cognitive



reappraisal and acceptance strategies after MBSR compared to READ, although there seems to be an advantage for cognitive reappraisal. We cannot rule out, however, that those effects are partly driven by higher baseline stress levels in the MBSR group.

Regarding the clinical relevance of MBIs, disentangling active and efficient psychological mechanisms is an urgent milestone in order to support its validity as a clinical intervention (Katz et al., 2018). In line with previous research, our study evidenced the acquisition of cognitive reappraisal (Garland et al., 2011, 2015, 2017), but also of acceptance (Britton et al., 2017; Lindsay, et al., 2018; Lindsay & Creswell, 2017, 2019) as specific ER strategies involved in MBIs, identifying them as underlying psychological constructs and as potential functional targets to further generalize and extend its applicability (Schnell & Herpertz, 2018). To the best of our knowledge, this is the first RCT investigating comparatively both cognitive reappraisal and acceptance as psychological mechanisms of MBSR. However, it has also been suggested that MBSR could exert its salutary effects through targeting different cognitive mechanisms, like attention or self-awareness (Holzel et al., 2011; Tang et al., 2015), which were not assessed here. Future studies should concomitantly evaluate these mechanisms to further establish its connection to mental health benefits, but also to ER and its specific mechanisms such as cognitive reappraisal and acceptance.

#### *Emotion Regulation as a mechanism mediating stress-reduction of MBSR: Brain*

To further the understanding of active and efficacious stress-reducing mechanisms of MBSR, we applied fMRI in our subjects while they were regulating stress for self and others pre and post intervention. The results yielded widespread increases in brain activation across emotion regulation strategies as a response to MBSR versus the reading intervention in the self and other conditions, interestingly though and somewhat in contrast with the behavioral findings, this was especially evident when using acceptance as strategy to downregulate aversive emotions.

During self ER using acceptance, the results showed training effects in the MBSR versus the READ group in the temporal, parietal and insular cortices, which have previously been associated with emotion generation and regulation (Etkin et al., 2015; Frank et al., 2014; Kohn et al., 2014), but also with somatosensory and interoceptive awareness (Craig, 2009; Santarnecchi et al., 2014; Sereno & Huang,



2014). Interestingly, no prefrontal cortex regions showed effects specific to MBSR training, suggesting that acceptance as ER strategy might be implemented by a distinctive neuronal network coherent with recent quantitative meta-analyses of emotion regulation (Frank et al., 2014; Kohn et al., 2014; Morawetz et al., 2017). This is in line with the notion of acceptance as an *embodied emotion regulation* strategy (distinctive for MBIs compared to other psychotherapies), involving the engagement of sensory and interoceptive cortices but not prefrontal cortex as active substrates (Guendelman et al., 2017). Taken together, this indicates that acceptance is indeed targeted and a potent mechanism behind MBSR and that neuroimaging can independently contribute to elucidating mechanisms behind training effects.

Surprisingly, there was no brain activation gain over time in the MBSR group versus the READ group when subjects regulated themselves using reappraisal, although the behavioral results identified this strategy as active mechanism behind MBSR. We think that this result is best interpreted in the context of a strong main effect of time, which suggests that both groups MBSR *and* READ increased brain activation in a similar ER network (Table 1). We speculate that given the cognitive demands of the READ intervention, which involves reframing of a given story that is similar to the reframing inherent to cognitive reappraisal, READ might have fostered the brain's cognitive control systems. Interestingly, a previous RCT comparing an MBI and a READ group also found increased cognitive control performance and brain changes in the READ group (Allen et al., 2012).

Our results showed that MBSR compared to READ led to increased activation in precuneus, TPJ, angular and supramarginal gyrus when subjects regulated their partner using both acceptance and reappraisal. The respective brain areas have previously been associated with social cognition more generally (Kanske et al., 2016; Schilbach et al., 2012; Valk et al., 2016) and also more recently with social emotion regulation specifically (Hallam et al., 2014; Xie et al., 2016).

Our findings thus demonstrate that MBSR seems to induce neuroplasticity for emotion regulation in social settings, therefore corroborating our primary outcome hypothesis. Herein we demonstrate for the first time not only behavioral evidence for a generalization of MBIs to the social realm, i.e. beneficial behavioral effects in stressful social settings. We also show that both emotion regulation mechanisms acceptance and cognitive reappraisal seem to underlie the effects of MBSR.

### *Brain Functional Plasticity associations with home practice and stress-regulation gains:*

We found emotion regulation longitudinal brain changes in left MTG (self ER acceptance), left precuneus (other ER reappraisal) and right SMG (other ER acceptance) in the MBSR versus READ group to be positively associated with meditation practice in a dose-dependent manner. This lends credibility to the brain activation having indeed changed as a function of the MBSR training and speaks in favors of regular practice as well as homework in the context of MBIs. Our finding is in line with previous studies reporting an association between hours of meditation practice and cortical thickness changes in expert meditators (Fox et al., 2014; Kang et al., 2013). Furthermore, functional neuroplasticity in left MTG (self ER acceptance), left precuneus (other ER reappraisal) and right SMG (other ER acceptance) were associated with gains in stress regulation in MBSR compared to READ, indicating the functional relevance and mechanistic underpinning of the activated brain network for emotion regulation gains.

The right TPJ, which has previously been identified as a crucial region for social cognition in general and for other ER, emerged as a possible functional biomarker for predicting which participants will benefit from MBSR with respect to regulating emotions in social contexts. This opens new possibilities for tailoring and personalizing clinical decision-making in the use of MBIs. In an effort to advance patient-centered psychiatry (i.e., answering the question *who will benefit from what*) it is crucial to identify psychological and biological baseline characteristics (such as brain activation) that can predict clinical benefits at individual level (Fernandes et al., 2017; Simon, 2008). Although previous studies have suggested female gender (Rojiani, Santoyo, Rahrig, Roth, & Britton, 2017) and immunological markers (Reich et al., 2014) as predictors of mental health benefits from MBIs, to the best of our knowledge, our study is the first showing a functional brain signature as predictive of emotional benefit in the context of MBSR. Nevertheless, considering the costs of fMRI assessments and the moderate predictive power in our findings, future studies are needed before incorporating this brain marker into clinical practice.

Overall our findings demonstrate that ER brain changes scaled positively with the amount of meditation practice and the stress reduction benefits, highlighting these brain changes as practice-related, efficient and active mechanisms underlying

MBIs salutary effects.

There are several strengths and limitations of our study. The newly developed SORT paradigm was experienced as a believable interaction scenario according to the results of our disclosure interviews, despite the fact that subjects had to go through the experimental procedure twice. To the best of our knowledge this is the first study investigating other ER in an intervention study that uses a real second person as regulation target (the confederate) in an fMRI setting. However, since subjects were blind to their group only at the baseline assessment, it is possible that demand-effects could have played a role during the second MRI experiment. Moreover, it is possible that dyadic contextual factors like age and gender differences between the regulator and the confederate affected stress regulation outcomes in the other ER condition. Future studies should consider such effects and it would furthermore be of interest to set up the study as true second person experiment where the partner is indeed the target of emotion regulation efforts of the participant and where the success of the ER efforts would be validated by self-reported and biological measurements in the partner. Lastly, our study fell short in recruiting male participants with 83% of our participant being female. It has been described in naturalistic studies, however, that women make use of meditation programs more frequently than men (Macinko & Upchurch, 2019). Future studies should control better for gender imbalances given that gender has been shown to influence ER capacities (McRae et al., 2008).

## **Conclusion**

In this study we focused on disentangling MBIs stress-reducing benefits through investigating ER mechanisms and its generalization to social scenarios. Our neuroimaging-based RCT demonstrated that MBSR relative to READ increased capacity for ER through both cognitive reappraisal and acceptance in the self and other conditions. Relative to READ, MBSR led to increased brain activation over time for regulating the self with acceptance (temporal-, parietal-, insular cortices) and others' with acceptance and cognitive reappraisal (precuneus, TPJ), thus confirming our primary outcome hypothesis. Distant social generalization effects on cognitive empathy and compassion, however, were not found. This study identifies both cognitive reappraisal and acceptance as active ER mechanisms of MBSR and shows that effects extend in a graded manner from self to social

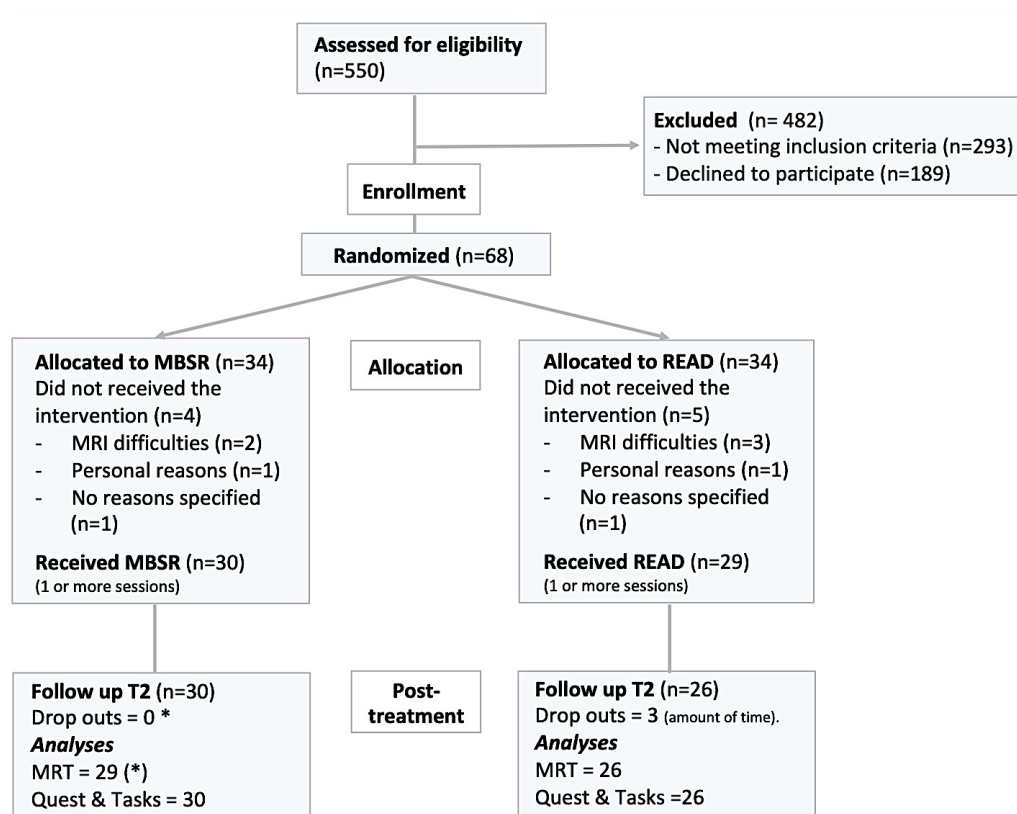
settings. Overall, the study provides fresh insights into the determinants, psychological and neuronal mechanisms underlying ER as a key active factor in MBI.

### Figures and Tables:

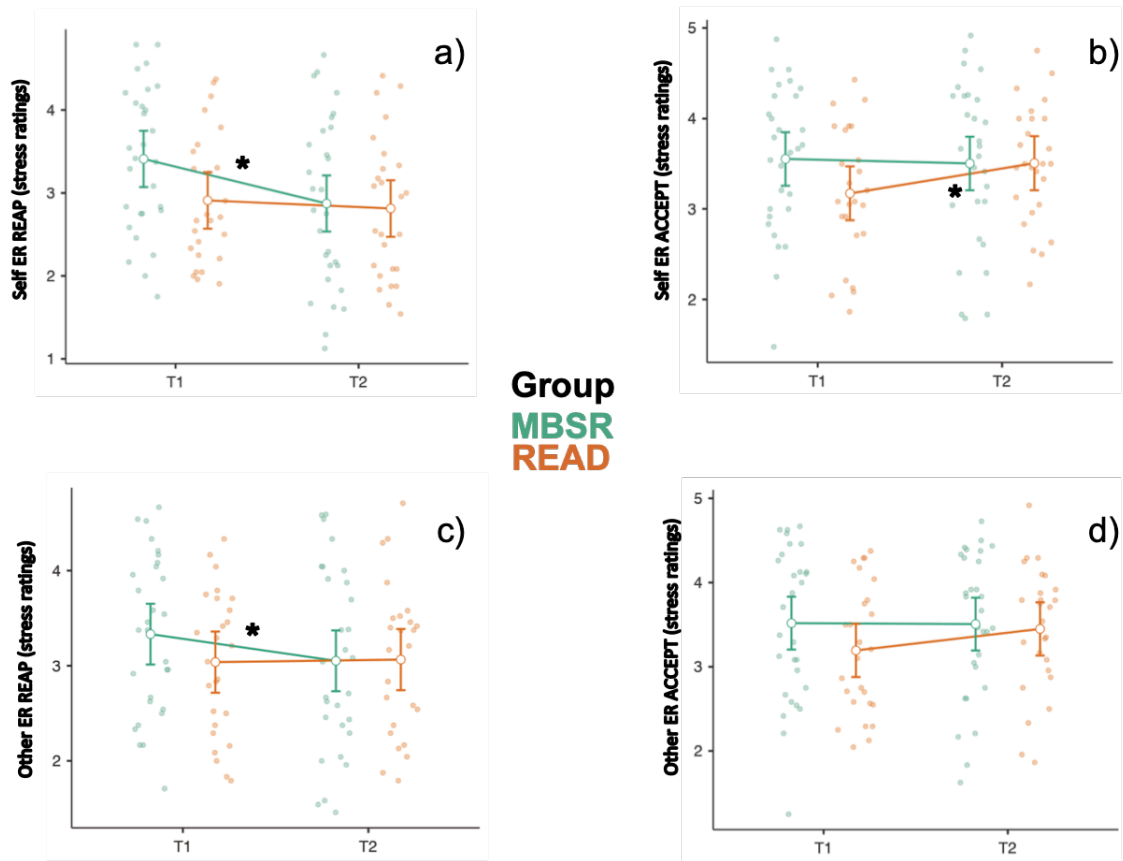
**Table So.** Demographics characteristics at baseline for subjects randomized to MBSR versus READ.

	<b>MBSR</b> <i>n</i> = 30	<b>READ</b> <i>n</i> = 29	<b>t-test or <math>\chi^2</math></b>
Females, n (%)	25 (83%)	24 (83%)	$\chi^2_{21} = 0.00$
Age, mean years (SD)	40.2 (10.8)	36.8 (10)	$t_{60} = 1.31$
After School Education, mean years (SD)	6.20 (2.46)	6.39 (2.61)	$t_{60} = 0.27$

*SD, standard deviation; n = sample size; t-test = independent sample t test;  $\chi^2$  = chi square.*



**Figure 1.** CONSORT diagram flow of participant's recruitment, allocation and follow up. MBSR = mindfulness based stress reduction; READ = reading/listening & sharing group. \* One subject attended one session and did rest of the training from home.



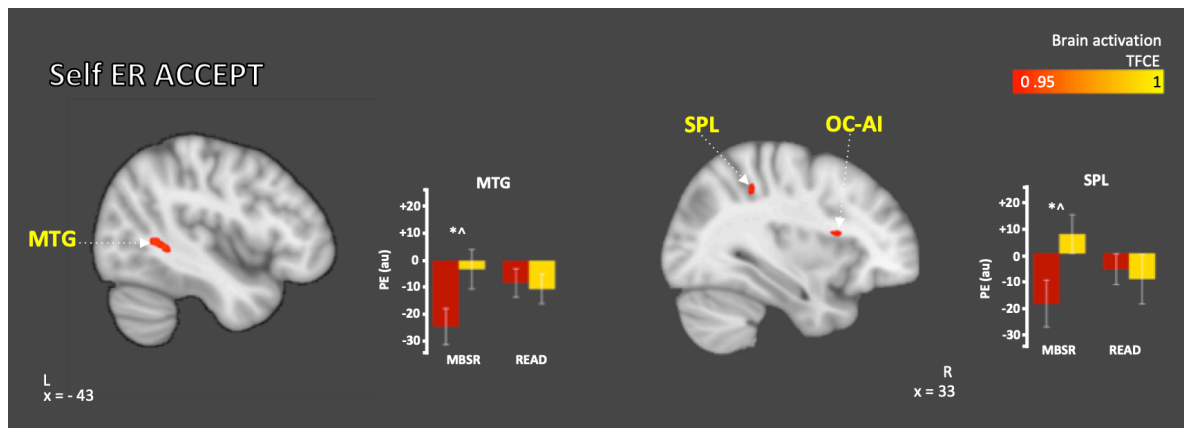
**Figure 3.** Effects of MBSR vs READ groups on mean self reported stress ratings during the SORT – fMRI experiment. Repeated measures ANOVA (group by time interactions) for each condition, after pairwise comparisons with Holms corrections (\*  $p = < .05$ ), revealed: a) decreased stress ratings during self emotion regulation (Self ER) with reappraisal (REAP) in MBSR; b) increased stress ratings during Self ER with acceptance (ACCEPT) in READ; c) decreased stress ratings during other emotion regulation (Other ER) with REAP in MBSR; d) no difference in time between the groups in stress ratings during Other ER with ACCEPT. Error bars correspond to 95% confidence intervals.

**Table 1.** Longitudinal functional brain changes for Self ER REAP (main effect of time)

Brain region	MNI Coordinates							Groups PE comparisons	
	H	CS	X	Y	Z	PE max	1 – p Max	(Cohen's-d, FDR-p, BF <sub>10</sub> )	
								<i>MBSR</i>	<i>READ</i>
SPL, AG.	L	1274	-34	-58	40	5.38	0.984	0.70 (*,^)	0.33
LOC-sup, SPL.	L	620	-16	-64	62	5.09	0.973	0.73 (*,^)	0.25
Intracalc. cortex.	R	80	16	-68	12	4.36	0.959	0.58 (*)	0.61 (*)

Note: results are derived from a Group by Time factorial GLM on Self ER REAP contrast. Main effect of time is shown here. All results are thresholded and corrected for multiple comparisons with adjusted p value <0.05 (equivalent to .95-1 using TFCE; 1 – p Max). The last two columns inform follow-up within group comparisons of PEs, using: Cohen's d effect size, false discovery rate adjusted p value (FDR-p; p value <.016 = \*), and Bayes factor 10 (BF<sub>10</sub>; BF<sub>10</sub> > 10 = ^). Abbreviations: H, hemisphere; CS, cluster size in the number of activated voxels; L, left; R, right; SPL, Superior Parietal Lobule; AG, angular gyrus; LOC-sup, Lateral occipital cortex superior division; PE: parameter estimate; PE max: maximum value of the PE for the cluster.



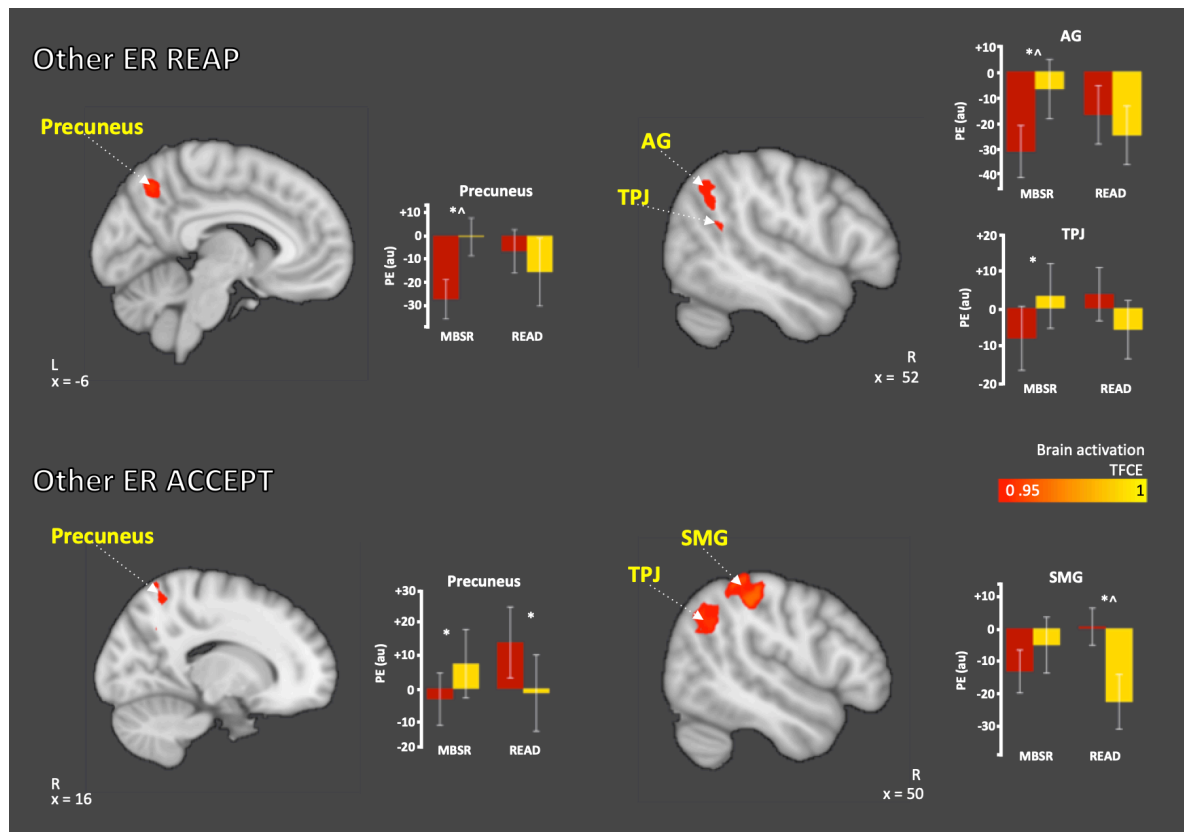


**Figure 4.** Brain training effects during self emotion regulation with acceptance (Self ER ACCEPT), changes in fMRI BOLD signal depicted as thresholded and corrected p values  $<0.05$  (TFCE ranges .95-1). For Self ER ACCEPT, a significant group by time interaction and follow up comparisons revealed higher brain activation in regions associated with emotion generation (MTG, OC-AI) and regulation (SPL, OC-AI) in the MBSR group. Bar graphs show parameter estimates (PE) in arbitrary units (au) for each TFCE cluster. Post-hoc comparisons: significant at FDR p value = \*; strong evidence for alternative model,  $BF_{10} > 10 = ^\wedge$ . Brain coordinates and PE values are given in table 2. Abbreviations: SPL, superior parietal lobule; LOC sup., lateral occipital cortex superior division; MTG, middle temporal gyrus; OC-AI, opercular cortex – anterior insula.

**Table 2.** Longitudinal functional brain changes for Self ER ACCEPT (group by time interaction)

Brain region	MNI Coordinates							Groups PE comparisons	
	H	CS	X	Y	Z	PE max	1 – p Max	(Cohen's-d, FDR-p, BF <sub>10</sub> )	
								<i>MBSR</i>	<i>READ</i>
MTG	L	156	-42	-54	4	4.39	0.964	0.85 (*,^^)	-0.16 (#)
SPL	R	134	38	-42	44	4.34	0.961	0.85 (*,^^)	-0.17 (#)
Intracalc. cortex.	L	107	-24	-78	10	4.9	0.965	0.85 (*,^^)	-0.08 (#)
OC-AI.	R	21	32	14	16	4.84	0.959	0.63 (*,^)	-0.45
PCC	L	21	-14	-46	28	4.45	0.955	0.5	-0.59 (*)

Note: results are derived from a Group by Time factorial GLM on Self ER ACCEPT contrast. All results are thresholded and corrected for multiple comparisons with adjusted p value <0.05 (equivalent to .95-1 using TFCE; 1 – p Max). The last two columns inform follow-up within group comparisons of PE's, using: Cohen's d effect size, false discovery rate adjusted p value (FDR-p; p value <.01 = \*), and Bayes factor 10 (BF<sub>10</sub>; BF<sub>10</sub> > 100 = ^^; BF<sub>10</sub> > 10 = ^; BF<sub>10</sub> < .33 = #). Abbreviations: H, hemisphere; CS, cluster size in the number of activated voxels; L, left; R, right; MTG, middle temporal gyrus; SPL, superior parietal lobule; OC, opercular cortex; AI, anterior insula; PCC, posterior cingulate cortex; PE: parameter estimate; PE max: maximum value of the PE for the cluster.



**Figure 5.** Brain training effects during other emotion regulation with cognitive reappraisal (Other ER REAP) and acceptance (Other ER ACCEPT), changes in fMRI BOLD signal depicted as thresholded and corrected p values <0.05 (TFCE ranges .95-1). For Other ER REAP a significant group by time interaction and follow up comparisons showed higher brain activation in regions associated with social emotion regulation and mentalizing in the MBSR group. For Other ER ACCEPT, a significant group by time interaction & follow up comparisons revealed higher brain activation in a region associated with social emotion regulation and mentalizing in the MBSR group, but also lower brain activation in a region associated with social cognition in the READ group. Bar graphs show parameter estimates (PE) in arbitrary units (au) for each TFCE cluster. Post-hoc comparisons: significant at FDR p value = \*; strong evidence for alternative model,  $BF_{10} > 10$  = ^. Brain coordinates and PE values on tables 4 and 5. Abbreviations: AG, angular gyrus; TPJ, temporo-parietal junction; SMG, supra marginal gyrus.

**Table 3.** Longitudinal functional brain changes for Other ER REAP (group by time interaction)

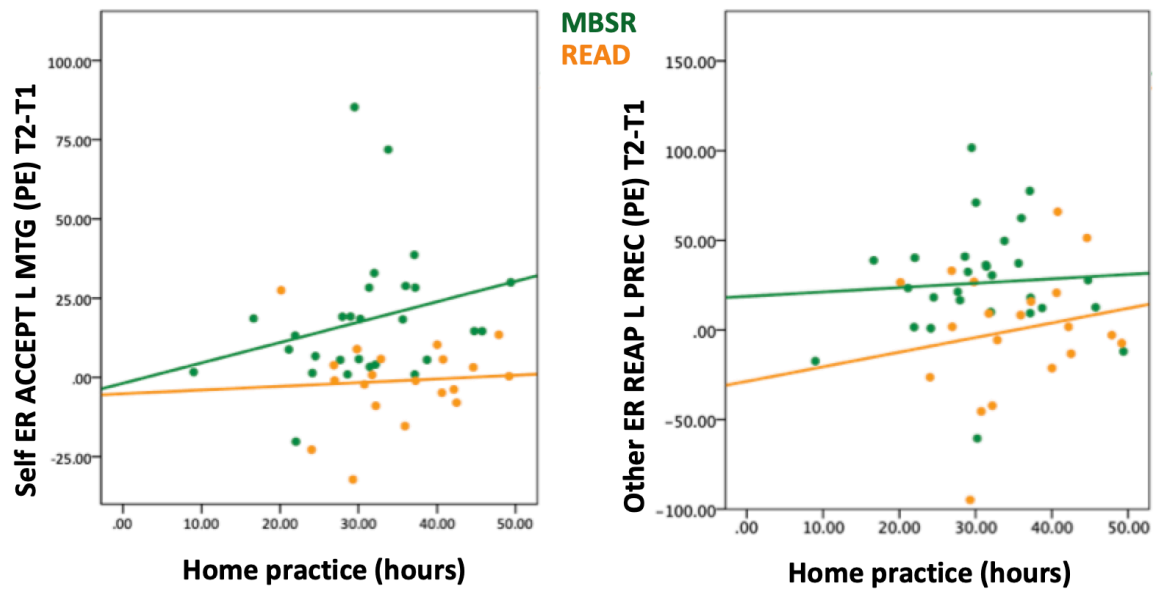
Brain region	MNI Coordinates							Groups PE comparisons	
	H	CS	X	Y	Z	PE max	1 – p Max	(Cohen's-d, FDR-p, BF <sub>10</sub> )	
								<i>MBSR</i>	<i>READ</i>
Precuneus	L	391	-6	-66	48	4.46	0.966	0.84 (*,^^)	-0.23
AG, TPJ.	R	111	52	-56	32	3.93	0.959	0.87 (*,^^)	-0.20
TPJ post, MTG.	R	45	48	-48	16	4.24	0.958	0.54 (*)	-0.48
Cuneal Cortex	R	43	14	-68	20	3.77	0.953	0.67 (*,^)	-0.34
PCC	R	12	12	-50	28	4.07	0.953	0.53 (*)	-0.40

Note: results are derived from a Group by Time factorial GLM on Other ER REAP contrast. All results are thresholded and corrected for multiple comparisons with adjusted p value <0.05 (equivalent to .95-1 using TFCE; 1 – p Max). The last two columns inform follow-up within group comparisons of PE's, using: Cohen's d effect size, false discovery rate adjusted p value (FDR-p; p value <.01 = \*), and Bayes factor 10 (BF<sub>10</sub>; BF<sub>10</sub> > 100 = ^^; BF<sub>10</sub> > 10 = ^). Abbreviations: H, hemisphere; CS, cluster size in the number of activated voxels; L, left; R, right; TPJ, temporo-parietal junction; AG, angular gyrus; MTG, middle temporal gyrus; PCC, posterior cingulate cortex; PE: parameter estimate; PE max: maximum value of the PE for the cluster.

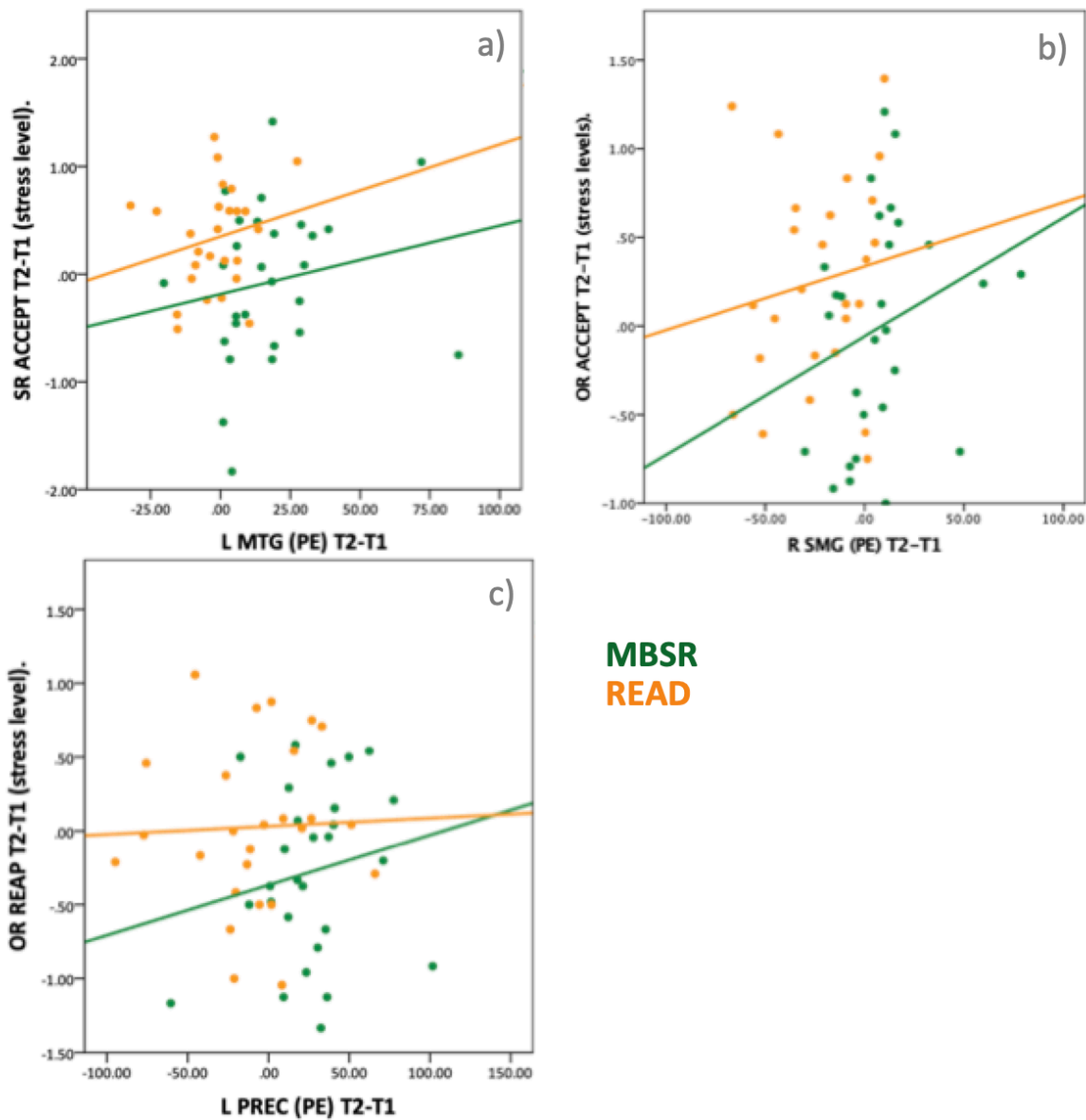
**Table 4.** Longitudinal functional brain changes for Other ER ACCEPT (group by time interaction)

Brain region	MNI Coordinates						Groups PE comparisons		
	H	CS	X	Y	Z	PE max	1 – p Max	<i>MBSR</i>	<i>READ</i>
SMG, TPJ, IPL.	R	1124	50	-30	48	4.47	0.973	0.33	-0.95 (*,^^)
Precuneus	R	138	16	-56	56	4.14	0.958	0.45 (*)	-0.58 (*)

Note: results are derived from a Group by Time factorial GLM on Other ER ACCEPT contrast. All results are thresholded and corrected for multiple comparisons with adjusted p value <0.05 (equivalent to .95-1 using TFCE; 1 – p Max). The last two columns inform follow-up within group comparisons of PE's, using: Cohen's d effect size, false discovery rate adjusted p value (FDR-p; p value <.025 = \*), and Bayes factor 10 ( $BF_{10}$ ;  $BF_{10} > 100 = ^^$ ;  $BF_{10} > 10 = ^$ ). Abbreviations: H, hemisphere; CS, cluster size in the number of activated voxels; L, left; R, right; SMG, supra marginal gyrus; TPJ, temporo-parietal junction; IPL, inferior parietal lobule; PE: parameter estimate; PE max: maximum value of the PE for the cluster.



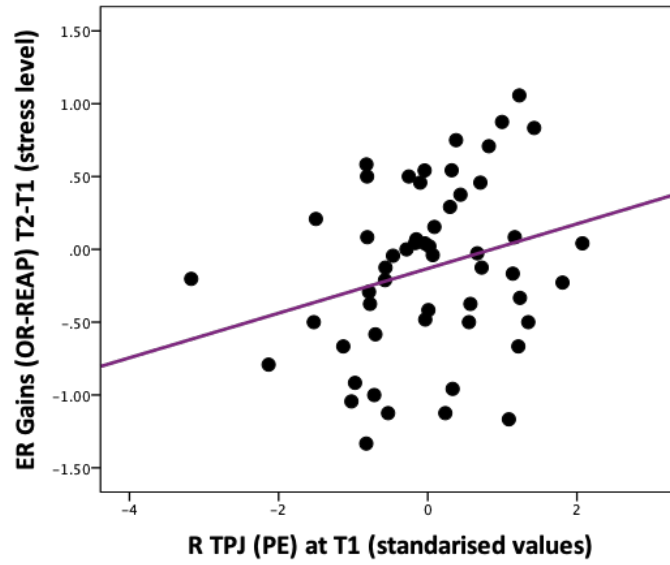
**Figure 6.** Relationship between home practice (hours) and increases in brain activation (PE change score). Despite both groups had the same amount of home practice, covariation analyses revealed that only in MBSR it predicts increases in brain activation during Self ER ACCEPT (in L MTG) and during Other ER REAP (L Precuneus). The higher the amount of meditation practice (in hours) the higher the change in brain activation in L MTG and L precuneus in the MBSR compared to the READ group.



**Figure 7.** Relationship between increases in brain activity (PE change score) and decreases in stress ratings (change scores) during the self-other emotion regulation task for the fMRI scanner. Covariation analyses revealed that only in MBSR group, changes in brain activation (PE change score) were positively related to behavioral gains in emotion regulation (lower stress ratings).

In the MBSR compared to the READ group, brain activation changes were linked to higher capacity for lower own stress levels when performing *self emotion regulation* with acceptance, (for L MTG, Fig 7a) and *other emotion regulation* with acceptance (for R SMG, Fig 7b) and cognitive reappraisal (for L PREC, Fig 7c).





**Figure 8.** Relationship between pre-intervention brain activation and increases in emotion regulation (ER) skills. Right TPJ functional activation (PE) at T1 predicted gains in capacity for lowering own stress (stress ratings change score) during other emotion regulation with cognitive reappraisal in the fMRI task. The lower the activation at baseline, the higher the improvement of ER during social interaction.

## **General Discussion**

This thesis investigates the relationship between mindfulness and ER and social cognition along different methodological approaches: conceptual and evidence revision, trait level (individual differences) and behavioral mechanisms, and cross-sectional and longitudinal functional brain correlates. The project aims at disentangling the fine-grained ER mechanisms of mindfulness (as trait and MBSR), the relationship between ER and social cognition (emotional and cognitive empathy) and the ER brain-behavioral plasticity induced by a MBIs (MBSR). This chapter will discuss the results of the thesis in line with the main objectives. Integrating empirical and conceptual approaches, I propose a model that I explain in section 4.5. Given the pervasiveness and interrelatedness of ER and social cognition phenomena and its crucial relevance for clinical psychology, the model offers new insights regarding the relationship between personal distress and self ER, empathy and social ER in the context of social interactions.

### **4.1. Mindfulness, Emotion Regulation and Social Cognition: From traits to behavior**

Along the thesis, each article (see figure II for summary) versed on the relationship between two of the main themes mindfulness, ER and social cognition, using a specific methodological approach. The MFN-ER review study investigated mindfulness' ER mechanisms across different empirically-derived models, dissecting the interplay of different psychological-brain processes and ER strategies connected to mindfulness salutary effects. The MFN-SC study focused on dispositional mindfulness in BPD patients and healthy participants, exploring self-compassion as a mechanism (mediator) linking mindfulness and ER. The ER-EMP study investigated the behavioral and functional brain mechanisms of self and social ER, looking at the moderating role of individual differences in empathy, linking personal distress, ER and social cognition. Finally, the MBI-ER-EMP study a neuro-imaging RCT compared an MBI (MBSR) with a READ group, further exploring the acquisition of specific mindfulness ER strategies (cognitive reappraisal and acceptance) for self and social ER, their underlying effective neuro-plastic mechanisms, and its potential generalization effect over socio-emotional capacities (compassion and cognitive empathy).

#### **4.1.1. Mindfulness, Self-Compassion & Emotion Regulation at Trait level**

The MFN-SC study showed that BPD patients have lower mindfulness traits and ER skills than the matched and general population controls, replicating previous work in the field (Keng & Wong, 2017; Selby, Fehling, Panza, & Kranzler, 2015). Our study extends these findings: we demonstrated that mindfulness is negatively correlated with deficits in ER, and that this effect is mediated by self-compassion. Despite the mediation effects differed between the sub-samples of the study (in *study 1*: indirect-only mediation; in *study 2*: complementary mediation), we propose self-compassion as a potential mechanism linking mindfulness as trait with ER. Basically, dispositional mindfulness would lead to a more accepting and kind attitude towards the self, responding adaptively in moments of emotional pain. In this way self-compassion has been recognized as an ER mechanism of mindfulness (Holzel et al., 2011).

As researched in the MFN-ER review study, the literature has shown consistent results indicating that individual differences in mindfulness are associated with ER skills, emotional adjustment and mental health. In this line, studies of MBIs have shown that self-compassion, among others, mediated longitudinal salutary effects in depressive patients (van der Velden et al., 2015) and healthy population (Evans, Wyka, Blaha, & Allen, 2018). Even more, a recent meta-analysis showed that self-compassion is not only increased by MBIs, but also in standard psychotherapies (Wilson, Mackintosh, Power, & Chan, 2019). Finally, a meta-analysis across healthy and clinical populations found that subjects with higher self-compassion have lower psychopathology and higher well-being (Muris & Petrocchi, 2017). In this way, self-compassion is a relevant new construct and a promising ER mechanism to target in clinical practice and certainly in future clinical psychology research.

#### **4.1.2. Mindfulness, Emotion Regulation & Social Cognition at Behavioral level**

As shown in the MFN-ER review study, not only cross-sectional but also longitudinal studies have evidenced that ER is one of the key active mechanisms behind MBIs salutary benefits. Contrasting with psychological assessments via questionnaires, ER behavioral experiments require the implementation of ER as a *pragmatic mental strategy* modifying the current emotional state, thus reducing

subject's distress. In this regard, to the best of our knowledge, no previous studies have explicitly assessed ER strategies using a behavioral experimental paradigm in the context of a MBI (MBSR). The MBI-ER-EMP study tackled the question of whether the MBSR targets a “preferential” ER strategy, such as *cognitive reappraisal* and *acceptance*. This RCT advanced this debate, providing favorable evidence for both strategies, for the case of self ER both strategies were effective in reducing own distress in the SORT fMRI-paradigm, in line with studies that have found evidence for increased *cognitive reappraisal* (Garland et al., 2011, 2015, 2017) and *acceptance* (Britton et al., 2017; Lindsay et al., 2018; Lindsay et al., 2019) in MBIs. In the context of MBSR, new studies should establish what type of mindfulness practices (i.e. meditation or body awareness or psycho-education components), might differentially influence *cognitive reappraisal* and/or *acceptance*. Future research, using dismantling longitudinal designs (the ones that compare between interventions active mechanisms), could compare different mindfulness programs teaching only *cognitive reappraisal* versus only *acceptance* ER strategies, in this way being able to isolate its specific mechanisms. For example, a study showed that a brief stand-alone *cognitive reappraisal* longitudinal intervention was effective to reduce self-reported distress when exposed to a conditioned threat (Shore, Cohen Kadosh, Lommen, Cooper, & Lau, 2017).

Given the complexity and dynamicity of human experiences, it might be more adaptive to have a range of ER strategies, rather than only one. In many cases, to cognitively change the way we appraise something would be adequate for a given situation (i.e. when seeing a horror movie, we can just say “this is just a movie”), but in other situations like when experiencing grief, being able to accept the situation as it is might be more adaptive. Besides this, authors have proposed an empirically derived model linking ER and mindfulness, in which both strategies would work synergistically, with acceptance being a pre-step for reappraisal: First one need to accept the situation that is going to be “reappraised” subsequently (Curtiss et al., 2017). In this way, highlighting the relevance of both types of strategies in the process of ER. Our findings support the notion that MBSR targets both strategies; at the practical level each one could have its own advantage and specificity depending on the situation and context.

Using the newly developed SORT, the MBI-ER-EMP study showed that MBSR

enhanced the capacity for reducing personal distress while regulating other's emotions (social ER), this effect was specific when using *cognitive reappraisal*. Interestingly, this finding hints toward a certain generalization effect over the social cognition domain, yet I argue that this is due to the critical involvement of (self) ER processes during social ER. Thus, the MBSR might target an *individual-level* component (like ER) involved in stressful social interactions. In addition, we found no training effect (comparing MBSR and READ groups) for social ER using the *acceptance* strategy. This could be explained by the fact that the social ER condition was more stressful than the self ER condition (as shown in the ER-EMP study), thus the *acceptance* strategy falls short in counteracting personal distress in this condition. Moreover, a social desirability effect might be in place, since it is psychologically and culturally paradoxical to try to help another person in suffering telling them to “just accept” their distress.

Nevertheless, as in self ER, it might be that both strategies have a specific beneficial effect on the social functioning; for example, a behavioral study has shown that *cognitive reappraisal* could reduce the emotional egocentricity bias (the projection of own's emotional state into others) when judging other's emotions (Naor, Shamay-Tsoory, Sheppes, & Okon-Singer, 2018). Even more, a recent large dismantling training study revealed that a MBIs infused with an *acceptance* module (compared with a standard MBI) was able to reduce loneliness and increase real-life social contacts in healthy subjects (Lindsay et al., 2019). In this way, despite the fact that *acceptance* may be less efficient in reducing personal distress while regulating others, it might as well foster social connection. Future studies should further investigate the interpersonal consequences of specific ER strategies when applied in social interactions.

Despite previous findings suggesting that MBIs enhance empathy and social functioning (Luberto et al., 2018 for a meta-analysis), the MBI-ER-EMP study, using a well validated behavioral task for empathy (the MET) showed no effect of the MBSR (compared to READ) on cognitive empathy (inferring other's emotional states) or compassion (wishing to alleviate other's suffering). In line with our finding, a recent large longitudinal study compared a mindfulness intervention with a compassion-based intervention, demonstrating that only the later increased compassion (Hildebrandt et al., 2017; Trautwein et al., 2020; for a meta-analysis Kreplin et al., 2018). Taking together the findings from

the self ER, social ER and empathy task, I argue that we found evidence suggesting that MBSR has a stepped effect, from self to social functioning.

Interestingly though, considering models that link individual-level mental processes (like ER) and social cognition (like empathy), it is plausible that modulating ER capacity might influence the latter, given the crucial role of emotions (and thus ER) in empathy. I suggest this could explain why the MBSR group (and maybe MBIs in general) did not enhance cognitive empathy and compassion (beyond social ER), given that increasing ER might dampen empathy. This point will be further addressed in the proposed model, in the next chapter 4.5.

## **4.2. Self & Social Emotion Regulation and the role of individual differences in Empathy (Emotional & Cognitive)**

### **4.2.1. Emotion Regulation & Empathy**

For many years, diverse theoretical models have tried to understand empathy and its relationship with individual-level determinants like ER (De Waal & Preston, 2017; Decety & Jackson, 2004). The ER-EMP study provided support to those models, showing that subjects with higher personal distress (lower ER skills in the SORT) during self ER and social ER conditions (but also during the Permit for the other condition), had higher compassionate feelings (for positive and negative stimuli, as measured in the MET). In other words, subjects who have more empathetic concern for others have also lower ER capacity when regulating own or other's emotions. This finding comes along with literature highlighting that empathizing with others in pain comes "with a cost" for the observer (Batson et al., 1987; Saarela et al., 2007). Concurrently, our results also support the interpretation that subjects higher in ER have lower compassion, though from these we cannot infer causality, they suggests that people that over-regulate their emotions have lower compassionate feelings for others.

Noteworthy, no association between personal distress during regulating self or others and cognitive empathy was found, indicating that subject's ER abilities do not vary with subject's cognitive empathy skills. This result gives more specificity to the relationship between primarily emotional processes, ER (regulating emotions) and emotional empathy or compassion (intending to alleviate other's pain). This is in line with the findings that emotional and cognitive empathy or mentalizing are distinct and dissociable psychological processes (Kanske et al., 2015; Shamay-

Tsoory, Aharon-Peretz, & Perry, 2009).

In this way, with the ER-EMP study we provide evidence for ER as a determinant for empathy, grounding empathy – intrinsically interpersonal- in basic emotional personal processes, bridging the gap between individual and social psychological phenomena. In the context of daily social interactions, overall these results highlight the dynamic interaction between self-related (like self ER) and socio-emotional (compassion) processes, in which given a certain social context, and personal ER resources, subjects might need to valuate their ER state in order to *empathetically* engage (and connect) with others, balancing personal distress and emotional distance. This idea is further developed in the proposed model, in the next chapter 4.5.

#### **4.2.2. Social Emotion Regulation mechanisms**

To the best of our knowledge, the ER-EMP study is the largest fMRI study on social ER, exploring its brain mechanisms and the emotional “costs” and benefits of regulating other’s distress. To note, our findings revealed that regulating negative emotions of others reduced own stress for the regulator, coherent with a previous study (Niven et al., 2012). During the SORT, the *permitting others’ emotions* (without regulating them) condition resulted in higher distress for the observer, instead, taking the active role of regulating other’s emotions (social ER) resulted in lower distress for the regulator (relative to the permit condition). This resembles other altruistic behaviors in mammals, when helping others also positively affects the carer’s mental state (De Waal & Preston, 2017).

Authors have distinguished two types of social ER, when being regulated by others (intrinsic social ER) and when regulating another person (extrinsic social ER) (Zaki & Williams, 2013). Early studies have shown that people higher in *extrinsic* social ER have prospectively larger real and virtual social networks (Niven, Garcia, van der Löwe, Holman, & Mansell, 2015), but also individuals with higher tendency to *intrinsic* social ER report higher empathy and social connection (Williams, Morelli, Ong, & Zaki, 2018). Contrary to these findings, our results indicate that subjects with higher personal distress while regulating others (lower *extrinsic* social ER) have higher emotional empathy (compassion). This suggests that higher empathetic feelings (and its potential ensuing social connection) are linked to higher emotional pain when trying to make the other feel better. However, this



discrepancy could be due to the specific setup of the paradigm, i.e. not measuring the efficacy of the social ER in the other's (target) distress. Further limitations regarding the SORT are presented in the chapter 4.4. Overall, our study suggests an inherent linkage between *extrinsic* and *intrinsic* social ER, providing evidence for social ER as a new socio-emotional skill for regulating own and other's distress when facing stressful social interactions.

The ER-EMP study provides plausible evidence for a neurobiological mechanism of social ER, using functional brain measurements (fMRI) together with skin conductance response (SCR) and self-reported distress levels, showing the involvement of the precuneus and right TPJ in social ER (specific for the contrast social ER > self ER). These areas have been widely linked to mentalizing or cognitive empathy (Kanske et al., 2015; Shamay-Tsoory et al., 2009). Interestingly, the higher the activation of these areas was associated with lower self-reported distress and physiological stress response (SCR) in the regulator, suggesting their role in ER rather than socio-cognitive processes. Furthermore, the functional connectivity profile of the precuneus (during social ER), showing increased connectivity with parietal cortical areas and decreased connectivity with temporal and precentral cortices, could be interpreted as an increased involvement of ER processes (linked to parietal regions – Kohn et al., 2014) and a decreased recruitment of socio cognitive processes, specially those related to empathic distress and mirroring (linked to precentral & temporal regions – Ashar et al., 2017).

Theoretical models have suggested that social ER is realized by a combination of social cognition and ER neuronal mechanisms (Reeck et al., 2016). Here we offer further evidence for this model, highlighting the crucial role of the precuneus and TPJ in social ER, but also in lowering personal distress in the regulator during social ER. Future studies should attempt to disentangle intrinsic and extrinsic social ER brain correlates (being regulated by or regulating another person). Special focus should be on investigating social and emotional sub-processes involved in social ER, like emotion recognition, mentalizing, but also ER strategy selection and implementation. Ideally, new studies should measure simultaneously two subjects, including self-reported, physiological and brain assessments, i.e. using hyper-scanning technologies, where two real subjects engage in the same experiment in two interconnected but separate brain scanners. Finally, new studies

should attempt to link neuronal mechanisms with daily life social ER behaviors, i.e. using portable mobile assessments.

#### **4.2.3. Emotion Regulation basic mechanisms**

Despite ER's crucial relevance for basic and clinical psychology and neuroscience, there are still several pending points to further advance ER research. New studies could take advantage of the Research Domain Criteria (RDoC) perspective, studying ER at different levels including genetics, molecular and cellular determinants, and its linkage to behavior, but also from looking at the involvement of different basic systems proposed in RDoC, like negative and positive valence and arousal-regulatory domains (Fernandez, Jazaieri, & Gross, 2016). This approach could help to disentangling more specific pathways, determinants and mechanisms, linking biological, behavioral, psychological and social domains in ER.

Lately authors have described ER psychological processes as including: identifying a targeted emotion, selecting an ER strategy, implementing the strategy and monitoring the result of the implementation, including the modifications of the implementation if necessary (Gross, 2015). In this way, ER is conceived as a dynamic decision-making process, for example between implementing the strategy and monitoring if the precise goal is achieved (Etkin et al., 2015). Notably, future studies could investigate these psychological processes in both self and social ER. Related to this, lately it has been suggested that ER can be better understood under the predicting processing frame, in which the emotion that needs to be regulated elicits a prediction error (for example signals related to sub-cortical regions) and the ER strategy acts as the top-down descending prediction minimizing the prediction error (Etkin et al., 2015). New studies could take advantage of this approach, for example, by building computational models to better disentangle bottom-up (as sub-cortical but also bodily signals) and top-down (cortical) interactions through the lens of the predicting processing frame. This view is in line with the embodied, interoceptive account of emotions in general (Seth & Friston, 2016), which considers physiological and homeostatic processes (as bottom-up prediction errors) as crucial for emotions. Here I suggest this framework could also provide new insights for ER processes looking at bottom-up, top-down and brain-body interactions. A sketch of the potential of this approach is presented in the MFN-ER review study, discussing the involvement of bottom-up and top-down

processes implicated in mindfulness' ER mechanisms.

### **4.3. Mindfulness induced Brain-Behavioral Plasticity on Self & Social Emotion Regulation**

The MBI-ER-EMP study is one of the first showing both behavioral and functional brain plasticity of ER abilities due to MBIs, specifically investigating fine grained self and social ER mechanisms. Relative to the READ group, the MBSR showed increased brain activation for self ER with acceptance, specifically in regions (parietal, temporal and insular cortices) linked to arousal, somato-sensory/perceptual processing, interoceptive awareness, attention reorienting and ER (Craig, 2009; Morawetz et al., 2017; Sereno & Huang, 2014). This indicates that *acceptance* as a strategy could elicit re-orientation of awareness towards bodily (interoceptive-perceptual) components of the emotional experience, resembling exposure techniques from CBT therapy (Holzel et al., 2011). At the behavioral level only the MBSR group benefited from this strategy, overall, confirming it as an effective ER strategy specifically trained in MBSR. Coherently with the hypotheses and frame advanced in the MFN-ER review study, the MBSR through the *acceptance* strategy targeted the left middle temporal gyrus as ER mechanism (its activity scaled positively with distress-reducing benefits and home practice), a brain region that have been involved in both emotion generation (Ochsner et al., 2009; Otto, Misra, Prasad, & McRae, 2014) and in ER (Frank et al., 2014; Kohn et al., 2014). Even more, no longitudinal changes in the pre-frontal cortices were found (i.e. dorso-lateral prefrontal cortex). These findings seem to indicate specific bottom-up ER processes related to the MBRS salutary effects, as proposed in the MFN-ER review study.

Concerning the neuronal correlates of self ER with *cognitive reappraisal*, the main effect of time suggests a trend towards increased brain activation for both groups, specifically in regions (parietal cortices) linked to re-interpretation, perspective taking, attention selection and ER (Morawetz et al., 2017). This could be due to the cognitive demands of the READ group, i.e. the repetitive engagement of attentional resources, leading to training effect in attention related regions in this group. In fact, a previous study comparing a MBI with a READ group also found increase neuronal and attentional responses in the active control group (Allen et al., 2012). These brain findings are in line with previous studies of *cognitive reappraisal*, suggesting that implementing this strategy changes the cognitive frame as of the

knowledge or perspective towards the targeted emotional state (Buhle et al., 2014). At the behavioral level the MBSR group largely benefited from this strategy, thus confirming it as an effective ER strategy specifically trained in MBSR.

Regarding the neuronal correlates of social ER, the MBI-ER-EMP study showed an increased brain activation in the MBSR (relative to READ group) specifically in regions (i.e. precuneus and TPJ) that have been associated with mentalizing or cognitive empathy (Bzdok et al., 2012; Valk et al., 2016). At the same time, these same regions have been shown to have a crucial involvement in social ER (Hallam et al., 2014; Xie et al., 2016), but also during experimental paradigms where subjects actively interact with others (Redcay & Schilbach, 2019). Interestingly, this study found a convergent pattern of neuro-plastic changes for social ER strategies (*acceptance* and *cognitive reappraisal*), both increasing right parietal cortex (as TPJ) and precuneus activation, suggesting that MBSR might target an underlying common brain mechanism for social ER. These findings are also coherent with the ER-EMP study, highlighting the relevance of middle and lateral parietal cortices in regulating other's emotional distress during social interactions.

In addition, functional neuro-plastic changes in main clusters for self ER with *acceptance* (left MTG), and for social ER with *acceptance* (right SMG) and *cognitive reappraisal* (left precuneus) positively scaled with mindfulness home practice, indicating the relevance of daily meditation assignments for the intended functional brain changes. These findings support the notion that mindfulness meditation (besides other components) is one of the key active ingredients of the MBSR program. Coherently, functional brain activations gains in the same clusters (for self and social ER) positively scaled with stress reduction benefits, indicating that neuro-plastic changes are indeed involved in enhancing capacity for reducing personal distress while regulating owns' and others' emotions. Overall, these findings confirm that functional brain changes resulting from the MBSR program: i) are training-dependent, they have a dose-dependent relationship with mindfulness practice, ii) have an effective mechanistic involvement, their activation gains are linked to enhanced ER abilities. In this way, the MBI-ER-EMP study evidenced for the first time concomitant fine grained ER mechanisms at the psychological and brain levels.

#### **4.4. Theoretical and Methodological Issues**

This thesis examined the relationship between mindfulness, ER and social cognition using different methodological approaches. The MFN-ER review study encompassed a comprehensive narrative review of the relationship between mindfulness and ER from psychological, clinical and neuroimaging studies. Summarizing extensive and diverse literature, from dispositional mindfulness to expert meditators, usually presented in a disintegrated way. The MFN-ER review study laid the ground for the following studies, suggesting psychological and brain mechanisms involved in mindfulness as trait and MBIs. The MFN-SC study not only showed dispositional mindfulness deficits in BPD (compared to matched and unmatched controls), but also demonstrated a mechanism linking mindfulness as trait and self-reported ER abilities. State of the art mediation analyses revealed that self-compassion mediated the effect of mindfulness on ER deficits as measured by well established self-reported questionnaires. Nevertheless, recent large empirical studies in the field have warned about the lack of relationship between self-reported questionnaires and experimental behavioral measurements (for impulsivity, Bernoster, De Groot, Wieser, Thurik, & Franken, 2019; for cognitive empathy, Murphy & Lilienfeld, 2019). Highlighting potential conflation, low external and ecological validity among other limitations of self-reported measurements.

The SORT is a newly developed experimental paradigm intending to behaviorally measure ER abilities by contrasting a personal and a social context (self vs social ER), and the usage of diverse ER strategies (cognitive reappraisal vs acceptance vs permit – the latter as baseline). It poses high ecological validity, given that regulators have to actively interact with the subject outside the scanner using verbal communication as in daily life social interactions. The experiment attempts to mimic social scenarios in which one subject (the regulator) modulates another person's emotional state, actively adapting its performance through both the dynamic information from the other (arousal index, i.e., red/yellow pumping dot) and the tailored aversive sounds. In this way, the SORT is in line with latest accounts in the field of social and cognitive neurosciences, which recommends the usage of controlled, yet naturalistic experimental settings. The SORT entails a structured interaction (beyond a passive stimulus exposure), an emotional engagement of the participant (regulators have to actively modify other's and own

distressing emotions), while only one individual is being measured (instead of two) (Redcay & Schilbach, 2019; Schilbach et al., 2013). This last point certainly precludes inferences regarding the efficacy of social ER trials in regulating distress in the target (in this setup a confederate). Future studies could further investigate this point, using two real subjects, evaluating for both distress at the behavioral and neuro-physiological level.

The MBI-ER-EMP study consisted in a RCT, comparing the MBSR (the most widely used MBI) with an active controlled READ group. The latter group matched several unspecific factors relevant for psychotherapy research, including group effects (social support), frequency and duration of weekly meetings, amount of home assignments, expertise of both group's leaders, and expectation (the READ was also framed as a mental health intervention). The RCT design is the gold standard for clinical studies attempting to establish efficacy and/or active mechanisms, given experimenters control the independent variable (the two groups) it is best suited to establish causality. Our study specifically aimed to unravel fine grained ER mechanism in MBSR, but also its generalization effects to social cognition. To do so, beyond standard questionnaires, two behavioral tasks and neuro-imaging and physiological measurements were applied. Even more, in line with personalized medicine and in an attempt to establish predictive biomarkers for guiding clinicians decision making (Fernandes et al., 2017), the MBI-ER-EMP study is (to the best of our knowledge) the first showing a functional brain signature as predictive of ER benefits in the context of a MBIs.

From a purely methodological perspective, and consistent with the open science framework, the MBI-ER-EMP study included pre-registration of hypotheses and primary/secondary outcomes (at [clinicaltrials.gov](https://clinicaltrials.gov)), and *a priori* statistical power estimations. Also up to date neuroimaging analytical strategies were implemented, like using threshold free cluster enhancement (TFCE) for multiple comparison correction and inferential statistics. Based on the observed data this method uses permutations for estimating confidence intervals, this approach is meant to define cluster-like structures and maintaining voxel-wise information, surpassing the limitations of conventional p-value based inferential statistics (Winkler, Ridgway, Webster, Smith, & Nichols, 2014). Both neuroimaging studies used whole-brain analyses and implemented recommended standards for cluster forming thresholding (equivalent to  $p < 0.01$ ) and correction for multiple comparisons



(equivalent to  $p < 0.05$ ) (Poldrack et al., 2008).

#### **4.5. The Distress-Regulation Model of Social Interactions**

Just as social cognition is regarded as an unspecific term referring to the understanding of other's mental states (Happé et al., 2017), similar problem exist with empathy. Although from early times it has been conceived as a multi-dimensional concept, encompassing self-centered and other-centered feelings and dispositions (i.e. personal distress, empathic concern, or even perspective taking) (Davis, 1980), recently authors have pointed out several inconsistencies regarding its borders with other concepts (like ER), its nature (cognitive or emotional), its target (self or other), its behavioral outcomes, among others (Cuff, Brown, Taylor, & Howat, 2014). Starting from previous theoretical models and the findings along the thesis, the present model attempts to articulate the notions of social ER and empathy within the context of social interactions, disentangling emotional and ER processes along with basic self- and other-perception processes.

More specifically, the Distress-Regulation model of social interactions intends to distinguish between the concepts of self and social ER and empathy, and to disentangle their relationship considering the inherent complexity of real-life social engagements. In line with recent embodied - interoceptive – predictive processing approaches to emotions in general (Barrett, 2016; Seth & Friston, 2016), which assumes the affective dimension as constitutive for organisms, the model conceives emotions and ER as crucial features for individuals' adaptivity and agency in the social contexts (Christoff, Cosmelli, Legrand, & Thompson, 2011). In line with these accounts, our's assumes a *continuous exchange* of emotional states (i.e. information) between subjects in social interactions. In simple terms, in every moment and simultaneously, each individual *needs* to perceive and regulate their own emotions, and also to perceive and regulate other's emotions. Coherent with contemporary evolutionary and developmental theories, these processes can occur in an *explicit* or *implicit* way, and can have diverse state-dependent and long-term consequences for subjects' biological and mental wellbeing (Atzil, Gao, Fradkin, & Barrett, 2018; De Waal & Preston, 2017).

The model has two basic dimensions, the Distress-Regulation axis represents the amount to which one regulates or perceive distress, closely connected to the painfulness and uncontrollability of emotional states. From a predictive processing



approach, it includes the degree of uncertainty indexed by prediction errors, which result from the comparison between bottom-up and top-down processing (i.e. being bottom-up signals related to stress neuro-hormonal systems / mid-brain, amygdala, insula), along with the engagement of diverse regulatory mechanisms indexed by descending predictions (i.e. top-down signals, implemented by mental strategies and brain systems / pre-frontal and parietal cortices). The Self-Other dimension represents the focus or source of the emotional state to be perceived or regulated. This axis implies diverse processes related to ‘self-awareness’ (i.e. sensory-integration and self-other distinction), and ‘other-awareness’, or the perception or “reception” of others’ mental states (i.e. diverse social cognition routes like mentalizing, empathy) (See figure III for a diagram).

According to diverse social contingencies, starting with current self and others’ emotional states, different dyadic (self & other) and dynamic "experiential" modalities can result (i.e. *compatible*: both subjects in a regulated or balanced state or *not-compatible*: both in high distress or unregulated states). Self-states with high distress (low regulation) would parallel to personal distress, self states with balanced emotional state (low distress) would correspond to self ER. Other’s unregulated emotional states would match with empathy, the taking in of other’s pain. Then, social ER corresponds to the active attempts to modulate others’ emotional states (i.e. using different gestures, physical contiguity or verbal exchanges). From a dynamic perspective, the model proposes that the perception of others in emotional pain would increase perceiver’s distress via lowering ER for the self, interestingly, and along with previous literature and own findings, subjects with lower ER have higher compassion (emotional empathy) for others. Suggesting that emotional connection (aka emotional empathy) is achieved via lowering regulation of own emotions and thus increasing individual’s emotional engagement. For example, as an implication of this model, it might be that subjects with lower ER abilities through higher compassion (i.e. emotional connection) might recruit others for regulating them, thus displaying higher *intrinsic* social ER.

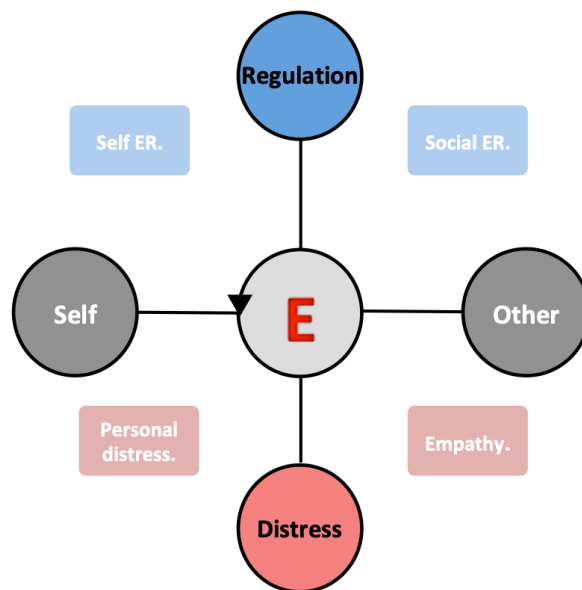
At the same time, perceiving others in distress and its continuous ‘detrimental’ effects in the self would signal the need to regulate either the self or the other. Nevertheless, while self ER could be effective for restoring emotional balance it also *closes down* the self to other’s pain within the current social interaction. Instead, social ER entails the implementation of regulatory strategies and behaviors

towards the other's distress, as our findings indicate regulation of the self as well, in this way keeping the regulator (the self) *opened up* to the other during the current interaction. Simultaneously, regulating other's emotions can be conceived as a pragmatic and skilled way of comforting others, but also it could be a strategic way of influencing other's minds which in turn could reduce the emotional connection, like when trying to influence other's emotions driven by own selfish interests (i.e. after making a mistake, a partner attempts to cheer-up the other to avoid being blamed). Overall, the model implies that in social interactions subjects need to ponder between emotional connection (empathy - with its costs) and emotional influence (social ER), both having a different effect on the self (the regulator), on the other and on the dynamic of the interaction. So far, the model attempts to show how personal level mental processes (specially ER) interact with interpersonal (emotional) phenomena within social interactions.

Finally, the Distress-Regulation model of social interactions explicitly attempts to advance the field addressing three main points, i) it distinguishes and integrates the role of personal ER in empathy, by conceiving ER as a central determinant of individuals' empathy; ii) it dissects social ER and empathy, deflating the "over-arching" notion of empathy, narrowing its meaning to "perceiving or resonating with other's emotions", in line with the original German term *Einfühlung*, 'to take in other's feelings'. Then, social ER would correspond to the acting and influencing others' emotions, working side by side with empathy; iii) the model conceives these factors in the context of ecological social interactions. In these each subject engage in personal ER, but simultaneously expresses emotions to others, so each one perceive others' emotions (empathy) but also act (or react) on other's emotions (social ER) building up cycles of interactions. For the model, these emotional exchanges are at core of the dynamic and recursive dialectics of social interactions (see figure III).

As a direct implication for the field of clinical psychology and more specifically for psychotherapy research, the model can readily illuminate several aspects of the so called "common factors". These unspecific aspects (not related to the therapeutic technique it self), include at the center the interpersonal facets of the therapist (e.g. involved in building the therapeutic relationship), which have shown to have a reliable positive predictive effect on therapeutic outcomes (Horvath & Symonds, 1991; Martin, Garske, & Davis, 2000; Xu & Tracey, 2015). In this way

psychotherapy relies on the supportive social interaction of patient and therapist (Barker & Pistrang, 2002), which demands from the therapists the capacity to shift their focus between them self (own emotional reactions) and the other (clients' problems and emotions), but also to flexibly and skillfully move between *connecting* with the other (empathy – with its costs) and *influencing* the other (regulating others – which regulated the self as well). Interestingly, attachment- and interactive- based models of psychotherapy mechanisms have highlighted, besides empathy, the crucial relevance of social ER as one core aspect of the therapeutic relationship (Beebe & Lachmann, 1998; Dales & Jerry, 2008). So far, according with the Distress-Regulation model, to adequately achieve the therapeutic goals, and to build and sustain the therapeutic relationship, psychotherapists should master both empathy and social ER abilities, in this way navigating the dynamic complexity of (therapeutic) social interactions.



**Figure III.** The Distress-Regulation Model of Social Interactions.

## **4.6. Conclusions**

This thesis examined the relationship between mindfulness and ER and social cognition using different methodological approaches. Mindfulness and ER showed a positive relationship across different empirical models like dispositional mindfulness, MBIs and expert meditators. Coherent with this, trait mindfulness was positively associated with self-reported ER abilities, interestingly, showing self-compassion as a mediator mechanism linking mindfulness and ER. This was valid for both BPD and healthy subjects. In relating ER and social cognition, ER seems to be a predictor of emotional empathy (compassion), but not cognitive empathy (emotion recognition), with higher (or lower) ER skills linked to lower (higher) empathetic feelings for others. Concomitantly, the capacity to regulate others' emotions was linked to lower personal distress, showing 'mentalizing' brain regions (i.e. precuneus and TPJ) being active in regulating others and own distress. Thus, this indicates psychological and functional brain mechanisms of social ER.

Within the active-controlled neuro-imaging RCT, a mindfulness intervention (MBSR compared to READ) was associated with higher ER abilities, for self ER (with cognitive reappraisal & acceptance), for social ER (with cognitive reappraisal), but not with changes in social cognition (emotional and cognitive empathy). Neuronal plastic changes scaled positively with meditation practice and ER benefits, suggesting active and efficient mechanisms were in place. Finally, the Regulation-Distress model of social interaction integrated these findings together, dissociating and highlighting the differential involvement of self and social ER and empathy in the context of social interactions. Further studies are needed to corroborate and extend these findings and the model suggested. So far, the thesis highlights the intrinsic linkage between personal and social emotional phenomena, in relating ER and social cognition, hand in hand with the transforming potential of novel therapeutic interventions.

## **Abbreviations**

ER, emotion regulation.

BPD, borderline personality disorder.

READ, reading, listening and sharing group (active control group).

MBSR, mindfulness-based stress reduction (active intervention group).

MBIs, mindfulness-based interventions.

RCT, randomized controlled trial.

fMRI, functional Magnetic Resonance Imaging.

SORT, self-other emotion regulation task.

MET, multifaceted empathy test.

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