Bending Not Breaking

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Flexibility and mindfulness as resilience factors for pain and recovery

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Flexibility and mindfulness as resilience factors for pain and recovery

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CHAPTER 1

General introduction

GENERAL INTRODUCTION

Pain

The experience of pain is highly subjective. The International Association for the Study of Pain describes pain as 'an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage' (Raja et al., 2020, p. 1977). From this definition, the multidimensional character of pain becomes evident. The sensory-discriminative component concerns the intensity, quality, and spatio-temporal features of the pain sensation, whereas the affective-motivational aspect is reflected in the aversiveness and negative valence ('unpleasantness') of pain (Auvray et al., 2010; Melzack & Casey, 1986). Lastly, the cognitive-evaluative component refers to cognitive processes such as attention, anticipation, and appraisal that modify pain perception.

Pain is a crucial experience that informs us about potential physical harm or illness. It results in the activation of protective behavior including avoidance, escape, and social alarm (Eccleston & Crombez, 1999; Sullivan, 2008). However, acute pain transitions into chronic pain when it persists beyond three months (Merskey, 1986). As such, it loses its adaptive function and becomes detrimental. Chronic pain is a complex experience that is known to significantly influence physical, social and cognitive functioning. It constitutes a serious health burden affecting an estimated 20.4% of U.S. adults in 2016 (Dahlhamer et al., 2018), resulting in high health care costs and decreased work productivity (Medicine, 2011). In 2016, low back and neck pain was the health condition with the highest health care spending in the U.S. ($134.5 billion), followed by musculoskeletal disorders including joint and limb pain, myalgia, and osteoporosis ($129.8 billion), thereby exceeding the costs for diabetes ($111.2 billion) and ischemic heart disease ($89.3 billion) (Dieleman et al., 2020).

Recovery from pain

Psychosocial constructs may play a role in the transition from acute to chronic pain, as well as the maintenance of chronic pain (e.g., Edwards et al., 2016). A useful approach to study psychosocial factors contributing to the development of chronic pain is to focus on factors explaining individual differences in recovery from pain, as chronic pain can be considered an instance of non(complete)-recovery. Psychosocial factors may either put the individual at risk of, or protect against, slow recovery or the development of chronic pain (e.g., Basten-Günther et al., 2019; Iverson et al., 2017; Meints & Edwards, 2018). Taken together, the identification of both vulnerability and protective factors that influence the course of recovery is of fundamental importance to the development of a comprehensive model to predict and prevent pain chronicity.

Various methods and study designs can be employed to study recovery from pain. First, longitudinal designs are appropriate to study the course of recovery following physical trauma. Likewise, individuals scheduled for surgery form a valuable participant sample to study the factors influencing the transition of acute postsurgical pain into chronic pain. Previous research has investigated psychological risk and protective factors predicting non-recovery from pain after surgery (e.g., Giusti et al., 2021; Pinto et al., 2017). For instance, recent systematic reviews and meta-analyses have indicated that preoperative emotional distress, including anxiety, catastrophizing (i.e., exaggerated negative beliefs) and depression, are positively associated with both acute and chronic postoperative pain and disability (Giusti et al., 2021; Jackson et al., 2016; Martinez-Calderon et al., 2018). Similarly, people recovering from musculoskeletal (Vranceanu et al., 2014) and whiplash injury (Andersen et al., 2016; Bostick et al., 2013) who reported high levels of catastrophizing at baseline, were more likely to transition to chronic pain five to eight months later. Conversely, dispositional optimism has been reported to protect against acute postoperative pain (Pinto et al., 2017), and the development of chronic pain after surgery (Giusti et al., 2021) and injury (Booth-Kewley et al., 2014). In addition, self-efficacy, resilience, and expectations of recovery were shown to protect against the perpetuation of pain intensity and disability in patients with chronic shoulder pain (Martinez-Calderon et al., 2018). Also, high self-efficacy was found to be related to faster recovery from whiplash injury (Ritchie & Sterling, 2016).

Another methodological approach to examine recovery is the implementation of experimental analogues of recovery through inducing experimental pain with prolonged recovery times. One such pain method is the Delayed-Onset Muscle Soreness (DOMS) procedure for experimentally inducing muscle pain (e.g., Udermann et al., 2002). Alternatively, recovery from pain can be studied using the Submaximum Effort Tourniquet Technique (SETT) that induces ischemic pain (Moore et al., 1979). By obstructing the blood flow to the tissue (e.g., the non-dominant arm) using a tourniquet, a tonic deep aching pain is induced that is more similar to pathologic pain in terms of duration and severity (Moore et al., 1979). SETT and DOMS recovery times are typically longer than recovery times from pain induced by other pain induction procedures, such as electrocutaneous stimulation and the cold pressor task. The SETT was selected as a laboratory analogue of pain recovery in the experimental studies that are part of the current dissertation, as it is the most practical procedure of the two to implement in the lab.

Psychological flexibility

Despite increasing insights in psychosocial factors contributing to the transition from acute into chronic pain, the exact mechanisms underlying pain chronicity remain largely unknown. One candidate mechanism is a relatively new concept known as psychological flexibility. Within Acceptance and Commitment Therapy (ACT), psychological flexibility is broadly defined as the overarching process of being aware of the present moment and being capable to accept both wanted and unwanted experiences, as well as choosing to continue or adjust behavior in line with chosen values in reaction to those experiences (Hayes et al., 2012). Equally important to this definition is the ability to maintain or adjust emotions and cognitions in order to meet changing situational demands while keeping one's goals and values in mind (Block & Block, 1980; Kashdan & Rottenberg, 2010). Psychological flexibility is considered to be a hallmark of resilience (i.e., the ability to bounce back from adversity) and positive mental health outcomes (Kashdan & Rottenberg, 2010).

In the field of pain, higher levels of psychological flexibility have been shown to be associated with higher pain endurance, higher tolerance for, and faster recovery from experimentally induced pain (Feldner et al., 2006). In chronic pain patients psychological *in*flexibility has repeatedly been associated with disability (e.g., Feinstein et al., 2011; McCracken, 1998; McCracken & Velleman, 2010), higher pain intensity (Talaei-Khoei et al., 2017), anxiety and reduced quality of life (Feinstein et al., 2011). Moreover, Wicksell and Olsson (2010) have argued that psychological inflexibility is particularly worthwhile to study in the development of chronic postsurgical pain.

Taken together, these findings highlight the adaptive quality of psychological flexibility for experimentally induced acute pain as well as chronic pain. However, the role of psychological flexibility in the transition of acute pain into chronic pain (i.e., non-recovery) warrants further research. Because psychological flexibility is a complex concept reflecting a broad set of different processes, its assessment is challenging. This is illustrated by the diversity in measurement instruments and study designs employed in psychological flexibility research, including self-report measures (e.g., Francis et al., 2016), longitudinal designs making use of ecological momentary assessment (e.g., Benson et al., 2019), behavioral tasks specifically tapping into cognitive and/or emotional aspects of psychological flexibility (e.g., Boselie et al., 2017; Genet et al., 2013), and psychophysiological measures (e.g., Waugh et al., 2011). The current dissertation focuses on two specific processes considered essential to the overarching construct of psychological flexibility, namely emotional (Bonanno et al., 2004; Waugh et al., 2008) and cognitive flexibility (Whiting et al., 2015).

Emotional flexibility

Emotional flexibility refers to the ability to regulate emotions flexibly in order to meet situational demands, to recover when the emotion-provoking event has subsided, and in that way create a best possible match with the ever-changing external environment (Aldao et al., 2015; Beshai et al., 2018; Westphal et al., 2010). Moreover, it entails the flexible use of various emotion regulation strategies that are appropriate for the circumstances at that particular moment, and is adaptive to the extent that it promotes personally relevant goal pursuit (Aldao et al., 2015).

Considering the emotional component of pain, emotional flexibility may also be of relevance for coping with pain. That is, coping with pain naturally involves regulating emotions in response to a painful event. A considerable body of research has indeed indicated that emotion regulation is of relevance for pain perception. For example, emotion regulation deficits are typically related to higher levels of pain and distress (e.g., Keefe et al., 2001). In fact, a systematic review has suggested that maladaptive emotion regulation may be an important risk factor in the development of chronic pain (Koechlin et al., 2018).

Two aspects of emotional flexibility, both considered to promote effective emotion regulation (Gross, 2007), are the focus of the present dissertation. The first operationalization is *flexible emotional responsiveness* and refers to the ability to produce emotional responses flexibly to changing positive and negative environments (Hollenstein et al., 2013; Westphal et al., 2010). Accordingly, positive emotions should be evoked by positive events, and negative emotions should be evoked by negative events (Waugh et al., 2011). With regard to pain, flexible emotional responding would refer to the ability to identify pain and to respond with negative emotions, as well as to recover from those emotional responses the moment the painful event has passed. Furthermore, emotionally flexible people would also be able to experience positive emotions during positive events despite being in pain.

The second aspect of emotional flexibility is *affective flexibility*, a domain-specific instantiation of cognitive flexibility (see next section on cognitive flexibility), that is conceptualized as the flexible processing of emotional information by switching between the processing of emotional aspects and neutral information of the environment (Genet et al., 2013; Genet & Siemer, 2011; Malooly et al., 2013). Affective flexibility in the context of pain is reflected in the ability to switch between the neutral, sensory aspects (e.g., location, type of pain, pain intensity) and the affective, evaluative aspects of the pain experience. In medical settings such as a scheduled surgery, affective flexibility refers to patients being capable of focusing on the objective aspects (i.e., the surgical procedure) instead of focusing on the aversive aspects of the situation. Given the emotional dimension of pain, we propose affective flexibility to be an important explanatory factor in individual differences in the experience of, and recovery from pain.

Cognitive flexibility

Another element of the overarching concept of psychological flexibility is *cognitive flexibility*. Cognitive flexibility refers to the ability to change goals and to shift between different thoughts and behaviors as to fit changing environmental demands (Lezak, 1995). Shifting and inhibition, both aspects of executive functioning, are involved in cognitive flexibility (Miyake et al., 2000). Deficits in cognitive flexibility are the result of difficulties in inhibiting inappropriate thoughts and goals, and by problems in shifting between goals and mental sets (Genet et al., 2013). In turn, those deficits have been associated with a wide scope of mental disorders like borderline personality disorder (Ruocco, 2005), depression (Lee et al., 2012), anorexia nervosa (Abbate-Daga et al., 2011) and obsessive-compulsive disorder (Sadock & Sadock, 2007; Sternheim et al., 2014). Therefore, cognitive flexibility is considered an adaptive quality.

A number of studies has reported on the negative influence of pain on cognitive flexibility. These studies have demonstrated that acute pain both in naturalistic (e. g. Attridge et al., 2017; Attridge et al., 2016) and experimental settings (e. g. Attridge et al., 2016; Boselie et al., 2014; Eccleston, 1995; Moore et al., 2012; Van Ryckeghem et al., 2012), as well as chronic pain (Karp et al., 2006; Verdejo-García et al., 2009) can have negative effects on the performance on tasks designed to measure cognitive flexibility. For example, research has demonstrated that acute experimental pain diminishes shifting performance (Boselie et al., 2014; Van Ryckeghem et al., 2012). Others have reported the opposite effect, that is, cognitive flexibility also influences pain experience (Bjekić et al., 2018; Karsdorp et al., 2014; Oosterman et al., 2010). Specifically, impairments in cognitive flexibility have been proposed to be a precursor of more intense and prolonged pain experiences, and accordingly, contribute to pain chronicity (as reviewed in Moriarty et al., 2011). Furthermore, a prospective study reported that deficits in cognitive flexibility independently predicted the presence of chronic postsurgical pain as well as high pain intensity levels six and 12 months post-surgery (Attal et al., 2014). The current dissertation focused on both emotional and cognitive flexibility, as we were interested in their unique and combined predictive value for pain experience and recovery.

Mindfulness

According to the psychological flexibility model, psychological flexibility involves six interrelated processes that are represented in a hexagon structure (McCracken & Morley, 2014). These processes include acceptance (as opposed to avoidance of thoughts and emotions), cognitive defusion (creating distance from our thoughts instead of believing that one's thoughts are truths), flexible present-focused attention (or present-moment awareness of current emotions and sensations), self as observer (or self as context; taking a broader perspective on one's thoughts and emotions), values (knowledge of one's values), and committed action (persistence within a course of action guided by those values) (McCracken & Morley, 2014). It follows from this model that practicing mindfulness meditation may be one way to improve psychological flexibility (Duarte & Pinto-Gouveia, 2017; Labelle et al., 2015; Marais et al., 2020). A recent study demonstrated that an 8-week mindfulness-based intervention (MBI) improved psychological flexibility in academics (Marais et al., 2020). In addition, research has shown that psychological flexibility mediated the beneficial effects of mindfulness-based programs on burnout in medical staff (Duarte & Pinto-Gouveia, 2017), and on stress and mood symptoms in cancer patients (Labelle et al., 2015).

Mindfulness is a type of meditation practice that originates from reflective Eastern spiritual traditions and is directed at promoting a controlled, nonjudgmental, and non-evaluative awareness of moment-to-moment experiences (Kabat-Zinn, 1990). It involves a continued, open and accepting awareness of thoughts, feelings, physical sensations, and mental representations, without reflecting on or evaluating these perceptions. Instead of altering the content of experience, mindfulness focusses on changing the context, one's relationship, to this experience.

Various MBIs have been developed and their physical and mental health benefits have been established in clinical (e.g., Bawa et al., 2015; Chiesa & Serretti, 2011b; Cillessen et al., 2019; Demarzo et al., 2015) and nonclinical populations (e.g., Chiesa & Serretti, 2009; Eberth & Sedlmeier, 2012; Khoury et al., 2015; Lomas et al., 2019). One such intervention is mindfulness-based stress reduction (MBSR) that has been found effective in improving a wide scope of physical and mental health disorders, such as chronic pain, depression, insomnia, and addictive disorders (e.g., Chen et al., 2020; Chi et al., 2018; Goldberg et al., 2018; Khoo et al., 2019; Strauss et al., 2014). Healthy individuals also seem to benefit from MBSR: a meta-analysis demonstrated that MBSR does not only effectively reduce stress, anxiety and depression levels, but also improves quality of life in nonclinical populations (Khoury et al., 2015).

Mindfulness, pain, and recovery

Specific to the field of pain, research has indicated that MBIs can improve physical functioning and reduce pain and psychological distress in chronic pain patients (e.g., Khoo et al., 2019; Majeed et al., 2018; Reiner et al., 2013). A systematic review and two meta-analyses provide evidence for the effectiveness of MBIs for chronic pain (Chiesa & Serretti, 2011a; Garland et al., 2019; Veehof et al., 2016), however, their effect on acute pain has not been robustly established. Although Shires et al. (2020) confirmed in their systematic review and meta-analysis that MBIs effectively increase pain threshold and pain tolerance in experimental settings, they did not find evidence for MBIs' potential to decrease pain intensity and pain-related distress in either experimental or clinical studies.

Empirical evidence does not only exist for the effects of MBIs on experimental pain sensitivity, but has also emerged for the relation between mindfulness and (postoperative) recovery (e.g., Chavez et al., 2020; Dowsey et al., 2019; Ratcliff, 2015). For instance, MBSR prior to lumbar spine surgery reduced back pain 30 days later (Yi et al., 2019). At three months after surgery, the MBSR group reported higher physical functioning, lower disability, and lower pain interference compared to the control group that received standard care only (Chavez et al., 2020). At 12 months after surgery, pain interference was still lower in the MBSR group than in the control group (Chavez et al., 2020). Similarly, receiving MBSR before total joint arthroplasty resulted in reduced pain levels and enhanced joint function 12 months after surgery in comparison to treatment as usual (Dowsey et al., 2019).

In addition to pain and functional recovery, mindfulness can also affect physiological recovery. Previous studies found that participants with higher levels of dispositional mindfulness (Fogarty et al., 2015) or after six weeks of mindfulness training (Crosswell et al., 2017) showed faster recovery of physiological stress responses. Relevant in the present context is the potential effect of mindfulness on wound healing. Faster healing of physical injuries or surgical incisions might imply faster recovery of the pain and restoration of functional capacities. Research has shown that psychosocial stress impairs wound healing across different types of wound models and stressors (Bosch et al., 2007; Cole-King & Harding, 2001; Ebrecht et al., 2004; Garg et al., 2001; Kiecolt-Glaser et al., 2005; Maple et al., 2015). Stress-reducing psychosocial interventions on the other hand, can lead to faster wound healing. For instance, previous findings indicated that brief relaxation improved skin barrier recovery after mild injury, i.e., tape-stripping (Robinson et al., 2015). Correspondingly, Law et al. (2020) recently showed that environmental multisensory enrichment in the form of a companion robot improved the recovery of skin permeability after tape-stripping following a laboratory stressor. In addition, expressive writing and brief relaxation with guided imagery improved the healing of skin biopsy wounds (Robinson et al., 2017; Weinman et al., 2008) and surgical wounds (Broadbent et al., 2012). Given that previous research has consistently demonstrated the stress-reducing effects of MBIs (e.g., Khoury et al., 2015), mindfulness in relation to wound healing could be an interesting avenue for further study.

Mechanisms of mindfulness

Enhancements in psychological flexibility (Duarte & Pinto-Gouveia, 2017; Labelle et al., 2015; Marais et al., 2020), and its subcomponents emotional flexibility (Zeidan et al., 2012; Zeidan & Vago, 2016) and cognitive flexibility (Gu et al., 2015; Zeidan et al., 2012), are among the mechanisms that have been proposed to underlie the analgesic effects of mindfulness. First, considering affective flexibility, a two-part study by Ortner et al. (2007) revealed that the level of mindfulness experience in meditators was related to a decrease in reactivity to both positive and negative stimuli, and that participants were faster in disengaging from negative stimuli after a 7-week mindfulness training. These findings suggest that people exhibiting higher levels of mindfulness may be better able to inhibit or disengage from (irrelevant) affective information and to shift more easily between processing stimuli of different emotional valence.

Second, a systematic review and meta-analysis found support for cognitive flexibility as explanatory mechanism of mindfulness (Gu et al., 2015). More specifically, mindfulness seems to improve processes related to cognitive flexibility (as reviewed in Gallant, 2016). For instance, research showed that MBSR increases the performance on a shifting task in older adults (Moynihan et al., 2013).

Lastly, physiological wound healing processes may function as explanatory mechanisms for the effect of mindfulness on physiological recovery. Pro-inflammatory cytokines such as interleukin(IL)-8 and tumor necrosis factor (TNF)-α are crucial for successful wound healing, and their up-regulation is seen during the inflammatory phase of healing (Werner & Grose, 2003). Rosenkranz et al. (2013) studied the impact of MBSR on IL-8 and TNF-α levels in skin blisters in reaction to a laboratory stressor and an inflammatory stimulus (i.e., capsaicin exposure). Although no overall intervention effect was observed, the authors found that more intensive MBSR practice was related to a decrease in TNF-α levels from pre- to post-intervention in response to psychosocial stress and an inflammatory stimulus. All in all, research into the mediators of the effect of mindfulness on pain experience and (physiological) recovery is still in its infancy, and therefore, deserves further consideration.

Aims of the present dissertation

The general aim of the current dissertation is to examine psychological flexibility (i.e., emotional and cognitive flexibility) and mindfulness in relation to pain experience and recovery. More specifically, the protective role of psychological flexibility and mindfulness are studied in controlled experimental lab studies. In light of this main goal, the current dissertation has the following aims:

1. To investigate whether two aspects of emotional flexibility (i.e., flexible emotional responsiveness and affective flexibility) predict tolerance for and recovery from experimentally induced pain;
2. To examine the additive value of affective flexibility in explaining the experience of pain, above and beyond that of cognitive flexibility;
3. To investigate whether mindfulness can influence the experience of pain, and can contribute to pain recovery and recovery of wounds;
4. To study whether the effect of mindfulness on recovery is mediated by i) affective and/or cognitive flexibility, and/or by ii) physiological wound healing processes.

Outline

Chapter 2 describes a cross-sectional observational study that examined the relationship between two aspects of emotional flexibility (i.e., flexible emotional responsiveness and affective flexibility) and pain sensitivity. We used a Tourniquet pain procedure (i.e., the SETT) to induce ischemic pain. We hypothesized that more emotional flexibility would be associated with higher pain tolerance and a quicker recovery from pain in terms of pain intensity and pain unpleasantness ratings.

A second cross-sectional observational study that examined the unique and combined predictive value of affective and cognitive flexibility for the experience of experimentally induced heat pain is presented in **chapter 3**. We added a non-affective measure of cognitive flexibility with the aim to determine whether affective flexibility could predict the experience of pain beyond variation explained by general cognitive flexibility. It was hypothesized that better performance on both flexibility measures would be associated with higher heat pain threshold and tolerance. As a secondary aim, we also examined whether more affective and/or cognitive flexibility would be associated with lower subjective pain ratings (i.e., anticipated and retrospective pain intensity, pain unpleasantness and fear of pain ratings).

Chapter 4 presents an experimental study that investigated the effects of mindfulness on pain experience and recovery, as well as on cognitive and affective flexibility. We hypothesized that participants in the mindfulness condition would exhibit a higher pain tolerance and reduced subjective stress ratings than participants in the control condition. In addition, faster recovery in terms of pain intensity and pain unpleasantness ratings was expected in participants in the mindfulness condition. We also predicted that mindfulness would improve both cognitive and affective flexibility and explored their mediating role in the effect of mindfulness on pain outcomes.

Chapter 5 reports on an experimental study that examined the effects of an 8-week MBSR intervention on recovery measured as the healing speed of skin blisters, and explored local pro-inflammatory cytokine and growth factor levels in wound fluid as potential mediators of recovery. Skin blisters were induced on the forearm using a suction method. Skin permeability as indexed by trans-epidermal water loss (TEWL), and wound size were determined once daily at day 3, 4, 5, 6, 7, and 10 after wounding. Cytokines (i.e., IL-1β, IL-6, IL-8 and TNF-α) and growth factors (i.e., VEGF, PlGF and the soluble Fms-like tyrosine kinase-1) were measured in wound exudates taken at 3, 6, and 22 h after injury. We hypothesized that individuals receiving the MBSR training would display a faster decrease in TEWL and wound size over the course of 10 days.

A summary and integrative discussion of the main results obtained in the individual studies as part of the current dissertation are presented in **chapter 6**. This final chapter also describes potential study implications and limitations, as well as recommendations for future research.

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REFERENCES

Abbate-Daga, G., Buzzichelli, S., Amianto, F., Rocca, G., Marzola, E., McClintock, S. M., & Fassino, S. (2011). Cognitive flexibility in verbal and nonverbal domains and decision making in anorexia nervosa patients: a pilot study. *BMC Psychiatry, 11*(1), 162. https://doi.org/10.1186/1471-244x-11-162

Aldao, A., Sheppes, G., & Gross, J. J. (2015). Emotion regulation flexibility. *Cognitive Therapy and Research, 39*(3), 263-278. https://doi.org/10.1007/s10608-014-9662-4

Andersen, T. E., Karstoft, K.-I., Brink, O., & Elklit, A. (2016). Pain-catastrophizing and fear-avoidance beliefs as mediators between post-traumatic stress symptoms and pain following whiplash injury – A prospective cohort study. *European Journal of Pain, 20*(8), 1241-1252. https://doi.org/10.1002/ejp.848

Attal, N., Masselin-Dubois, A., Martinez, V., Jayr, C., Albi, A., Fermanian, J., Bouhassira, D., & Baudic, S. (2014). Does cognitive functioning predict chronic pain? Results from a prospective surgical cohort. *Brain, 137*(Pt 3), 904-917. https://doi.org/10.1093/brain/awt354

Attridge, N., Eccleston, C., Noonan, D., Wainwright, E., & Keogh, E. (2017). Headache impairs attentional performance: a conceptual replication and extension. *Journal of Pain, 18*(1), 29.

Attridge, N., Keogh, E., & Eccleston, C. (2016). The effect of pain on task switching: pain reduces accuracy and increases reaction times across multiple switching paradigms. *PAIN, 157*(10), 2179-2193. https://doi.org/10.1097/j.pain.0000000000000627

Auvray, M., Myin, E., & Spence, C. (2010). The sensory-discriminative and affective-motivational aspects of pain. *Neurosci Biobehav Rev, 34*(2), 214-223. https://doi.org/10.1016/j.neubiorev.2008.07.008

Basten-Günther, J., Peters, M., & Lautenbacher, S. (2019). Optimism and the Experience of Pain: A Systematic Review. *Behav Med, 45*(4), 323-339. https://doi.org/10.1080/08964289.2018.1517242

Bawa, F. L., Mercer, S. W., Atherton, R. J., Clague, F., Keen, A., Scott, N. W., & Bond, C. M. (2015). Does mindfulness improve outcomes in patients with chronic pain? Systematic review and meta-analysis. *Br J Gen Pract, 65*(635), e387-400. https://doi.org/10.3399/bjgp15X685297

Benson, L., English, T., Conroy, D. E., Pincus, A. L., Gerstorf, D., & Ram, N. (2019). Age differences in emotion regulation strategy use, variability, and flexibility: An experience sampling approach. *Dev Psychol, 55*(9), 1951-1964. https://doi.org/10.1037/dev0000727

Beshai, S., Prentice, J. L., & Huang, V. (2018). Building Blocks of Emotional Flexibility: Trait Mindfulness and Self-Compassion Are Associated with Positive and Negative Mood Shifts. *Mindfulness, 9*(3), 939-948. https://doi.org/10.1007/s12671-017-0833-8

Bjekić, J., Živanović, M., Purić, D., Oosterman, J. M., & Filipović, S. R. (2018). Pain and executive functions: a unique relationship between Stroop task and experimentally induced pain. *Psychological Research, 82*(3), 580-589. https://doi.org/10.1007/s00426-016-0838-2

Block, J. H., & Block, J. (1980). *The role of ego-control and ego-resiliency in the origination of behavior* (W. A. Collings, Ed. Vol. 13). Erlbaum.

Bonanno, G. A., Papa, A., Lalande, K., Westphal, M., & Coifman, K. (2004). The importance of being flexible: the ability to both enhance and suppress emotional expression predicts long-term adjustment. *Psychol Sci, 15*(7), 482-487. https://doi.org/10.1111/j.0956-7976.2004.00705.x

Booth-Kewley, S., Schmied, E. A., Highfill-McRoy, R. M., Sander, T. C., Blivin, S. J., & Garland, C. F. (2014). A Prospective Study of Factors Affecting Recovery from Musculoskeletal Injuries. *Journal of Occupational Rehabilitation, 24*(2), 287-296. https://doi.org/10.1007/s10926-013-9456-7

Bosch, J. A., Engeland, C. G., Cacioppo, J. T., & Marucha, P. T. (2007). Depressive Symptoms Predict Mucosal Wound Healing. *Psychosomatic Medicine, 69*(7). https://doi.org/10.1097/PSY.0b013e318148c682

Boselie, J. J., Vancleef, L. M., & Peters, M. L. (2017). Increasing Optimism Protects Against Pain-Induced Impairment in Task-Shifting Performance. *J Pain, 18*(4), 446-455. https://doi.org/10.1016/j.jpain.2016.12.007

Boselie, J. J., Vancleef, L. M., Smeets, T., & Peters, M. L. (2014). Increasing optimism abolishes pain-induced impairments in executive task performance. *PAIN, 155*(2), 334-340. https://doi.org/10.1016/j.pain.2013.10.014

Bostick, G. P., Carroll, L. J., Brown, C. A., Harley, D., & Gross, D. P. (2013). Predictive capacity of pain beliefs and catastrophizing in Whiplash Associated Disorder. *Injury, 44*(11), 1465-1471. https://doi.org/10.1016/j.injury.2012.10.007

Broadbent, E., Kahokehr, A., Booth, R. J., Thomas, J., Windsor, J. A., Buchanan, C. M., Wheeler, B. R. L., Sammour, T., & Hill, A. G. (2012). A brief relaxation intervention reduces stress and improves surgical wound healing response: A randomised trial. *Brain, Behavior, and Immunity, 26*(2), 212-217. https://doi.org/10.1016/j.bbi.2011.06.014

Chavez, J. L., Porucznik, C. A., Gren, L. H., Guan, J., Joyce, E., Brodke, D. S., Dailey, A. T., Mahan, M. A., Hood, R. S., Lawrence, B. D., Spiker, W. R., Spina, N. T., & Bisson, E. F. (2020). The Impact of Preoperative Mindfulness-Based Stress Reduction on Postoperative Outcomes in Lumbar Spine Degenerative Disease: 3-Month and 12-Month Results of a Pilot Study. *World Neurosurg, 139*, e230-e236. https://doi.org/10.1016/j.wneu.2020.03.186

Chen, T. L., Chang, S. C., Hsieh, H. F., Huang, C. Y., Chuang, J. H., & Wang, H. H. (2020). Effects of mindfulness-based stress reduction on sleep quality and mental health for insomnia patients: A meta-analysis. *J Psychosom Res, 135*, 110144. https://doi.org/10.1016/j.jpsychores.2020.110144

Chi, X., Bo, A., Liu, T., Zhang, P., & Chi, I. (2018). Effects of Mindfulness-Based Stress Reduction on Depression in Adolescents and Young Adults: A Systematic Review and Meta-Analysis. *Front Psychol, 9*, 1034. https://doi.org/10.3389/fpsyg.2018.01034

Chiesa, A., & Serretti, A. (2009). Mindfulness-based stress reduction for stress management in healthy people: a review and meta-analysis. *J Altern Complement Med, 15*(5), 593-600. https://doi.org/10.1089/acm.2008.0495

Chiesa, A., & Serretti, A. (2011a). Mindfulness-based interventions for chronic pain: a systematic review of the evidence. *J Altern Complement Med, 17*(1), 83-93. https://doi.org/10.1089/acm.2009.0546

Chiesa, A., & Serretti, A. (2011b). Mindfulness based cognitive therapy for psychiatric disorders: A systematic review and meta-analysis. *Psychiatry Research, 187*(3), 441-453. https://doi.org/10.1016/j.psychres.2010.08.011

Cillessen, L., Johannsen, M., Speckens, A. E. M., & Zachariae, R. (2019). Mindfulness-based interventions for psychological and physical health outcomes in cancer patients and survivors: A systematic review and meta-analysis of randomized controlled trials. *Psychooncology, 28*(12), 2257-2269. https://doi.org/10.1002/pon.5214

Cole-King, A., & Harding, K. G. (2001). Psychological Factors and Delayed Healing in Chronic Wounds. *Psychosomatic Medicine, 63*(2), 216-220. https://doi.org/10.1097/00006842-200103000-00004

Crosswell, A. D., Moreno, P. I., Raposa, E. B., Motivala, S. J., Stanton, A. L., Ganz, P. A., & Bower, J. E. (2017). Effects of mindfulness training on emotional and physiologic recovery from induced negative affect. *Psychoneuroendocrinology, 86*, 78-86. https://doi.org/10.1016/j.psyneuen.2017.08.003

Dahlhamer, J., Lucas, J., Zelaya, C., Nahin, R., Mackey, S., DeBar, L., Kerns, R., Von Korff, M., Porter, L., & Helmick, C. (2018). Prevalence of Chronic Pain and High-Impact Chronic Pain Among Adults — United States, 2016. *Morbidity and Mortality Weekly Report, 67*(36), 1001–1006. https://doi.org/10.15585/mmwr.mm6736a2

Demarzo, M. M. P., Montero-Marin, J., Cuijpers, P., Zabaleta-del-Olmo, E., Mahtani, K. R., Vellinga, A., Vicens, C., López-del-Hoyo, Y., & García-Campayo, J. (2015). The Efficacy of Mindfulness-Based Interventions in Primary Care: A Meta-Analytic Review. *The Annals of Family Medicine, 13*(6), 573-582. https://doi.org/10.1370/afm.1863

Dieleman, J. L., Cao, J., Chapin, A., Chen, C., Li, Z., Liu, A., Horst, C., Kaldjian, A., Matyasz, T., Scott, K. W., Bui, A. L., Campbell, M., Duber, H. C., Dunn, A. C., Flaxman, A. D., Fitzmaurice, C., Naghavi, M., Sadat, N., Shieh, P., Squires, E., Yeung, K., & Murray, C. J. L. (2020). US Health Care Spending by Payer and Health Condition, 1996-2016. *JAMA, 323*(9), 863-884. https://doi.org/10.1001/jama.2020.0734

Dowsey, M., Castle, D., Knowles, S., Monshat, K., Salzberg, M., Nelson, E., Dunin, A., Dunin, J., Spelman, T., & Choong, P. (2019). The effect of mindfulness training prior to total joint arthroplasty on post-operative pain and physical function: A randomised controlled trial. *Complementary Therapies in Medicine, 46*, 195-201. https://doi.org/10.1016/j.ctim.2019.08.010

Duarte, J., & Pinto-Gouveia, J. (2017). Mindfulness, self-compassion and psychological inflexibility mediate the effects of a mindfulness-based intervention in a sample of oncology nurses. *Journal of Contextual Behavioral Science, 6*(2), 125-133. https://doi.org/10.1016/j.jcbs.2017.03.002

Eberth, J., & Sedlmeier, P. (2012). The Effects of Mindfulness Meditation: A Meta-Analysis. *Mindfulness, 3*(3), 174-189. https://doi.org/10.1007/s12671-012-0101-x

Ebrecht, M., Hextall, J., Kirtley, L.-G., Taylor, A., Dyson, M., & Weinman, J. (2004). Perceived stress and cortisol levels predict speed of wound healing in healthy male adults. *Psychoneuroendocrinology, 29*(6), 798-809. https://doi.org/10.1016/S0306-4530(03)00144-6

Eccleston, C. (1995). Chronic pain and distraction: an experimental investigation into the role of sustained and shifting attention in the processing of chronic persistent pain. *Behav Res Ther, 33*(4), 391-405. https://doi.org/10.1016/0005-7967(94)00057-q

Eccleston, C., & Crombez, G. (1999). Pain demands attention: a cognitive-affective model of the interruptive function of pain. *Psychol Bull, 125*(3), 356-366.

Edwards, R. R., Dworkin, R. H., Sullivan, M. D., Turk, D. C., & Wasan, A. D. (2016). The Role of Psychosocial Processes in the Development and Maintenance of Chronic Pain. *The Journal of Pain, 17*(9 Suppl), T70-T92. https://doi.org/10.1016/j.jpain.2016.01.001

Feinstein, A. B., Forman, E. M., Masuda, A., Cohen, L. L., Herbert, J. D., Moorthy, L. N., & Goldsmith, D. P. (2011). Pain intensity, psychological inflexibility, and acceptance of pain as predictors of functioning in adolescents with juvenile idiopathic arthritis: a preliminary investigation. *J Clin Psychol Med Settings, 18*(3), 291-298. https://doi.org/10.1007/s10880-011-9243-6

Feldner, M. T., Hekmat, H., Zvolensky, M. J., Vowles, K. E., Secrist, Z., & Leen-Feldner, E. W. (2006). The role of experiential avoidance in acute pain tolerance: A laboratory test. *Journal of Behavior Therapy and Experimental Psychiatry, 37*(2), 146-158. https://doi.org/10.1016/j.jbtep.2005.03.002

Fogarty, F. A., Lu, L. M., Sollers, J. J., Krivoschekov, S. G., Booth, R. J., & Consedine, N. S. (2015). Why It Pays to be Mindful: Trait Mindfulness Predicts Physiological Recovery from Emotional Stress and Greater Differentiation among Negative Emotions. *Mindfulness, 6*(2), 175-185. https://doi.org/10.1007/s12671-013-0242-6

Francis, A. W., Dawson, D. L., & Golijani-Moghaddam, N. (2016). The development and validation of the Comprehensive assessment of Acceptance and Commitment Therapy processes (CompACT). *Journal of Contextual Behavioral Science, 5*(3), 134-145. https://doi.org/10.1016/j.jcbs.2016.05.003

Gallant, S. N. (2016). Mindfulness meditation practice and executive functioning: Breaking down the benefit. *Conscious Cogn, 40*, 116-130. https://doi.org/10.1016/j.concog.2016.01.005

Garg, A., Chren, M. M., Sands, L. P., Matsui, M. S., Marenus, K. D., Feingold, K. R., & Elias, P. M. (2001). Psychological Stress Perturbs Epidermal Permeability Barrier Homeostasis: Implications for the Pathogenesis of Stress-Associated Skin Disorders. *Archives of Dermatology, 137*(1), 53-59. https://doi.org/10.1001/archderm.137.1.53

Garland, E. L., Brintz, C. E., Hanley, A. W., Roseen, E. J., Atchley, R. M., Gaylord, S. A., Faurot, K. R., Yaffe, J., Fiander, M., & Keefe, F. J. (2019). Mind-Body Therapies for Opioid-Treated Pain: A Systematic Review and Meta-analysis. *JAMA internal medicine, 180*(1), 91-105. https://doi.org/10.1001/jamainternmed.2019.4917

Genet, J. J., Malooly, A. M., & Siemer, M. (2013). Flexibility is not always adaptive: affective flexibility and inflexibility predict rumination use in everyday life. *Cogn Emot, 27*(4), 685-695. https://doi.org/10.1080/02699931.2012.733351

Genet, J. J., & Siemer, M. (2011). Flexible control in processing affective and non-affective material predicts individual differences in trait resilience. *Cogn Emot, 25*(2), 380-388. https://doi.org/10.1080/02699931.2010.491647

Giusti, E. M., Lacerenza, M., Manzoni, G. M., & Castelnuovo, G. (2021). Psychological and psychosocial predictors of chronic postsurgical pain: a systematic review and meta-analysis. *PAIN, 162*(1), 10-30. https://doi.org/10.1097/j.pain.0000000000001999

Goldberg, S. B., Tucker, R. P., Greene, P. A., Davidson, R. J., Wampold, B. E., Kearney, D. J., & Simpson, T. L. (2018). Mindfulness-based interventions for psychiatric disorders: A systematic review and meta-analysis. *Clinical Psychology Review, 59*, 52-60. https://doi.org/10.1016/j.cpr.2017.10.011

Gross, J. J. (2007). *Handbook of emotion regulation*. Guilford Press.

Gu, J., Strauss, C., Bond, R., & Cavanagh, K. (2015). How do mindfulness-based cognitive therapy and mindfulness-based stress reduction improve mental health and wellbeing? A systematic review and meta-analysis of mediation studies. *Clin Psychol Rev, 37*, 1-12. https://doi.org/10.1016/j.cpr.2015.01.006

Hayes, S. C., Pistorello, J., & Levin, M. E. (2012). Acceptance and Commitment Therapy as a Unified Model of Behavior Change. *The Counseling Psychologist, 40*(7), 976-1002. https://doi.org/10.1177/0011000012460836

Hollenstein, T., Lichtwarck-Aschoff, A., & Potworowski, G. (2013). A model of socioemotonal flexibility at three time scales. *Emot Rev, 5*, 397–405. https://doi.org/10.1177/1754073913484181er.sagepub.com

Iverson, G. L., Gardner, A. J., Terry, D. P., Ponsford, J. L., Sills, A. K., Broshek, D. K., & Solomon, G. S. (2017). Predictors of clinical recovery from concussion: a systematic review. *Br J Sports Med, 51*(12), 941-948. https://doi.org/10.1136/bjsports-2017-097729

Jackson, T., Tian, P., Wang, Y., Iezzi, T., & Xie, W. (2016). Toward Identifying Moderators of Associations Between Presurgery Emotional Distress and Postoperative Pain Outcomes: A Meta-Analysis of Longitudinal Studies. *J Pain, 17*(8), 874-888. https://doi.org/10.1016/j.jpain.2016.04.003

Kabat-Zinn, J. (1990). *Full Catastrophe Living*. Delacorte.

Karp, J. F., Reynolds, C. F., III, Butters, M. A., Dew, M. A., Mazumdar, S., Begley, A. E., Lenze, E., & Weiner, D. K. (2006). The Relationship Between Pain and Mental Flexibility in Older Adult Pain Clinic Patients. *Pain Medicine, 7*(5), 444-452. https://doi.org/10.1111/j.1526-4637.2006.00212.x

Karsdorp, P. A., Geenen, R., & Vlaeyen, J. W. (2014). Response inhibition predicts painful task duration and performance in healthy individuals performing a cold pressor task in a motivational context. *Eur J Pain, 18*(1), 92-100. https://doi.org/10.1002/j.1532-2149.2013.00348.x

Kashdan, T. B., & Rottenberg, J. (2010). Psychological flexibility as a fundamental aspect of health. *Clinical Psychology Review, 30*(7), 865-878. https://doi.org/10.1016/j.cpr.2010.03.001

Keefe, F. J., Lumley, M., Anderson, T., Lynch, T., Studts, J. L., & Carson, K. L. (2001). Pain and emotion: new research directions. *J Clin Psychol, 57*(4), 587-607.

Khoo, E. L., Small, R., Cheng, W., Hatchard, T., Glynn, B., Rice, D. B., Skidmore, B., Kenny, S., Hutton, B., & Poulin, P. A. (2019). Comparative evaluation of group-based mindfulness-based stress reduction and cognitive behavioural therapy for the treatment and management of chronic pain: A systematic review and network meta-analysis. *Evid Based Ment Health, 22*(1), 26-35. https://doi.org/10.1136/ebmental-2018-300062

Khoury, B., Sharma, M., Rush, S. E., & Fournier, C. (2015). Mindfulness-based stress reduction for healthy individuals: A meta-analysis. *Journal of Psychosomatic Research, 78*(6), 519-528. https://doi.org/10.1016/j.jpsychores.2015.03.009

Kiecolt-Glaser, J. K., Loving, T. J., Stowell, J. R., Malarkey, W. B., Lemeshow, S., Dickinson, S. L., & Glaser, R. (2005). Hostile Marital Interactions, Proinflammatory Cytokine Production, and Wound Healing. *Archives of General Psychiatry, 62*(12), 1377-1384. https://doi.org/10.1001/archpsyc.62.12.1377

Koechlin, H., Coakley, R., Schechter, N., Werner, C., & Kossowsky, J. (2018). The role of emotion regulation in chronic pain: A systematic literature review. *J Psychosom Res, 107*, 38-45. https://doi.org/10.1016/j.jpsychores.2018.02.002

Labelle, L. E., Campbell, T. S., Faris, P., & Carlson, L. E. (2015). Mediators of Mindfulness-Based Stress Reduction (MBSR): Assessing the Timing and Sequence of Change in Cancer Patients. *Journal of Clinical Psychology, 71*(1), 21-40. https://doi.org/10.1002/jclp.22117

Law, M., Jarrett, P., Nater, U. M., Skoluda, N., & Broadbent, E. (2020). The Effects of Sensory Enrichment After a Laboratory Stressor on Human Skin Barrier Recovery in a Randomized Trial. *Psychosomatic Medicine, 82*(9), 877-886. https://doi.org/10.1097/psy.0000000000000858

Lee, R. S., Hermens, D. F., Porter, M. A., & Redoblado-Hodge, M. A. (2012). A meta-analysis of cognitive deficits in first-episode Major Depressive Disorder. *J Affect Disord, 140*(2), 113-124. https://doi.org/10.1016/j.jad.2011.10.023

Lezak, M. D. (1995). *Neuropsychological assessment* (3 ed.). Oxford University Press.

Lomas, T., Medina, J. C., Ivtzan, I., Rupprecht, S., & Eiroa-Orosa, F. J. (2019). A Systematic Review and Meta-analysis of the Impact of Mindfulness-Based Interventions on the Well-Being of Healthcare Professionals. *Mindfulness, 10*(7), 1193-1216. https://doi.org/10.1007/s12671-018-1062-5

Majeed, M. H., Ali, A. A., & Sudak, D. M. (2018). Mindfulness-based interventions for chronic pain: Evidence and applications. *Asian Journal of Psychiatry, 32*, 79-83. https://doi.org/10.1016/j.ajp.2017.11.025

Malooly, A. M., Genet, J. J., & Siemer, M. (2013). Individual differences in reappraisal effectiveness: the role of affective flexibility. *Emotion, 13*(2), 302-313. https://doi.org/10.1037/a0029980

Maple, H., Chilcot, J., Lee, V., Simmonds, S., Weinman, J., & Mamode, N. (2015). Stress predicts the trajectory of wound healing in living kidney donors as measured by high-resolution ultrasound. *Brain, Behavior, and Immunity, 43*, 19-26. https://doi.org/10.1016/j.bbi.2014.06.012

Marais, G., Lantheaume, S., Fiault, R., & Shankland, R. (2020). *Mindfulness-based programs improve psychological flexibility, mental health, well-being and time management in academics*. https://doi.org/10.31234/osf.io/9w4zp

Martinez-Calderon, J., Meeus, M., Struyf, F., Miguel Morales-Asencio, J., Gijon-Nogueron, G., & Luque-Suarez, A. (2018). The role of psychological factors in the perpetuation of pain intensity and disability in people with chronic shoulder pain: a systematic review. *BMJ Open, 8*(4), e020703. https://doi.org/10.1136/bmjopen-2017-020703

McCracken, L. M. (1998). Learning to live with the pain: acceptance of pain predicts adjustment in persons with chronic pain. *PAIN, 74*(1), 21-27. https://doi.org/10.1016/s0304-3959(97)00146-2

McCracken, L. M., & Morley, S. (2014). The Psychological Flexibility Model: A Basis for Integration and Progress in Psychological Approaches to Chronic Pain Management. *The Journal of Pain, 15*(3), 221-234. https://doi.org/10.1016/j.jpain.2013.10.014

McCracken, L. M., & Velleman, S. C. (2010). Psychological flexibility in adults with chronic pain: a study of acceptance, mindfulness, and values-based action in primary care. *PAIN, 148*(1), 141-147. https://doi.org/10.1016/j.pain.2009.10.034

Medicine, I. o. (2011). *Relieving pain in America: A blueprint for transforming prevention, care, education and research.* Washington, DC: The National Academies Press. .

Meints, S. M., & Edwards, R. R. (2018). Evaluating psychosocial contributions to chronic pain outcomes. *Prog Neuropsychopharmacol Biol Psychiatry, 87*(Pt B), 168-182. https://doi.org/10.1016/j.pnpbp.2018.01.017

Melzack, R., & Casey, K. L. (1986). Sensory, motivational, and central determinants of pain: a new conceptual model. In *The skin senses* (pp. 423-443). Thomas, Springfield, IL.

Merskey, H. (1986). *Classification of chronic pain: Descriptions of chronic pain syndromes and definitions of pain terms*. Pain.

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The unity and diversity of executive functions and their contributions to complex “Frontal Lobe” tasks: a latent variable analysis. *Cogn Psychol, 41*(1), 49-100. https://doi.org/10.1006/cogp.1999.0734

Moore, D. J., Keogh, E., & Eccleston, C. (2012). The interruptive effect of pain on attention. *Q J Exp Psychol (Hove), 65*(3), 565-586. https://doi.org/10.1080/17470218.2011.626865

Moore, P. A., Duncan, G. H., Scott, D. S., Gregg, J. M., & Ghia, J. N. (1979). The submaximal effort tourniquet test: its use in evaluating experimental and chronic pain. *PAIN, 6*(3), 375-382.

Moriarty, O., McGuire, B. E., & Finn, D. P. (2011). The effect of pain on cognitive function: a review of clinical and preclinical research. *Prog Neurobiol, 93*(3), 385-404. https://doi.org/10.1016/j.pneurobio.2011.01.002

Moynihan, J. A., Chapman, B. P., Klorman, R., Krasner, M. S., Duberstein, P. R., Brown, K. W., & Talbot, N. L. (2013). Mindfulness-based stress reduction for older adults: effects on executive function, frontal alpha asymmetry and immune function. *Neuropsychobiology, 68*(1), 34-43. https://doi.org/10.1159/000350949

Oosterman, J. M., Dijkerman, H. C., Kessels, R. P., & Scherder, E. J. (2010). A unique association between cognitive inhibition and pain sensitivity in healthy participants. *Eur J Pain, 14*(10), 1046-1050. https://doi.org/10.1016/j.ejpain.2010.04.004

Ortner, C. N. M., Kilner, S. J., & Zelazo, P. D. (2007). Mindfulness meditation and reduced emotional interference on a cognitive task. *Motivation and Emotion, 31*(4), 271-283. https://doi.org/10.1007/s11031-007-9076-7

Pinto, P. R., McIntyre, T., Araújo-Soares, V., Costa, P., Ferrero, R., & Almeida, A. (2017). A comparison of predictors and intensity of acute postsurgical pain in patients undergoing total hip and knee arthroplasty. *Journal of pain research, 10*, 1087-1098. https://doi.org/10.2147/JPR.S126467

Raja, S. N., Carr, D. B., Cohen, M., Finnerup, N. B., Flor, H., Gibson, S., Keefe, F. J., Mogil, J. S., Ringkamp, M., Sluka, K. A., Song, X.-J., Stevens, B., Sullivan, M. D., Tutelman, P. R., Ushida, T., & Vader, K. (2020). The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. *PAIN, 161*(9), 1976-1982. https://doi.org/10.1097/j.pain.0000000000001939

Ratcliff, C. G. (2015). *Brief Guided Mindfulness Meditation for Women Undergoing Stereotactic Breast Biopsy: Effects on Patient Self-Report, EEG Activity, and Physiological Measures.* (Unpublished doctoral dissertation). University of Houston, Houston, Texas.

Reiner, K., Tibi, L., & Lipsitz, J. D. (2013). Do Mindfulness-Based Interventions Reduce Pain Intensity? A Critical Review of the Literature. *Pain Medicine, 14*(2), 230-242. https://doi.org/10.1111/pme.12006

Ritchie, C., & Sterling, M. (2016). Recovery Pathways and Prognosis After Whiplash Injury. *Journal of Orthopaedic & Sports Physical Therapy, 46*(10), 851-861. https://doi.org/10.2519/jospt.2016.6918

Robinson, H., Jarrett, P., & Broadbent, E. (2015). The Effects of Relaxation Before or After Skin Damage on Skin Barrier Recovery: A Preliminary Study. *Psychosomatic Medicine, 77*(8), 844-852. https://doi.org/10.1097/psy.0000000000000222

Robinson, H., Jarrett, P., Vedhara, K., & Broadbent, E. (2017). The effects of expressive writing before or after punch biopsy on wound healing. *Brain, Behavior, and Immunity, 61*, 217-227. https://doi.org/10.1016/j.bbi.2016.11.025

Rosenkranz, M. A., Davidson, R. J., MacCoon, D. G., Sheridan, J. F., Kalin, N. H., & Lutz, A. (2013). A comparison of mindfulness-based stress reduction and an active control in modulation of neurogenic inflammation. *Brain, Behavior, and Immunity, 27*, 174-184. https://doi.org/10.1016/j.bbi.2012.10.013

Ruocco, A. C. (2005). The neuropsychology of borderline personality disorder: a meta-analysis and review. *Psychiatry Res, 137*(3), 191-202. https://doi.org/10.1016/j.psychres.2005.07.004

Sadock, B. J., & Sadock, V. A. (2007). *Synopsis of psychiatry* (10 ed.). Wolters Kluwer Business.

Shires, A., Sharpe, L., Davies, J. N., & Newton-John, T. R. O. (2020). The efficacy of mindfulness-based interventions in acute pain: a systematic review and meta-analysis. *PAIN, 161*(8). https://doi.org/10.1097/j.pain.0000000000001877

Sternheim, L., van der Burgh, M., Berkhout, L. J., Dekker, M. R., & Ruiter, C. (2014). Poor cognitive flexibility, and the experience thereof, in a subclinical sample of female students with obsessive-compulsive symptoms. *Scand J Psychol, 55*(6), 573-577. https://doi.org/10.1111/sjop.12163

Strauss, C., Cavanagh, K., Oliver, A., & Pettman, D. (2014). Mindfulness-based interventions for people diagnosed with a current episode of an anxiety or depressive disorder: a meta-analysis of randomised controlled trials. *PLoS One, 9*(4), e96110. https://doi.org/10.1371/journal.pone.0096110

Sullivan, M. J. (2008). Toward a biopsychomotor conceptualization of pain: implications for research and intervention. *Clin J Pain, 24*(4), 281-290. https://doi.org/10.1097/AJP.0b013e318164bb15

Talaei-Khoei, M., Fischerauer, S. F., Lee, S. G., Ring, D., & Vranceanu, A. M. (2017). Pain Catastrophizing Mediates the Effect of Psychological Inflexibility on Pain Intensity and Upper Extremity Physical Function in Patients with Upper Extremity Illness. *Pain Pract, 17*(1), 129-140. https://doi.org/10.1111/papr.12494

Udermann, B., Mayer, J., Graves, J., & Lori, L. (2002). Development of an exercise protocol to elicit delayed-onset muscle soreness in the lumbar extensors. *Int Sports J*(Summer), 128–135.

Van Ryckeghem, D. M., Crombez, G., Eccleston, C., Liefooghe, B., & Van Damme, S. (2012). The interruptive effect of pain in a multitask environment: an experimental investigation. *J Pain, 13*(2), 131-138. https://doi.org/10.1016/j.jpain.2011.09.003

Veehof, M. M., Trompetter, H. R., Bohlmeijer, E. T., & Schreurs, K. M. (2016). Acceptance- and mindfulness-based interventions for the treatment of chronic pain: a meta-analytic review. *Cogn Behav Ther, 45*(1), 5-31. https://doi.org/10.1080/16506073.2015.1098724

Verdejo-García, A., López-Torrecillas, F., Calandre, E. P., Delgado-Rodríguez, A., & Bechara, A. (2009). Executive function and decision-making in women with fibromyalgia. *Arch Clin Neuropsychol, 24*(1), 113-122. https://doi.org/10.1093/arclin/acp014

Vranceanu, A. M., Bachoura, A., Weening, A., Vrahas, M., Smith, R. M., & Ring, D. (2014). Psychological factors predict disability and pain intensity after skeletal trauma. *J Bone Joint Surg Am, 96*(3), e20. https://doi.org/10.2106/jbjs.L.00479

Waugh, C. E., Thompson, R. J., & Gotlib, I. H. (2011). Flexible emotional responsiveness in trait resilience. *Emotion, 11*(5), 1059-1067. https://doi.org/10.1037/a0021786

Waugh, C. E., Wager, T. D., Fredrickson, B. L., Noll, D. C., & Taylor, S. F. (2008). The neural correlates of trait resilience when anticipating and recovering from threat. *Social cognitive and affective neuroscience, 3*(4), 322-332. https://doi.org/10.1093/scan/nsn024

Weinman, J., Ebrecht, M., Scott, S., Walburn, J., & Dyson, M. (2008). Enhanced wound healing after emotional disclosure intervention. *British Journal of Health Psychology, 13*(1), 95-102. https://doi.org/10.1348/135910707X251207

Werner, S., & Grose, R. (2003). Regulation of wound healing by growth factors and cytokines. *Physiol Rev, 83*(3), 835-870. https://doi.org/10.1152/physrev.2003.83.3.835

Westphal, M., Seivert, N. H., & Bonanno, G. A. (2010). Expressive flexibility. *Emotion, 10*(1), 92-100. https://doi.org/10.1037/a0018420

Whiting, D., Deane, F., Simpson, G., McLeod, H., & Ciarrochi, J. (2015). Cognitive and psychological flexibility after a traumatic brain injury and the implications for treatment in acceptance-based therapies: A conceptual review. *Neuropsychological rehabilitation*, 1-37. https://doi.org/10.1080/09602011.2015.1062115

Wicksell, R. K., & Olsson, G. L. (2010). Predicting and preventing chronic postsurgical pain and disability. *Anesthesiology, 113*(6), 1260-1261. https://doi.org/10.1097/ALN.0b013e3181da89f8

Yi, J. L., Porucznik, C. A., Gren, L. H., Guan, J., Joyce, E., Brodke, D. S., Dailey, A. T., Mahan, M. A., Hood, R. S., Lawrence, B. D., Spiker, W. R., Spina, N. T., & Bisson, E. F. (2019). The Impact of Preoperative Mindfulness-Based Stress Reduction on Postoperative Patient-Reported Pain, Disability, Quality of Life, and Prescription Opioid Use in Lumbar Spine Degenerative Disease: A Pilot Study. *World Neurosurgery, 121*, e786-e791. https://doi.org/10.1016/j.wneu.2018.09.223

Zeidan, F., Grant, J. A., Brown, C. A., McHaffie, J. G., & Coghill, R. C. (2012). Mindfulness meditation-related pain relief: Evidence for unique brain mechanisms in the regulation of pain. *Neuroscience Letters, 520*(2), 165-173. https://doi.org/10.1016/j.neulet.2012.03.082

Zeidan, F., & Vago, D. R. (2016). Mindfulness meditation-based pain relief: a mechanistic account. *Annals of the New York Academy of Sciences, 1373*(1), 114-127. https://doi.org/10.1111/nyas.13153

CHAPTER 2

Emotional flexibility and recovery from pain

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ABSTRACT

This study aimed to investigate the relationship between two aspects of emotional flexibility (EF, i.e., flexible emotional responsiveness and affective flexibility) and tolerance for, and recovery from, experimentally-induced pain. Fifty-two adults completed a flexible emotional responsiveness task in which emotional responses on multiple dimensions were registered while watching positive and negative pictures. Affective flexibility was measured using a switching task with positive and negative pictures. Pain tolerance was assessed as the time participants endured an ischemic pain task and total time until recovery in terms of pain intensity and pain unpleasantness was registered. Flexible emotional responsiveness - reflected in divergent corrugator responses to positive and negative stimuli - was associated with faster recovery from pain unpleasantness. Affective flexibility was associated with recovery in terms of pain intensity, with faster switches from neutral towards affective aspects of positive stimuli being predictive of faster recovery. Results did not provide evidence for an association between EF and pain tolerance. The findings suggest that EF may protect against pain persistence.

Keywords

emotional flexibility, task switching, EMG, tourniquet, pain recovery

INTRODUCTION

One of the characteristics of everyday life is that people have to adapt to constantly changing circumstances. As these changes naturally include alterations between positive and negative contexts (Sarason et al., 1978), successful adaptation requires flexibility at the emotional level (Bonanno et al., 2004). Emotional flexibility (EF) is defined as the ability to flexibly regulate emotions in a context-appropriate manner, and to recover from the primary emotional response when the context changes, thereby creating a best possible match with the ever changing environment (Aldao et al., 2015; Beshai et al., 2018; Westphal et al., 2010). EF also refers to the flexible use of different emotion regulation strategies that fit the situation at hand, and is adaptive when this flexibility increases the chances of attaining personal relevant goals (Aldao et al., 2015). Hence, EF is essential for adequate emotion regulation.

Several studies have identified a link between EF and resilience, here defined as the ability to effectively adapt to both major and every day's life events (Block & Kremen, 1996). Waugh et al. (2011) demonstrated that high resilient participants showed more distinct emotions and facial expressions in response to alternating positive and negative stimuli and were thus better capable to switch their emotional responses in order to emotionally adapt to these stimuli. Likewise, more flexibility in switching between emotional contexts has been related to trait resilience (Genet & Siemer, 2011), more use of adaptive emotion regulation strategies such as reappraisal (Malooly et al., 2013), and less rumination (Genet et al., 2013).

EF may also affect how an individual copes with pain and as such, may function as a candidate mechanism in explaining individual differences in pain tolerance and recovery. Besides a sensory experience, pain is also considered to be an emotional experience (e.g., Craig, 2003). Given this emotional dimension of pain, coping with pain requires controlling your emotions or regulating your emotional responses to painful stimuli. Indeed, a large number of studies has consistently pointed out a role for emotion regulation in pain experience, thereby indicating that difficulties in emotion regulation are associated with higher distress and pain levels (e.g., Keefe et al., 2001). For instance, maladaptive emotion regulation is directly associated with pain-related disability, depressive symptoms, and pain chronicity (as systematically reviewed in Koechlin et al., 2018). EF in the context of pain refers to the capability to respond emotionally to painful events, and recover from these emotional responses when the pain episode is over. Along this line of reasoning, EF may act as a mechanism explaining why some individuals can better tolerate pain and recover faster from pain.

Experimental research generally focuses on two aspects of EF, which both are believed to facilitate effective emotion regulation (Gross, 2007). The first aspect, flexible emotional responsiveness, is the ability to flexibly produce emotional responses to alternating positive and negative circumstances (Hollenstein et al., 2013; Westphal et al., 2010). Hence, positive responses should harmonize with positive events and negative responses with negative events (Waugh et al., 2011). Identifying pain and responding effectively with negative emotions (i.e., flexible emotional responding) serves an adaptive function, as it results in the activation of protective behavior including avoidance, escape, and social alarm (Eccleston & Crombez, 1999; Sullivan, 2008). Flexible emotional responsiveness may therefore be essential for managing pain, as the function of acute pain is to signal potential physical harm or illness (Eccleston & Crombez, 1999).

The second component of EF is affective flexibility, a specific kind of cognitive flexibility, and refers to the capacity to switch between emotional information and neutral aspects of the environment (Genet et al., 2013; Genet & Siemer, 2011; Malooly et al., 2013). In pain research, ample evidence exists for the negative effect of acute and chronic pain on cognitive flexibility, including shifting and inhibition performance (e.g., Boselie et al., 2014; Karp et al., 2006; Van Ryckeghem et al., 2012; Verdejo-García et al., 2009). Furthermore, cognitive flexibility has been suggested to influence the experience of pain (Bjekić et al., 2018; Karsdorp et al., 2014; Oosterman et al., 2010) and even the development of chronic pain after surgery (Attal et al., 2014). Given these findings and the emotional characteristics of pain, it is reasonable to suggest that cognitive flexibility specific to emotional material (i.e., affective flexibility) plays a potentially important role in pain sensitivity. More precisely, affective flexibility can be proposed to function as an explanatory mechanism in how people manage and recover from their pain.

This study aims to provide a first test of the proposed relation between EF and pain by examining the associations between EF (i.e., flexible emotional responsiveness and affective flexibility) and pain sensitivity. To this purpose, an experimental pain induction procedure is used and both pain tolerance and recovery in terms of pain intensity and pain unpleasantness is assessed. EF is measured by means of two computer tasks that tap into flexible emotional responsiveness and affective flexibility, respectively. It is hypothesized that more EF is related to higher pain tolerance and a quicker recovery from both pain intensity and pain unpleasantness. Current findings will contribute to our knowledge on the potential of EF to explain individual differences in pain experience and recovery from pain.

METHODS

Participants

Participants were 56 healthy adults recruited to participate in a cross-sectional observational study through advertisements at Maastricht University and via an electronic research participation system (SONA). Exclusion criteria were pregnancy, a diagnosis of a psychiatric or neurological disorder, cardiovascular disease, injury or pain to the non-dominant arm, acute or chronic pain, blood pressure problems (hypertension/hypotension), the use of anticoagulants or medication with this feature, blood clotting problems, severe medical diseases (e.g., diabetes, asthma), the use of anxiolytics or antidepressants, and carrying an electronic implant. These criteria were all checked by means of self-report prior to scheduling a test appointment and at the moment the participants showed up for their test appointment at the lab. Four participants were not eligible and excluded at the start of the lab session because of non-compliance. The final sample consisted of 52 subjects (mean age 22.7 years; *SD* = 3.81; range: 18 – 39 years; 8 male). The pain induction had to be interrupted prematurely for two participants due to lack of time for the entire experiment, making the tolerance, pain intensity and pain unpleasantness recovery data for these participants invalid. The participants received either a 20-euro gift voucher or course credits as incentive. The study protocol received approval by the ethical review committee of the Faculty of Psychology and Neuroscience (ERCPN), Maastricht University.

Measures

Pain experience and recovery from pain

Handgrip strength

A Bremshey Sport® electronic hand dynamometer (Almere, The Netherlands) was utilized to measure maximum handgrip strength of the non-dominant hand in kg/lb. The mean across two maximum handgrips was calculated.

Submaximum Effort Tourniquet Technique

The Submaximum Effort Tourniquet Technique (SETT) was used to induce ischemic pain (Smith et al., 1966), a type of pain caused by restriction of blood supply to the tissue. This pain method produces a tonic deep aching pain which is more comparable to pain of pathologic origin in terms of severity and duration than most other pain stimuli (Moore et al., 1979). In comparison to other available experimental pain induction methods (e.g., the cold pressor task or thermal stimulation), the SETT typically takes longer time to fully recover from, making it a suitable method to examine (individual) differences in recovery from pain in a lab situation. Blood pressure was first determined with an automatic Omron M3 Intellisense blood pressure monitor (OMRON Corporation, Kyoto, Japan) applied to the non-dominant upper arm. Blood pressure was measured at the start of the experiment in order to verify that participants did not have hypertension (i.e., systolic blood pressure > 133 mmHg) and again prior to the start of the SETT. In case these two measurements deviated more than 10 mmHg, blood pressure was measured for a third time. Mean systolic blood pressure was calculated across the two measurements or in case of three measurements across the two values that were closest to one another. During the SETT, an aneroid Minimus® II sphygmomanometer cuff (Riester, GmbH, Jungingen, Germany) was attached to the non-dominant upper arm. The participant was requested to reach the arm towards the ceiling for 1 min in order to drain blood from the arm. The arm was then put to rest on the table and the cuff was inflated to 1.5 x the mean systolic blood pressure to obstruct blood flow. After 1 min, the participant squeezed a hand trainer 12 times for 2 sec with a 2-sec break in between squeezes. A digital metronome indicated the pace of these squeezes. Afterwards, the subject was asked to put the arm to rest again on the table.

Pain intensity and pain unpleasantness

Oral numerical rating scales (NRS) were employed for both *pain intensity* (0 = 'not painful at all'; 10 = 'unbearably painful') and *pain unpleasantness* (0 = 'not unpleasant at all'; 10 = 'extremely unpleasant') ratings during the SETT and recovery period. The timing of these ratings is described in more detail in the procedure section. The time from the last squeeze with the hand trainer to SETT termination was taken as measure for *pain tolerance* (sec). Time to total recovery in terms of pain intensity ('*pain intensity recovery*') and pain unpleasantness ('*pain unpleasantness recovery*') was assessed as the time (sec) from cuff deflation till the moment the participant gave a pain intensity or a pain unpleasantness rating of 0, respectively. For exploratory purposes, a few additional written visual analogue scales (VAS) scores were obtained before pain induction and at session completion, but these were not further analyzed.

Emotional responsiveness task

Task set-up

A slightly adjusted version of the task designed by Waugh et al. (2011) was utilized to measure flexible emotional responsiveness to alternating positive and negative pictures. Emotional responsiveness was continuously assessed across multiple modalities, namely self-reported affect, facial expressions, and defensive motivation as indexed by eye blink startle amplitude.

In short, each trial starts with the presentation of a cue (i.e., '+' or '-'), indicating whether the trial will be positive or negative, respectively. Trials consist of three pictures of the same valence that are presented consecutively for 4 sec each against a black background. Afterwards, the participant views a black screen for 2 sec. Pictures are taken from the International Affective Picture System (IAPS; Lang et al., 1997). Mean arousal values for the IAPS pictures as based on IAPS development studies do not differ significantly across trial type: positive = 5.41, negative = 5.38, $t(78) = -.33$, $p > .05$. Similarly, there are no differences in mean picture valence across trial type when positive images are reverse-scored: positive = 2.63, negative = 2.57, $t(78) = -.48$, $p > .05$.

The task is divided into two blocks of 41 trials each, making a total of 82 trials with 246 pictures. The blocks are separated by a 1-min break. Each block consists of a fixed order stimulus list for the 41 trials. The stimulus lists are created in a pseudo-random manner, thereby ensuring equal trial type distribution, no more than three successive presentations of the same trial type, and a positive first trial in each block. Emotional responses to the first trial of each block are eliminated from analyses. On a random 24 out of 40 trials per trial type (60% of the trials, disregarding the first trial of each block) an acoustic startle probe (50 msec) is administered binaurally through headphones. Startle probes are 95 dB(A) bursts of white noise with instantaneous rise time administered during the presentation of the second picture (1.5 sec after picture onset).

Self-reported affect

A rating dial is used to assess self-reported affect continuously throughout the emotional responsiveness task. The dial used in this study was custom-made by the instrumentation engineering department of the Faculty of Psychology and Neuroscience, Maastricht University and consists of a 44-mm diameter black dial with a triangle-shaped white pointer depicted on it that revolves 180°. In addition to the original task developed by Waugh et al. (2011), our task had an affective scale consisting of a grey 180° semicircle and a white pointer that was continuously presented below the stimuli on the screen throughout the entire task. This scale was added to make sure that participants are aware of the exact location of the pointer without having to switch their gaze between the screen and the dial. The anchor 0 ('negative') is positioned at 0° and the anchor 9 ('positive') at 180°, resulting in a neutral rating of 4.5 at 90°, yet not explicitly indicated. Only data for the first picture of each trial are used and thus registered at 4 sec after onset of the first picture of each series (Waugh et al., 2011). This moment was chosen because it minimizes the effect of the previous position of the dial on current ratings (Waugh et al., 2011). Furthermore, it is expected that affective responses have stabilized after this time. Scores were recoded by subtracting 4.5 in order to let negative scores indicate negative self-reported affect and positive scores indicate positive affect. Next, average affect was calculated per trial type. Lastly, a difference score between the affective ratings to positive and negative pictures was computed. This new variable was named DiffAffect. Due to technical difficulties, affect ratings for one participant had to be excluded from subsequent analyses.

EMG recordings

Facial expressions are measured in terms of muscle activity using facial electromyography (EMG) over two facial muscles: the zygomatic major and the corrugator supercilii muscles (Fridlund & Cacioppo, 1986). Zygomatic activity is recorded as an index for positive emotions, whereas activation of the corrugator is an index for negative emotions (Cacioppo et al., 1986; Tassinary & Cacioppo, 1992). Mean zygomatic and corrugator responses to the first picture are used for analyses.

In addition, acoustically elicited startle reflexes during the presentation of positive and negative pictures are assessed to measure defensive motivation, which involves the increase of aversive responses (startle response) in an unpleasant context (Lang et al., 1990). Specific to this task, startle reflexes are augmented when viewing negative pictures and diminished when viewing positive pictures. Startle reflexes are recorded over the orbicularis oculi in response to the second picture in order to prevent confounding of self-report and EMG responses to the first picture of a sequence with the administration of a startle probe.

Physiological data were recorded with a BrainAmp ExG® amplifier (Brain Products GmbH, Gilching, Germany). In line with recommendations made by Fridlund and Cacioppo (1986), three pairs of 4-mm Ag/AgCl surface electrodes were positioned over the zygomatic major, corrugator supercilii, and the orbicularis oculi muscles. A seventh 4-mm reference electrode was placed behind the ear on the mastoid part of the temporal bone. Electrodes were disc shaped, had a diameter of 2 mm with a gel bed of 4 mm in an external diameter of 11 mm. Before electrode placement, participants were asked to clean their face with cleansing milk and the skin was subsequently cleaned with 70% alcohol solution and gently scrubbed with skin prep gel (Nuprep®, Weaver and Company, CO, USA). Electrodes were filled with a conductive EMG paste (Ten20®, Weaver and Company, CO, USA) and attached to the skin surface using double-sided adhesive collars. Inter-electrode distance between electrodes centers was approximately 10 mm. Electrodes were placed on the side of the face that was opposite to the dominant side of the body. For three participants, the electrodes were placed on the right side of the face because of left handedness. Before the recordings started, impedance was checked to ideally be between 0 and 5 kΩ and to not exceed 20 kΩ (Tassinary et al., 2007). The raw EMG data was sampled at 1 kHz and bandpass filtered (10- to 1000-Hz) with the BrainVision Recorder software. BrainVision Analyzer software (version 2.0) was used to process the EMG and startle data offline.

EMG Preprocessing and data reduction

Corrugator and zygomatic activity

Raw EMG data were visually inspected for artefacts (i.e., noise, movement artefacts). Of the 4000 measurement points, 346 (8.7%) were rejected for the corrugator channel, and 221 (5.5%) for the zygomatic channel. Following offline filtering (28 Hz high-pass filter, 48 dB/octave), EMG data were rectified and smoothed (50-msec moving window average). The epoch that was analyzed for corrugator and zygomatic muscle activity covered the total duration of the first picture of each series (4 sec). For each muscle, mean EMG activity was baseline corrected by subtracting the average EMG activity during the last 2 min of a 5-min baseline measurement from the average corrugator and zygomatic activity during the first picture on each trial and expressed in μV. Data for two participants were excluded from further analyses, as no reliable baseline measurements were obtained. Following Waugh et al. (2011), outlier identification was done on the basis of within subject means and SD and were defined as being above or below 3 SD from the mean. Outliers were then replaced by the value corresponding to 3 SD above or below the mean. Next, mean zygomatic and corrugator activity per trial type was calculated. A Matlab script was developed in order to perform all data processing steps (Matlab 7.17, MathWorks Inc., USA).

Eye blink startle responses

After data acquisition, raw EMG signals were visually inspected for artefacts (i.e., noise, movement artefacts, and double blinks -50 to 150 msec relative to startle probe onset).

From the 2496 measurement points, 527 (21.1%) contained artifacts and were excluded. After offline filtering (100 Hz low-pass, 48 dB/octave), data were rectified and smoothed (20-msec time moving window average). The recommendations made by Tassinary et al. (2007) were followed for the scoring of startle responses. The window for onset latency for the startle reflex was set on 50 to 150 msec after probe onset. Peak amplitude was determined within this window and scored as a startle reflex when it was larger than 5 SD above the peak amplitude of a pre-stimulus window of 50 msec duration. Response amplitude (μV) was obtained by subtracting the average EMG value during the pre-stimulus period from the value at peak amplitude. Trials that were identified as nonresponse trials were rejected, which was the case for 19.9% of the trials. Considering artefact and nonresponse eyeblink rejection, 66.7% of the trials remained for further analyses. After standardization of the response amplitudes with within subject *T*- score transformations, outliers were corrected by substituting responses smaller or larger than 3 SD from the mean with the value corresponding to 3 SD above or below the mean (Waugh et al., 2011). Outlier identification was done on the basis of within subject means and SD.

Scoring of EMG data

We first checked whether positive trials were rated more positively, elicited higher zygomatic activity, lower corrugator activity, and lower startle amplitudes than negative trials using paired samples *t* tests. Next, a difference score between the facial muscle responses and startle amplitude to positive and negative pictures was calculated, resulting in the following three variables: DiffZyg (zygomatic response to positive pictures - zygomatic response to negative pictures), DiffCor (corrugator response to negative pictures – corrugator response to positive pictures), and DiffStartle (startle response to negative pictures – startle response to positive pictures). Higher difference scores reflect greater responses that are congruent to picture valence (e.g., higher corrugator activity in response to negative pictures) and thus more flexibility in emotional responsiveness.

Affective switching task

Task set-up

The affective task switching paradigm designed by Genet, Malooley, and Siemer (2013) was used to measure affective flexibility. In short, participants view emotionally valenced pictures on a computer screen and categorize these according to either an affective rule (determining whether the picture is positive or negative) or a neutral rule (determining whether the picture contains one or none humans, or two or more humans). Reaction times (RTs) are recorded in this task. The stimuli are 160 pictures from the IAPS (Lang, Bradley, & Cuthbert, 1999) that can be classified into four categories based on the two sorting rules. Pictures are displayed one by one in the center of a monitor with the active categorization rule (the cue) depicted on the left and right side of the picture; ' +' and '-' indicate positive and negative, '≤ 1' and '≥ 2' indicate one or fewer people and two or more people. The picture is displayed against either a white or grey background with the color of the background corresponding to the cue. Pictures are shown until a response is made by pressing one of two keys on a response box; the left-hand index finger was on the left button and the right-hand index finger on the right button. The picture category and cue are combined according to a pseudo-random order. There are eight task versions based on the mapping of the frame color (white or grey) to the active categorization rule (valence or number of people), and mapping of the response keys (left or right) to the categorization rule ('+' / '-' or '≤ 1' / '≥ 2').

The task consist of two 10-trial practice blocks in which one of two rules is practiced per block and two 160-trial test blocks in which both rules are presented. Trials can either be a switch (trials on which the categorization rule changes) or a repeat trial (trials on which the same rule is repeated). It is important to note that the valence of the pictures never changes in the switch trials; it is only the categorization rule that alternates. Similar numbers of switches and repeats were made in all four stimulus conditions. Switch costs are calculated by subtracting RTs on repeat trials from RTs on switch trials. Lower switch costs (i.e., faster responses to switch tasks) reflect higher affective flexibility.

Preprocessing and scoring of task switching data

Incorrect responses were obtained for 7.4% of the trials and excluded from subsequent analyses. Following previous research using the same task (Genet et al., 2013; Grol & De Raedt, 2017; Malooly et al., 2013), the impact of outliers was reduced for 0.006% of the trials by replacing RTs equal to or smaller than 250 msec with the value of 250 msec. In addition, individual outlying values, identified as RTs larger than 2.5 SD above the individual mean, were set equal to individual mean plus 2.5 SD (2.95% of the trials).

Based on both the active categorization rule and picture valence of the current and previous trials, mean RTs for eight trial types were computed: four repeat trial types (positive to positive rule, negative to negative rule, neutral to neutral rule for positive pictures, neutral to neutral rule for negative pictures), and four switch trial types (positive to neutral rule, negative to neutral rule, neutral to positive rule, neutral to negative rule).

Four types of switch costs were computed by subtracting RTs on repeat trials from RTs on switch trials. More specifically, switch costs for affective-to-neutral (AtoN) task sets were computed by subtracting RTs on affective repeat trials from RTs on affective-to-neutral trials: switch cost AtoN = Switch (affective to neutral) – Repeat (affective to affective). This type of switch cost was separately computed for positive (SC posAtoN) and negative (SC negAtoN) pictures. Similarly, the following formula was employed to calculate switch costs for neutral-to-affective (NtoA) task sets for positive (SC posNtoA) and negative (SC negNtoA) pictures separately: SC NtoA = Switch (neutral to affective) – Repeat (neutral to neutral).

Questionnaires

Psychological questionnaires were administered for exploratory purposes (i.e., exploring the relationship between the EF measures and psychological personality constructs, such as general resilience and fear constructs) and are not further reported in the current paper. These included the 9-item Acceptance and Action Questionnaire-II (AAQ-II; Bond et al., 2011; Fledderus et al., 2012), the Life Orientation Test-Revised (LOT-R, Scheier et al., 1994), the 10-item Connor-Davidson Resilience Scale (CD-RISC-10; Campbell-Sills & Stein, 2007), the Highly Sensitive Person (HSP) Scale (Aron & Aron, 1997), the Pain Catastrophizing Scale (Sullivan et al., 1995), the Fear of Pain Questionnaire-Short Form (Asmundson et al., 2008), the State-Trait Anxiety Inventory Y2 form (Spielberger et al., 1983) and four questions concerning stress levels.

Procedure

Recruitment and testing of participants took place from March until April 2016 at Maastricht University. On arrival to the lab, study eligibility was checked and written informed consent was obtained from each participant. The study could be completed in either Dutch or English; 34 (65.38%) participants chose English as language. Participants' non-dominant hand and arm were checked for wounds. A disruption of the skin was classified as a (healing) wound for which the skin integrity is/was broken and there is/was a hemorrhage. It was important to check for wounds, as occlusion of the blood flow during the SETT may cause new bleedings. No participant had to be excluded because of this criterion. The experimenter then performed the first blood pressure measurement. Participants were instructed not to speak and to relax during this measurement. Next, maximum handgrip strength was assessed by asking the participants to squeeze the hand dynamometer twice as strongly as possible. Basic sociodemographic information (age, gender, mother tongue, nationality, type and year of study) was then obtained and participants completed the psychological questionnaires on the computer using an online survey application (Qualtrics, Provo, UT).

After the experimenter had attached the facial electrodes, baseline EMG activity was measured during a 5-min resting period. In addition, a Polar® RS800CX (Polar CIC, USA) heart rate band was attached around the chest in order to assess heart rate variability. However, due to too many artifacts in the recordings, these data could not be used. Next, participants completed the emotional responsiveness task during which continuous facial EMG data were recorded. Participants rated their current feelings throughout the task (i.e., during the viewing of the cues, the pictures and the inter stimulus intervals) using the rating dial. Participants were explicitly instructed that they could turn the dial as frequently as their feelings altered throughout the task. They were also informed that they would hear loud sounds at random points throughout the task, but that they should try not to pay any attention to these sounds. The task started with the presentation of four example pictures (two positive and two negative pictures) and five example startle probes, followed by 82 trials with 246 pictures.

After the emotional responsiveness task, participants completed the affective switching task in which they categorized pictures according to the affective and non-affective rule. The eight versions of the task were counterbalanced across participants. The emotional responsiveness task always preceded the affective switching task. This way, the assessment of initial emotional responses in the emotional responsiveness task was not affected by prior exposure to similar pictures in the affective switching task.

After task completion, the experimenter took a second blood pressure measurement and explained the procedure for the SETT. Participants were told that it would be completely normal if their arm would turn white or become cold or numb during the SETT and that this would almost immediately disappear upon cuff deflation. Participants were not informed about the duration of the SETT: the task was ended by the experimenter when 20 min had passed, a maximum pain intensity score of 10 was given, or when the participant expressed the wish to stop. Participants were made familiar with the sound and pace of the digital metronome that indicated the pace at which the hand trainer had to be squeezed and were then allowed to practice. During the SETT, participants were asked to rate how painful and unpleasant the sensations in their entire arm felt. These two types of ratings were administered in immediate succession at 16 time points, namely at 0, 1, 2.5, 4.5, 5.5, 7.5, 9, 10.5, 11.5, 13.5, 15, 16, 17.5, 18, 19, and 20 min after completion of the last squeeze with the hand trainer. Less than 16 ratings were recorded in case earlier SETT termination took place due to a maximum pain intensity rating of 10 or the participant’s wish to stop. In addition, oral

NRSs for pain intensity and pain unpleasantness were administered at 0, 45, 105, 150, 205, 275, 335, 385, 430, 475, 535, and 600 sec (10 min) after cuff deflation until both pain intensity and pain unpleasantness ratings of 0 were given.

After participants had completed the SETT, they filled out an exit questionnaire that included questions concerning experiences during the SETT, the goal of the study, and the two switching tasks (attention and motivation to perform the tasks, pleasantness, interest in the task, task duration and difficulty). Upon leaving the lab, participants were queried for lingering sensations caused by the SETT. If so, participants would receive a phone call by the experimenter the same evening as to verify whether these sensations had worn off, which was the case for two participants. The experiment lasted approximately 2 h. Participants received a written debriefing via e-mail after the last participant had been tested. This experiment was part of a larger study in which diary data was also collected after the lab session. Results from these diary measurements will be described elsewhere.

Statistical analyses

The sample size was estimated using G*power (version 3.1.9.2) with hierarchical multiple regression analyses as our main analyses. A minimal sample size of 50 participants was required when a medium effect size (f = .15), a power of .85, and a significance level of .05 were taken into account (one-tailed). Statistical analyses were conducted using SPSS version 24 software (SPSS, Inc, IL, USA). Descriptive statistics were computed and data were checked to follow Gaussian distributions. Homogeneity of variance was checked and outliers were defined as being 3 SD below or above the mean and replaced by this value for pain-related variables. Our outcome measures were pain tolerance (sec), pain intensity recovery (sec), and pain unpleasantness recovery (sec) and were analyzed by using multiple hierarchical regression analyses. Significance levels were set at .05.

Two sets of hierarchical multiple regression analyses were performed with each set testing the predictive value of variables derived from either the emotional responsiveness task or the affective switching task for each of the pain-related outcome variables (i.e., pain tolerance, pain intensity recovery, and pain unpleasantness recovery). The first set of regression analyses tested the predictive value of the parameters of the emotional responsiveness task (i.e., DiffAffect, DiffCor, DiffZyg, and DiffStartle) with the three pain-related outcomes. The second tested the predictive value of the parameters of the affective switching task (i.e., SC posAtoN, SC negAtoN, SC posNtoA, and SC negNtoA) with the three pain-related outcomes. In all regression models, age, sex and maximum handgrip strength were entered at the first step and the different EF parameters at the second step. For the analyses of pain intensity and pain unpleasantness recovery, we also controlled for pain tolerance by adding this variable in the first step of the model. Age, sex and maximum hand grip strength did not significantly predict any of the outcome variables (β [-.27, .14], all *p*'s > .071) and were thus removed from all the regression models. In addition, a backward deletion method was also used for both sets of analyses. For significant models, both the full and the final model after deletion of the non-significant predictors are shown.

RESULTS

Pain tolerance and recovery scores

Fifteen (30%) of the 50 participants did not terminate the SETT before 20 min had passed, for whom a pain tolerance score of 1200 sec was registered. In the present sample, a mean pain tolerance of 762.26 sec (*SD* = 395.61), a mean pain intensity recovery of 254.00 sec (*SD* = 152.14) and a mean pain unpleasantness recovery of 369.00 sec (*SD* = 157.61) was obtained.

Emotional responsiveness task

Paired samples *t* tests were performed to test whether responses to positive trials differed from responses to negative trials in terms of affect ratings, corrugator and zygomatic activity, and startle blinks. For self-reported affect, positive trials were not rated more positively (*M* = -0.47, *SD* = 0.90) than negative trials (*M* = -0.46, *SD* = 0.74), $t(51) = 0.095$, $p = .93$. For the corrugator muscle, the baseline corrected activity in response to negative trials (*M* = 0.12, *SD* = 0.13) was, as predicted, higher than in response to positive trials (*M* = -0.12, *SD* = 0.12), $t(49) = -6.78$, $p < .001$, $d = 1.94$. In addition, positive trials elicited higher baseline corrected zygomatic activity (*M* = 0.091, *SD* = 0.12) than negative trials (*M* = -0.093, *SD* = 0.12), $t(49) = 5.24$, $p < .001$, $d = 1.50$. As expected, startle amplitudes were larger on negative trials (*M* = 50.91, *SD* = 1.94) than on positive trials (*M* = 49.12, *SD* = 2.18), $t(49) = -3.24$, $p = .002$, $d = .93$.

Table 1 shows the mean and SD of the difference between responses to positive vs. negative trials for the emotional responsiveness task variables as well as their inter-correlations. Greater differential corrugator responses to negative vs. positive pictures were related to greater differential zygomatic responses.

Table 1. Mean (*M*), standard deviation (*SD*) and Pearson correlations for difference scores for self-report affect, corrugator and zygomatic activity, and startle amplitude

Measure	*M* (*SD*)	1	2	3	4
1. DiffAffect[1]	-0.02 (0.53)	-			
2. DiffCor[2]	0.24 (0.25)***	.21	-		
3. DiffZyg[2]	0.18 (0.25)***	.06	.43**	-	
4. DiffStartle[2]	1.74 (3.91)**	-.05	-.13	.12	-

*Paired samples t tests. [1] N = 51; [2] N = 50. DiffAffect, the difference in affect ratings between positive and negative trials; DiffCor, the difference in corrugator activity between positive and negative trials (z); Diff-Zyg, difference in zygomaticus activity between positive and negative trials (z); DiffStartle, the difference in startle amplitude between positive and negative trials (T). ** p < .01; *** p < .001.*

Flexible emotional responsiveness as predictor for pain tolerance and recovery

We decided to not include DiffAffect as a predictor in the regression analyses, as no significant difference was found between responses on positive and negative trials.[1] Variance inflation factors (VIFs) were checked for each model (range 1.00 – 1.73) and did not suggest any problems concerning collinearity between predictors. For pain tolerance and pain intensity recovery as dependent variables, no significant regression models were identified (pain tolerance: R^2 = .054, F(3, 44) = .84, p = .48; pain intensity recovery: R^2 = .19, F(4, 43), = 2.56, p = .052). For pain unpleasantness recovery, the regression model reached significance (R^2 = .52, F(4, 43) = 11.81, p < .001), with only pain tolerance as a step 1 significant predictor (pain tolerance: β = .67, p < .001; DiffCor: β = -.21, p = .087; DiffZyg: β = -.066, p = .59, DiffStartle: β = .094, p = .39). After backward deletion of step 2 insignificant predictors, DiffCor resulted as an additional significant predictor (R^2 = .51, F(2, 45) = 23.76, p < .001; DiffCor: β = -.25, p = .020; pain tolerance: β = .67, p < .001). Hence, a greater differential response in terms of corrugator activity was associated with faster recovery in terms of pain unpleasantness.

[1] After outlier corrrection on DiffAffect, similar results were found for the regression analyses including and excluding DiffAffect as a predictor. In addition, DiffAffect never significantly contributed to the regression models.

Affective switching task

A paired samples *t* test revealed that in general, RTs on switch trials (*M* = 1321.18 msec, *SD* = 199.45 msec) were significantly larger than RTs on repeat trials (*M* = 1168.52 msec, *SD* = 166.81 msec), *t*(51) = -14.88, *p* < 0.001, *d* = 4.17.[2] Table 2 shows the mean and SD of the different types of switch costs as well as their correlations. In general, switch costs were highest when a switch from the affective to non-affective rule was required. The different types of switch costs correlated weak to moderately with one another, illustrating that these switch costs reflect distinct components of affective flexibility.

Table 2. Mean (*M*), standard deviation (*SD*) and Pearson correlations for the different types of switch costs

Measure	*M* (*SD*)	1	2	3	4
1. SC posAtoN	255.19 (171.71)	-			
2. SC negAtoN	375.39 (216.04)	.40**	-		
3. SC posNtoA	71.70 (167.24)	-.09	-.03	-	
4. SC negNtoA	-35.94 (163.25)	.00	-.30*	.05	-

*SC posAtoN, switch costs for positive picture and affective-to-neutral trial; SC negAtoN, switch costs for negative picture and affective-to-neutral trial; SC posNtoA, switch costs for positive picture and neutral-to-affective trial; SC negNtoA, switch costs for negative picture and neutral-to-affective trial. * p < .05; ** p < .01.*

Affective flexibility as predictor for pain tolerance and recovery

For each regression model, VIFs (range 1.00 – 1.76) indicated no problems of collinearity between predictors. For pain tolerance, no significant regression model was identified (R^2 = .076, *F*(4, 45) = .93, *p* = .46). Table 3 shows the results from hierarchical multiple regression analyses for pain intensity and pain unpleasantness recovery. For pain intensity recovery, longer recovery times were significantly predicted by higher costs resulting from switches toward the affective rule when viewing positive pictures (SC posNtoA) (R^2 = .28, *F*(5, 44) = 3.47, *p* = .010). Similar results were found when performing the backward procedure (R^2 = .24, *F*(2, 47) = 7.27, *p* = .002). For pain unpleasantness

[2] The proportion of correct responses was higher for repeat trials (*M* = 9.15, *SD* = 6.12) than for switch trials (*M* = 6.16, *SD* = 4.77) ***t*** (51) = -6.95, *p* < 0.001, *d* = 1.95, supporting the absence of a speed-accuracy trade-off.

Table 3. Hierarchical multiple regression for the prediction of pain intensity and pain unpleasantness recovery from the different types of switch costs after controlling for pain tolerance (*N* = 50)

Predictors	***B***	***SE B***	**β**	***p***
Pain intensity recovery				
Enter procedure				
Step 1				
Pain tolerance	0.14	0.05	0.36	.01
Step 2				
Pain tolerance	0.12	0.05	0.31	.03
SC posAtoN	-0.05	0.13	-0.06	.69
SC negAtoN	0.07	0.10	0.10	.50
SC posNtoA	0.30	0.12	0.33	.02
SC negNtoA	-0.15	0.13	-0.17	.23
Backward deletion model				
Pain tolerance	0.11	0.05	0.29	.03
SC posNtoA	0.30	0.12	0.33	.01
Pain unpleasantness recovery				
Enter procedure				
Step 1				
Pain tolerance	0.27	0.04	0.68	.00
Step 2				
Pain tolerance	0.25	0.04	0.63	.00
SC posAtoN	-0.03	0.11	-0.03	.76
SC negAtoN	0.12	0.09	0.17	.15
SC posNtoA	0.19	0.10	0.21	.05
SC negNtoA	-0.05	0.11	-0.06	.62
Backward deletion model				
Pain tolerance	0.25	0.04	0.64	.00
SC posNtoA	0.19	0.10	0.21	.06

Pain tolerance, time until SETT termination (sec); pain intensity recovery, time until total recovery in terms of pain intensity (sec); pain unpleasantness recovery, time until total recovery in terms of pain unpleasantness (sec); SC posAtoN, switch costs for positive picture and affective-to-neutral trial; SC negAtoN, switch costs for negative picture and affective-to-neutral trial; SC posNtoA, switch costs for positive picture and neutral-to-affective trial; SC negNtoA, switch costs for negative picture and neutral-to-affective trial.

recovery, the regression model reached significance (R^2 = .54, F(5, 44) = 10.21, p < .001), with only pain tolerance as a significant and SC posNtoA as a borderline significant predictor (pain tolerance: β = .63, p < .001; SC posAtoN: β = -.034, p = .76; SC negAtoN: β = .17, p = .15; SC posNtoA: β = .21, p = .053; SC negNtoA: β = -.056, p = .62). Backward deletion leaded to similar results (R^2 = .46, F(1, 48) = 41,32, p < .001).

DISCUSSION

The current study investigated the relationship between EF (i.e., flexible emotional responsiveness and affective flexibility) and tolerance for, and recovery from experimentally-induced ischemic pain. Two tasks were utilized to tap into these different aspects of EF, namely an emotional responsiveness task in which self-report affect and facial EMG were continuously registered, and an affective switching task. Ischemic pain was induced by using a Tourniquet pain procedure, which enabled us to measure both pain tolerance and recovery from pain. Neither EF measure was found related to pain tolerance. More flexible emotional responding in terms of corrugator muscle activity was associated with faster recovery from pain in terms of pain unpleasantness. Furthermore, affective flexibility was negatively related to recovery from pain in terms of pain intensity. This was especially the case when a shift from evaluating neutral aspects towards emotional aspects of positive stimuli was required. Taken together, these findings suggest that EF contributes to the recovery from pain.

The emotional responsiveness task was used as an index of the ability to flexibly generate emotional responses to changing stimuli. In general, distinct responses to alternating events with a relatively fast recovery afterwards are considered adaptive and an important characteristic of EF (e.g., Papousek et al., 2012). In contrast, prolonged but weak responses are believed to be maladaptive and a sign of inflexibility. For instance, depressive symptoms are related to reduced positive and negative emotional responses (Bylsma et al., 2008) and impaired recovery from an emotional event (Chida & Hamer, 2008). Greater differential responses to positive vs. negative pictures across different modalities in our task are considered to reflect the distinct short-lived responses characteristic for EF.

Along the lines of our hypotheses, greater differential responses to negative compared to positive pictures expressed in corrugator muscle activity were related to faster recovery from pain unpleasantness. More divergent corrugator activity to negative vs. positive stimuli reflects the capacity to adequately discriminate between negative and positive stimuli and respond accordingly (Waugh et al., 2011). This divergent corrugator response to negative compared to positive stimuli has already been associated to higher trait resilience (Waugh et al., 2011). Here, we found that it also predicts resilient responding in the face of pain, i.e., faster recovery from pain unpleasantness.

Differential zygomatic major and startle blink responses were not associated with pain tolerance or recovery. The corrugator muscle is more sensitive to valence than the zygomatic major (Larsen et al., 2003), which could explain why we only found an effect for the corrugator channel. In the same manner, differential startle responses to positive compared to negative pictures found in this study could have been too small to be predictive of pain outcomes. However, future research is needed to further elucidate the role of flexible emotional responsiveness across different response modalities in pain experience and recovery from pain.

Affective flexibility was assessed using an affective switching task. In this study faster switching from processing neutral towards affective aspects of positive pictures was related to faster recovery of pain intensity. Previously, it was shown that people who were faster in performing these specific type of switches were also more likely to use reappraisal for the down-regulation of affective responses to a sad movie fragment (Malooly et al., 2013). Hence, people who more easily direct themselves to the positive elements of their environment may apply adaptive emotion regulation strategies such as reappraisal to recover from an affective challenge like pain. In other words, more flexibility towards positive aspects of positive pictures can be considered adaptive.

Some possible limitations of the present study should be noted. First, participants did complete the EF tasks in anticipation of a potentially unpleasant / painful task, which might have interfered with task performance (e.g., Van Damme et al., 2004). Future research may counter this problem by administering the EF tasks and the painful task on separate test occasions. Second, our data did not reveal differential self-report affective responses to positive and negative stimuli. One explanation could be that participants did not adhere very well to the instruction to provide ratings for each picture shown. On average, participants only turned the rating dial on 14.13% of all trials. Furthermore, they reported to have experienced the emotional responsiveness task as quite boring and found it difficult to keep their attention with the task. However, our data do not allow determining whether lack of differential self-report ratings was due to experiencing difficulties in explicitly assigning these ratings or not complying with task instructions. Nevertheless, EMG data showed to be sensitive to picture valence, as indicated by differences in responses to positive and negative stimuli. A third limitation concerns the ceiling of 20 min in the SETT. A substantial number of participants did not reach pain tolerance within this time frame, making tolerance a less reliable outcome. Additionally, one might argue that it would have been valuable to study general affective switching performance in relation to pain and recovery from pain, rather than the different types of switch costs. Weak to moderate correlations between the types of switch costs were found in the current study, which replicates previous research and suggests that these switch costs tap into different components of affective flexibility (Genet et al., 2013; Malooly et al., 2013). Different emotion regulation strategies such as rumination (Genet et al., 2013) and reappraisal (Malooly et al., 2013) have been shown to be related to specific types of switch costs. Therefore, these findings stress that it is worthwhile to distinguish between the different types of switch costs. Lastly, we did not include a measure of general cognitive flexibility (Kashdan & Rottenberg, 2010). Poorer cognitive flexibility has been shown to be predictive of chronic postsurgical pain (Attal et al., 2014) and may be another interesting factor to study in the context of pain experience. Future studies could therefore include measures of both EF and cognitive flexibility to investigate the unique and combined predictive value of these concepts for pain experience and recovery. Additionally, the fact that this study only found evidence for associations between two specific measures of EF and recovery from pain intensity and pain unpleasantness requires replication in future studies. Lastly, generalizability of this study is limited, as we subjected pain-free healthy students, of which the majority was female, to an experimental pain procedure.

In sum, this study is the first to indicate associations between two aspects of EF (i.e., flexible emotional responsiveness and affective flexibility) and recovery from pain in terms of pain intensity and pain unpleasantness. More flexibility in emotional responsiveness was found related to faster recovery from pain unpleasantness. In addition, difficulties in switching toward the positive aspects of positive stimuli were found associated with slower recovery regarding pain intensity. No associations were observed between any of the EF measures and pain tolerance. Therefore, we suggest that EF may particularly play a role in how people recover from pain. These data afford novel insights into EF as a potential factor elucidating how people manage their pain and recover from it. Only when protective factors are studied in addition to risk factors, we will be able to formulate scientific theories that allow a comprehensive understanding of pain perception and chronicity. Extending present theoretical models with EF may further our knowledge about why some people are more prone to develop chronic pain, which may ultimately lead to tailor-made prevention and treatment programs. For instance, EF training prior to surgery might be a useful method in the prevention of slow post-operative recovery. In order to explore this potential, future studies should examine whether it would be possible to train EF and its different aspects. In this respect, studies on the trainability of cognitive flexibility already showed promising results (e.g., Grönholm-Nyman et al., 2017; Zhao et al., 2018). Further, current treatments for chronic pain such as mindfulness-based interventions that aim at increasing EF and/or cognitive flexibility (Gallant, 2016; Moynihan et al., 2013; Ortner et al., 2007) offer interesting new angles for future research on the relationship between EF and pain.

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Compliance with ethical standards

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Conflicts of interest

The authors declare that they have no conflict of interest.

Ethical Approval

All procedures performed in this study were in accordance with the standards of the ethical review committee of the Faculty of Psychology and Neuroscience (ERCPN), Maastricht University. Informed consent was obtained from all individual participants included in the study.

REFERENCES

Aldao, A., Sheppes, G., & Gross, J. J. (2015). Emotion regulation flexibility. *Cognitive Therapy and Research, 39*(3), 263-278. https://doi.org/10.1007/s10608-014-9662-4

Aron, E. N., & Aron, A. (1997). Sensory-processing sensitivity and its relation to introversion and emotionality. *J Pers Soc Psychol, 73*(2), 345-368.

Asmundson, G. J., Bovell, C. V., Carleton, R. N., & McWilliams, L. A. (2008). The Fear of Pain Questionnaire-Short Form (FPQ-SF): factorial validity and psychometric properties. *PAIN, 134*(1-2), 51-58. https://doi.org/10.1016/j.pain.2007.03.033

Attal, N., Masselin-Dubois, A., Martinez, V., Jayr, C., Albi, A., Fermanian, J., Bouhassira, D., & Baudic, S. (2014). Does cognitive functioning predict chronic pain? Results from a prospective surgical cohort. *Brain, 137*(Pt 3), 904-917. https://doi.org/10.1093/brain/awt354

Beshai, S., Prentice, J. L., & Huang, V. (2018). Building Blocks of Emotional Flexibility: Trait Mindfulness and Self-Compassion Are Associated with Positive and Negative Mood Shifts. *Mindfulness, 9*(3), 939-948. https://doi.org/10.1007/s12671-017-0833-8

Bjekić, J., Živanović, M., Purić, D., Oosterman, J. M., & Filipović, S. R. (2018). Pain and executive functions: a unique relationship between Stroop task and experimentally induced pain. *Psychological Research, 82*(3), 580-589. https://doi.org/10.1007/s00426-016-0838-2

Block, J., & Kremen, A. M. (1996). IQ and ego-resiliency: conceptual and empirical connections and separateness. *J Pers Soc Psychol, 70*(2), 349-361.

Bonanno, G. A., Papa, A., Lalande, K., Westphal, M., & Coifman, K. (2004). The importance of being flexible: the ability to both enhance and suppress emotional expression predicts long-term adjustment. *Psychol Sci, 15*(7), 482-487. https://doi.org/10.1111/j.0956-7976.2004.00705.x

Bond, F. W., Hayes, S. C., Baer, R. A., Carpenter, K. M., Guenole, N., Orcutt, H. K., Waltz, T., & Zettle, R. D. (2011). Preliminary psychometric properties of the Acceptance and Action Questionnaire-II: a revised measure of psychological inflexibility and experiential avoidance. *Behav Ther, 42*(4), 676-688. https://doi.org/10.1016/j.beth.2011.03.007

Boselie, J. J., Vancleef, L. M., Smeets, T., & Peters, M. L. (2014). Increasing optimism abolishes pain-induced impairments in executive task performance. *PAIN, 155*(2), 334-340. https://doi.org/10.1016/j.pain.2013.10.014

Bylsma, L. M., Morris, B. H., & Rottenberg, J. (2008). A meta-analysis of emotional reactivity in major depressive disorder. *Clin Psychol Rev, 28*(4), 676-691. https://doi.org/10.1016/j.cpr.2007.10.001

Cacioppo, J. T., Petty, R. E., Losch, M. E., & Kim, H. S. (1986). Electromyographic activity over facial muscle regions can differentiate the valence and intensity of affective reactions. *J Pers Soc Psychol, 50*(2), 260-268.

Campbell-Sills, L., & Stein, M. B. (2007). Psychometric analysis and refinement of the Connor-davidson Resilience Scale (CD-RISC): Validation of a 10-item measure of resilience. *J Trauma Stress, 20*(6), 1019-1028. https://doi.org/10.1002/jts.20271

Chida, Y., & Hamer, M. (2008). Chronic psychosocial factors and acute physiological responses to laboratory-induced stress in healthy populations: a quantitative review of 30 years of investigations. *Psychol Bull, 134*(6), 829-885. https://doi.org/10.1037/a0013342

Craig, A. D. (2003). A new view of pain as a homeostatic emotion. *Trends Neurosci, 26*(6), 303-307.

Eccleston, C., & Crombez, G. (1999). Pain demands attention: a cognitive-affective model of the interruptive function of pain. *Psychol Bull, 125*(3), 356-366.

Fledderus, M., Oude Voshaar, M. A., Ten Klooster, P. M., & Bohlmeijer, E. T. (2012). Further evaluation of the psychometric properties of the Acceptance and Action Questionnaire-II. *Psychol Assess, 24*(4), 925-936. https://doi.org/10.1037/a0028200

Fridlund, A. J., & Cacioppo, J. T. (1986). Guidelines for human electromyographic research. *Psychophysiology, 23*(5), 567-589.

Gallant, S. N. (2016). Mindfulness meditation practice and executive functioning: Breaking down the benefit. *Conscious Cogn, 40*, 116-130. https://doi.org/10.1016/j.concog.2016.01.005

Genet, J. J., Malooly, A. M., & Siemer, M. (2013). Flexibility is not always adaptive: affective flexibility and inflexibility predict rumination use in everyday life. *Cogn Emot, 27*(4), 685-695. https://doi.org/10.1080/02699931.2012.733351

Genet, J. J., & Siemer, M. (2011). Flexible control in processing affective and non-affective material predicts individual differences in trait resilience. *Cogn Emot, 25*(2), 380-388. https://doi.org/10.1080/02699931.2010.491647

Grol, M., & De Raedt, R. (2017). The Effect of Positive Mood on Flexible Processing of Affective Information. *Emotion*. https://doi.org/10.1037/emo0000355

Grönholm-Nyman, P., Soveri, A., Rinne, J. O., Ek, E., Nyholm, A., Stigsdotter Neely, A., & Laine, M. (2017). Limited Effects of Set Shifting Training in Healthy Older Adults. *Frontiers in Aging Neuroscience, 9*(69). https://doi.org/10.3389/fnagi.2017.00069

Gross, J. J. (2007). *Handbook of emotion regulation*. Guilford Press.

Hollenstein,T.,Lichtwarck-Aschoff,A.,&Potworowski,G.(2013).Amodelofsocioemotonalflexibility at three time scales. *Emot Rev, 5*, 397–405. https://doi.org/10.1177/1754073913484181

Karp, J. F., Reynolds, C. F., 3rd, Butters, M. A., Dew, M. A., Mazumdar, S., Begley, A. E., Lenze, E., & Weiner, D. K. (2006). The relationship between pain and mental flexibility in older adult pain clinic patients. *Pain Med, 7*(5), 444-452. https://doi.org/10.1111/j.1526-4637.2006.00212.x

Karsdorp, P. A., Geenen, R., & Vlaeyen, J. W. (2014). Response inhibition predicts painful task duration and performance in healthy individuals performing a cold pressor task in a motivational context. *Eur J Pain, 18*(1), 92-100. https://doi.org/10.1002/j.1532-2149.2013.00348.x

Kashdan, T. B., & Rottenberg, J. (2010). Psychological flexibility as a fundamental aspect of health. *Clinical Psychology Review, 30*(7), 865-878. https://doi.org/10.1016/j.cpr.2010.03.001

Keefe, F. J., Lumley, M., Anderson, T., Lynch, T., Studts, J. L., & Carson, K. L. (2001). Pain and emotion: new research directions. *J Clin Psychol, 57*(4), 587-607.

Koechlin, H., Coakley, R., Schechter, N., Werner, C., & Kossowsky, J. (2018). The role of emotion regulation in chronic pain: A systematic literature review. *J Psychosom Res, 107*, 38-45. https://doi.org/10.1016/j.jpsychores.2018.02.002

Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (1990). Emotion, attention, and the startle reflex. *Psychol Rev, 97*(3), 377-395.

Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (1997). *International Affective Picture System (IAPS): Technical manual and affective ratings.* NIMH Center for the Study of Emotion and Attention, University of Florida.

Larsen, J. T., Norris, C. J., & Cacioppo, J. T. (2003). Effects of positive and negative affect on electromyographic activity over zygomaticus major and corrugator supercilii. *Psychophysiology, 40*(5), 776-785.

Malooly, A. M., Genet, J. J., & Siemer, M. (2013). Individual differences in reappraisal effectiveness: the role of affective flexibility. *Emotion, 13*(2), 302-313. https://doi.org/10.1037/a0029980

Moore, P. A., Duncan, G. H., Scott, D. S., Gregg, J. M., & Ghia, J. N. (1979). The submaximal effort tourniquet test: its use in evaluating experimental and chronic pain. *PAIN, 6*(3), 375-382.

Moynihan, J. A., Chapman, B. P., Klorman, R., Krasner, M. S., Duberstein, P. R., Brown, K. W., & Talbot, N. L. (2013). Mindfulness-based stress reduction for older adults: effects on executive function, frontal alpha asymmetry and immune function. *Neuropsychobiology, 68*(1), 34-43. https://doi.org/10.1159/000350949

Oosterman, J. M., Dijkerman, H. C., Kessels, R. P., & Scherder, E. J. (2010). A unique association between cognitive inhibition and pain sensitivity in healthy participants. *Eur J Pain, 14*(10), 1046-1050. https://doi.org/10.1016/j.ejpain.2010.04.004

Ortner, C. N. M., Kilner, S. J., & Zelazo, P. D. (2007). Mindfulness meditation and reduced emotional interference on a cognitive task. *Motivation and Emotion, 31*(4), 271-283. https://doi.org/10.1007/s11031-007-9076-7

Papousek, I., Reiser, E. M., Weber, B., Freudenthaler, H. H., & Schulter, G. (2012). Frontal brain asymmetry and affective flexibility in an emotional contagion paradigm. *Psychophysiology, 49*(4), 489-498. https://doi.org/10.1111/j.1469-8986.2011.01324.x

Sarason, I. G., Johnson, J. H., & Siegel, J. M. (1978). Assessing the impact of life changes: development of the Life Experiences Survey. *J Consult Clin Psychol, 46*(5), 932-946.

Scheier, M. F., Carver, C. S., & Bridges, M. W. (1994). Distinguishing optimism from neuroticism (and trait anxiety, self-mastery, and self-esteem): a reevaluation of the Life Orientation Test. *J Pers Soc Psychol, 67*(6), 1063-1078. https://doi.org/10.1037//0022-3514.67.6.1063

Smith, G. M., Egbert, L. D., Markowitz, R. A., Mosteller, F., & Beecher, H. K. (1966). An experimental pain method sensitive to morphine in man: the submaximum effort tourniquet technique. *J Pharmacol Exp Ther, 154*(2), 324-332.

Spielberger, C. D., Gorsuch, R. L., Lushenne, R. E., Vagg, P. R., & Jacobs, G. A. (1983). *Manual for the Stait-Trait Anxiety Inventory*. Consulting Psychologists Press.

Sullivan, M., Bishop, S. R., & Pivik, J. (1995). The Pain Catastrophizing Scale: Development and validation. *Psychological Assessment, 7*(4), 524-532. https://doi.org/10.1037/1040-3590.7.4.524

Tassinary, L. G., & Cacioppo, J. T. (1992). Unobservable facial actions and emotion. *Psychological Science, 3*(1), 28-33. https://doi.org/10.1111/j.1467-9280.1992.tb00252.x

Tassinary, L. G., Cacioppo, J. T., & Vanman, E. J. (2007). The Skeletomotor System: Surface electromyography. In J. T. Cacioppo, L. G. Tassinary, & G. Berntson (Eds.), *Handbook of Psychophysiology:* (3 ed., pp. 267-300). Cambridge University Press.

Van Damme, S., Crombez, G., & Eccleston, C. (2004). The anticipation of pain modulates spatial attention: evidence for pain-specificity in high-pain catastrophizers. *PAIN, 111*(3), 392-399. https://doi.org/10.1016/j.pain.2004.07.022

Van Ryckeghem, D. M., Crombez, G., Eccleston, C., Liefooghe, B., & Van Damme, S. (2012). The interruptive effect of pain in a multitask environment: an experimental investigation. *J Pain, 13*(2), 131-138. https://doi.org/10.1016/j.jpain.2011.09.003

Verdejo-García, A., López-Torrecillas, F., Calandre, E. P., Delgado-Rodríguez, A., & Bechara, A. (2009). Executive function and decision-making in women with fibromyalgia. *Arch Clin Neuropsychol, 24*(1), 113-122. https://doi.org/10.1093/arclin/acp014

Waugh, C. E., Thompson, R. J., & Gotlib, I. H. (2011). Flexible emotional responsiveness in trait resilience. *Emotion, 11*(5), 1059-1067. https://doi.org/10.1037/a0021786

Westphal, M., Seivert, N. H., & Bonanno, G. A. (2010). Expressive flexibility. *Emotion, 10*(1), 92-100. https://doi.org/10.1037/a0018420

Zhao, X., Wang, H., & Maes, J. H. R. (2018). Training and transfer effects of extensive task-switching training in students. *Psychol Res.* https://doi.org/10.1007/s00426-018-1059-7

CHAPTER 3

The role of cognitive and affective flexibility in individual differences in the experience of experimentally induced heat pain

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ABSTRACT

Adaptation to the context in which we experience pain requires cognitive (CF) and affective flexibility (AF). Deficits in both flexibility types may be precursors of more intense and prolonged pain. This study aimed to examine the relation between CF and AF, and the experience of experimentally induced pain. Furthermore, correlations between behavioral and self-report measures of flexibility were explored. CF and AF were assessed with task-switching paradigms, using neutral (numbers ranging from 1 to 9, excluding 5) or affective stimuli (positive and negative pictures), respectively. Pain sensitivity measures, such as pain threshold (°C), pain tolerance (°C), and retrospective pain experience ratings (Visual Analogue Scale) were assessed for an experimentally induced heat pain stimulus. Self-reported CF was measured with a questionnaire. Results demonstrated no associations between the flexibility constructs and any of the pain outcome measures. Correlations between the behavioral and self-report measures of cognitive flexibility were absent or weak at best. Current results are discussed against the background of methodological considerations and prior empirical research findings, suggesting the contribution of AF in especially the recovery from pain.

Keywords

affective flexibility, cognitive flexibility, task switching, pain threshold/tolerance, heat pain

INTRODUCTION

People are typically confronted with constantly changing environments to which they must adapt in order to best navigate life. In the same way, the circumstances in which we experience pain are subject to change. Optimal adaptation to these contextual changes requires the use of cognitive and affective resources, and thus, flexibility at both the cognitive and affective level (Attal et al., 2014). Cognitive flexibility (CF) is conceptualized as the ability to adjust goals and to shift between different thoughts or behaviors in order to best match fluctuating environmental demands (Lezak, 1995). It involves two components of executive functioning, namely shifting and inhibition (Miyake et al., 2000). Consequently, insufficient CF is provoked by problems in inhibiting inappropriate thoughts and goals and by difficulties in shifting between goals and mental sets (Genet et al., 2013). CF can be considered an adaptive quality, as deficits in CF have been related to a variety of mental disorders such as depression (Lee et al., 2012), obsessive-compulsive disorder (Sadock & Sadock, 2007; Sternheim et al., 2014), borderline personality disorder (Ruocco, 2005), and anorexia nervosa (Abbate-Daga et al., 2011).

In the context of pain, a fair amount of research has demonstrated the negative impact of experimentally induced (e. g. Attridge et al., 2016; Boselie et al., 2014; Moore et al., 2012; Van Ryckeghem et al., 2012) and naturally occurring acute (e. g. Attridge et al., 2017; Attridge et al., 2016) and chronic pain (e. g. Eccleston, 1995; Karp et al., 2006; Verdejo-García et al., 2009) on various measures of CF. For instance, acute experimental pain has been shown to diminish shifting performance (Boselie et al., 2014; Van Ryckeghem et al., 2012). By contrast, CF has also been suggested to impact pain perception (Bjekić et al., 2018; Karsdorp et al., 2014; Oosterman et al., 2010). Moreover, deficits in CF have been suggested to be a precursor of more intense and prolonged pain experiences, and as such contribute to pain chronicity (as reviewed in Moriarty et al., 2011). A prospective study on postsurgical pain showed that the presence of chronic pain and high pain intensity 6 and 12 months after surgery were both independently predicted by impairments in CF (Attal et al., 2014).

A construct related to CF and suggested to be particularly interesting to examine in relation to pain is affective flexibility (AF; Malooly et al., 2013). AF is conceptualized as a domain-specific instantiation of CF, encompassing the ability to flexibly control the processing of emotional material, thereby switching between emotional and neutral information (Genet et al., 2013; Genet & Siemer, 2011; Malooly et al., 2013). AF has been suggested to underlie resilience (i.e., the ability to bounce back from adversity)

(Campbell-Sills & Stein, 2007) and has been found associated with less rumination (Genet et al., 2013). However, whether AF is adaptive may depend on the affective context in which it occurs; especially switches away from negative information and towards positive information have been shown to be adaptive (Genet et al., 2013; Malooly et al., 2013; Meesters et al., 2019).

Given the emotional characteristics of pain, AF has been suggested to be of relevance for the experience of pain. In a recent experimental study conducted in healthy college students, Meesters et al. (2019) reported an inverse relationship between AF and recovery from experimental pain. In this previous study, AF was measured with an affective task-switching paradigm (Malooly et al., 2013) - identical to the task used in the present study - that required participants to switch between processing the affective and neutral aspects of affective pictures. A Tourniquet pain procedure was used to induce ischemic pain by restricting the blood supply to the nondominant arm. Recovery in terms of pain intensity was assessed as the time from the moment of Tourniquet task termination until a pain intensity rating of 0 was given by the participant. The results showed that faster switches from neutral toward emotional characteristics of positive stimuli (i.e., AF) were predictive of faster recovery from ischemic pain in terms of pain intensity. These findings offered tentative support for the suggestion that AF, conceptualized as CF towards emotional material, might act as an explanatory mechanism in the experience and management of pain. However, the aforementioned study did not find an association between AF and pain tolerance. Whether the link between AF and pain is specific to recovery from pain remains elusive, as the pain tolerance measurement was hindered by a ceiling effect in that specific study (Meesters et al., 2019).

The current study was specifically set up to examine the relation between flexibility (i.e., CF and AF) and pain sensitivity using a heat pain induction task. CF and AF were assessed by a task switching paradigm employing neutral (CF; numbers ranging from 1 to 9, excluding 5) or affective stimuli (AF; positive and negative pictures), respectively. We hypothesized that better performance on both flexibility measures, and thus increased flexibility, would be associated with increased pain threshold and tolerance for pain, as well as lower retrospective pain experience ratings. For exploratory purposes, a self-report measure of CF was administered to explore its association to the pain outcomes and the behavioral measures of flexibility. Moreover, the incorporation of both AF and CF in the same study allows the examination of the relation between both constructs and their respective contribution to pain outcomes.

METHODS

Participants

Eighty-five healthy participants were recruited by means of advertisements at Maastricht University, on an electronic research participation system (SONA) and social media (i.e., Facebook). The following exclusion criteria were formulated: pregnancy, acute/chronic pain, injury or pain to the non-dominant arm, (a history of) cardiovascular problems, severe medical diseases (e.g., diabetes, asthma), diagnosis of a psychiatric (e.g., depression, anxiety disorder) or neurological (e.g., epilepsy) disorder, the use of anxiolytics or antidepressants, and/or poor vision that was not corrected. Additionally, at the start of the lab session we asked participants whether they had taken any analgesic medication earlier that day and if so, these were also excluded from participation. Self-report at the start of the experiment was used to check these criteria, resulting in the exclusion of two participants. The final sample consisted of 83 participants (mean age 21.3 years; *SD* = 2.76; 18 male). Participation was compensated by either a 7.50-euro gift voucher or course credits. Ethical approval was granted by the ethical review committee of the Faculty of Psychology and Neuroscience (ERCPN) of Maastricht University, and written informed consent was obtained from each participant at the start of the experiment.

Measures and materials

Pain induction apparatus and pain outcome measures

Pain induction: Thermal stimulation

A 30 x 30 mm^2 thermode as part of the Medoc Pathway Advanced Thermal Stimulator (MEDOC-ATS, Ltd Advanced Medical System, Ramat Yishai, Israel) was attached to the volar surface of the nondominant forearm at approximately 5 cm from the wrist. Two series of four thermal stimuli were delivered; each stimulus started at a preset baseline temperature (32°C) and gradually increased in temperature by 1°C s^{-1}. The stimulus promptly returned to baseline temperature at a rate of 8°C s^{-1} when the participant terminated the stimulus by a left or right mouse click or when the preset maximum temperature (51°C) was reached.

Pain threshold and pain tolerance

Pain threshold was determined for the first series of four thermal stimuli by instructing the participants to terminate the stimulus at the moment that they first started to experience pain. The average temperature (°C) of this series excluding the first trial was calculated to obtain a measure of pain threshold. Pain tolerance was assessed for the second series of four stimuli using the instruction to stop the stimulus at the moment that participants could no longer tolerate the pain. Again, the average temperature (°C) of this series excluding the first trial was computed to obtain a measure of pain tolerance.

Self-report anticipation and experience of pain intensity, pain unpleasantness, and fear of pain

Visual analogue scales (VASs) of 100 mm were used to measure anticipated and retrospective pain experience (i.e., pain intensity, pain unpleasantness, and fear of pain). The anchors of the VAS ratings ranged from 0 = ”not painful/unpleasant/fearful at all” to 100 = ”unbearably painful/extremely unpleasant/fearful”. VAS ratings pertaining to anticipated pain experience were administered twice; once prior to the first threshold measurement and once again prior to the first tolerance measurement. Ratings for anticipated pain experience were included for exploratory purposes and are not further reported in this paper. For retrospective pain experience, each VAS was administered after each heat stimulus and mean VAS scores across the last three trials of the threshold and tolerance series separately were computed.

Flexibility measures

Cognitive switching task setup

A task-switching paradigm identical to the one used by Boselie et al. (2017) was administered in order to assess CF. This task employs two different sorting rules for categorizing stimuli in order to measure switching and inhibiting abilities. Stimuli are numbers ranging from 1 to 9, excluding 5, and presented in succession on a monitor. Participants have to categorize these stimuli according to whether the number is odd or even (odd/even rule), or whether the number is higher or lower than 5 (higher/lower rule). Stimuli are preceded by a 500 msec prime (i.e., od/ev or hi/lo) indicating the next sorting rule. In order to remind the participant of the answer options, information about what answer option matches with which response key is simultaneously presented with the stimulus. There is no time limit for giving a response and the next prime and stimulus are presented upon pushing a key on a response box. The participants have their left-hand index finger on the left button and their right-hand index finger on the right button of this response box. There are four versions of this task based on the mapping of the active categorization rule (odd/even or higher/lower) to the response keys (left or right), which were counterbalanced across participants.

The task entails a 12-trial practice block and a 192-trial test block. In the practice block, the first six stimuli have to be sorted according to the higher/lower rule, and the second series of six stimuli have to be sorted following the odd/even rule. The test block has two different trial types, namely trials on which the sorting rule changes from one trial to the next (switch trials) and trials on which the sorting rule is repeated (repeat trials). The test block consists of 96 trials of each type with switch and repeat trials in semi-randomized fixed order. Reaction times (RT; msec) and accuracy are registered.

Affective switching task setup

An affective task-switching paradigm was employed to assess AF (Genet et al., 2013). The design of this computer task is similar to the cognitive switching task, but in this case participants sort affective pictures according to either an affective rule (determining whether the picture is positive or negative) or a neutral rule (determining whether the picture contains one or no humans, or two or more humans). The stimuli are 160 pictures from the International Affective Picture System (IAPS; Lang et al., 1997) that can be classified into four categories based on the two sorting rules. There are no primes in this task, but the pictures are shown with the active categorization rule (the cue) depicted on the left and right side of the picture: "+" and "-" indicate positive and negative, "≤ 1" and "≥ 2" indicate one or no people and two or more people. The picture is displayed against either a white or gray background with the color of the background corresponding to the cue. The picture category and cue are combined according to a pseudorandom order. There are eight task versions based on the mapping of the frame color (white or gray) to the active categorization rule (valence or number of people), and mapping of the response keys (left or right) to the categorization rule ("+" / "-" or "'≤ 1" / "≥ 2").

The task consists of two 10-trial practice blocks in which one of two rules is practiced per block and two 160-trial test blocks in which both rules are presented intermixed. For each trial, RT (ms) and accuracy are recorded. Trials are defined as either a switch or a repeat trial. A switch trial is a trial on which the categorization rule changes from the prior to the current trial, whereas a repeat trial is a trial on which the same categorization rule is repeated for the current trial. The first trial of each block is disregarded in data analyses, as it cannot be categorized as either a switch or repeat trial. It is important to note that the valence of the pictures never changes in the switch trials; it is only the categorization rule that alternates.

Mean RTs were calculated for eight different trial types, as defined on the basis of both the active categorization rule and picture valence of the previous and current trials. There were four switch trial types (i.e., positive to neutral rule, negative to neutral rule, neutral to positive rule, and neutral to negative rule) and four repeat trials types (positive to positive rule, negative to negative rule, neutral to neutral rule for positive pictures, neutral to neutral rule for negative pictures).

Reduced pain sensitivity is expected to be associated with greater flexibility (i.e., lower switch costs) in 1) switching toward processing affective features in a positive context, and 2) switching away from processing the affective features in a negative context, as well as with reduced flexibility (i.e., larger switch costs) in 3) switching away from processing affective characteristics of a positive context, and 4) switching toward processing affective features of a negative context.

Preprocessing and scoring of task-switching data

Analyses for both switching tasks were performed on mean RTs, excluding incorrect responses (cognitive switching task: 6.4% of the trials; affective switching task: 7.3% of the trials). Following previous studies using the same switching tasks (Boselie et al., 2017, 2018; Genet et al., 2013; Grol & De Raedt, 2018; Malooly et al., 2013), the effect of outlying RTs was limited by replacing 1) RTs ≤ 250 ms with the value of 250 ms (cognitive switching task: 0% of the trials; affective switching task: 0.014% of the trials), and 2) RTs larger than 2.5 *SD* above the individual mean RT with the individual mean plus 2.5 *SD* (cognitive switching task: 3.06% of the trials; affective switching task: 2.37% of the trials).

For the cognitive switching task, switch costs (ms) were calculated by subtracting RTs on repeat trials from RTs on switch trials (Boselie et al., 2017). Higher switch costs are indicative for slower responses to switch than repeat trials and reflect less CF. For the affective switching task, four types of switch costs were computed. In particular, affective-to-neutral (AtoN) switch costs were calculated by subtracting RTs on affective repeat trials from RTs on affective-to-neutral trials: switch cost AtoN = switch (affective to neutral) – repeat (affective to affective). This type of switch cost was separately computed for positive (SC posAtoN) and negative (SC negAtoN) pictures. Similarly, switch costs for neutral-to-affective (NtoA) task sets were computed for positive (SC posNtoA) and negative (SC negNtoA) pictures separately, using the formula: SC NtoA = switch (neutral to affective) – repeat (neutral to neutral). Higher switch costs are indicative of reduced flexibility in making the specific shift of interest (i.e., away from or toward the affective rule in a positive or negative context).

Self-report questionnaires

Basic sociodemographic information (age, gender, mother tongue, nationality, type and year of study) was obtained at the start of the survey. Some exit questions concerning the goal of the study and the two switching tasks (attention and motivation to perform the tasks, pleasantness, interest in the task, task duration and difficulty) were also inquired. Psychological questionnaires were administered in order to test the relationship between psychological constructs and switching abilities.

The Cognitive Flexibility Inventory (CFI; Dennis & Vander Wal, 2010) consists of 20 items measuring self-reported CF (e.g., "I consider multiple options before making a decision"; "I often look at a situation from different viewpoints"). Items are scored on a 7-point Likert scale with anchors at 1 ("strongly disagree") to 7 ("strongly agree"). Higher sum scores (range 20 – 140) reflect more CF. The CFI has good psychometric properties (Dennis & Vander Wal, 2010; Johnco et al., 2014). An internal consistency of $\alpha = .85$ was obtained for the current sample.

The Acceptance and Action Questionnaire-II (Bond et al., 2011; Fledderus et al., 2012), the 'difficulties engaging in goal-directed behaviors when experiencing negative emotions' subscale of the Difficulties in Emotion Regulation Scale (Gratz & Roemer, 2004), Life Orientation Test-Revised (Scheier et al., 1994), the Highly Sensitive Person Scale (Ruocco, 2005), the Cognitive Emotion Regulation Questionnaire (Garnefski & Kraaij, 2006), the Pain Catastrophizing Scale (Sullivan et al., 1995), the Fear of Pain Questionnaire-Short Form (Lee et al., 2012), the State-Trait Anxiety Inventory Y2 form (Spielberger et al., 1983), the Positive and Negative Affect Schedule 10-item version (Mackinnon et al., 1999), and four questions concerning stress levels were assessed for exploratory purposes beyond the scope of this paper and are therefore not further considered in this article.

Procedure

Upon arrival, study eligibility was verified and participants were informed about the test procedure. Written informed consent was obtained from each participant. Because wounds could potentially affect the experience of the thermal stimuli, the volar surface of the nondominant arm was checked for (healing) wounds, defined as a disruption of the skin for which the skin integrity is/was broken and there is/was a hemorrhage. None of the participants had any wounds. The lab session took approximately 1 hr and could be completed in either English or Dutch (65.1% of the participants chose English).

First, participants completed the two switching tasks. The order in which participants had to complete these tasks was counterbalanced. Task instructions were explained verbally and shown once again in text on the monitor at the start of each task. After both switching tasks were completed, the experimenter explained the pain induction procedure. The participants were told that the sensations caused by the stimulus could become unpleasant or painful. Before the start of the first stimulus, participants filled out the VAS ratings for anticipated pain experience. The difference between pain intensity and pain unpleasantness was clarified using a standardized written explanation employing a sound analogy reported in details elsewhere (Price & Harkins, 1987). The thermode was then attached to the volar surface of the nondominant forearm. During the pain procedure, participants had their nondominant arm resting in front of them on the table and their dominant hand on the stop mouse. The experimenter indicated verbally when a stimulus would be delivered. Pain threshold was measured first with an interstimulus interval of 30 s during which participants filled out the VAS ratings for retrospective pain experience. Before starting the pain tolerance measurements, participants were asked to fill in the anticipated VAS ratings. The interstimulus interval now was 90 s, and again participants filled out the retrospective VAS ratings during this period.

Following the removal of the thermode, the sociodemographic, psychological, and exit questionnaires were administered using an online survey application (Qualtrics, Provo, Utah, USA). Lastly, participants received either a 7.50-euro gift voucher or course credits as a reward for their participation and were debriefed.

Statistical analyses

The current study's sample size was determined a priori using G*Power (version 3.1.9.2) with hierarchical multiple regression analyses as the main analyses. A minimal sample size of 78 participants was set for a medium effect size ($f2 = .18$; Meesters et al., 2019), with one cognitive and four affective switch costs as predictors and one covariate (sex), a power of .80, and α of .05. SPSS version 24 software (SPSS, Inc., Chicago, Illinois, USA) was employed for statistical analyses. Descriptive statistics were retrieved, and normality and homogeneity of variance were checked showing that assumptions for subsequent statistical analyses were met. For pain-related data, the impact of outliers was reduced by substituting scores deviating more than 3 *SD* in positive or negative direction from the group mean by the group mean ±3 *SD*. Participants who did not reach pain threshold within the preset temperature limits (maximum 51°C) were omitted from all analyses incorporating pain outcome variables, as painful sensations were not succesfully induced in these participants. For pain tolerance, analyses were performed both including and excluding participants who reached the preset maximum temperature of 51°C. In case these analyses yield similar results, the results of analyses including the participants who reached the preset tolerance maximum are reported in this paper.

Pain threshold (°C), pain tolerance (°C), and retrospective pain experience ratings (i.e., pain intensity, pain unpleasantness, and fear of pain ratings for both threshold and tolerance) were the outcome variables of interest. The relationship between the different types of cognitive and affective switch costs and pain threshold, pain tolerance, and retroscpective pain experience ratings was examined using Pearson's correlation coefficients, thereby correcting for multiple testing ($\alpha < .01$). Hierarchical multiple regression analyses were used as the general analytical approach. Results from these analyses were considered significant when an α of $< .05$ was obtained. Two sets of hierarchical multiple regression analyses were conducted to test the predictive value of the cognitive and affective switch costs for all pain outcome variables. For the first set of analyses, age and sex were entered in the first step and the switch costs in the second step of the regression models. In case age and/or sex were not significantly related to the outcome variables, these predictors were removed from the regression model, but all other predictors were retained. For the second set of analyses, a backward deletion procedure was used for switch cost predictors after the deletion of age and sex in case of insignificance. Furthermore, the relation between various self-report measures of flexibility and the behavioral flexibility measures (i.e., both switching paradigms) was explored with Pearson's correlation coefficients, thereby correcting for multiple testing ($\alpha < .01$).

RESULTS

Descriptive statistics

One participant (1.20%) did not reach pain threshold within the preset temperature limits of the thermal stimulus (maximum 51°C) in any of the three threshold trials and was therefore excluded from all analyses involving pain outcome variables. Likewise, tolerance was not reached for six (7.2%) participants for whom a pain tolerance value of 51°C was registered. The mean and *SD* of pain threshold, pain tolerance, retrospective pain experience ratings, and self-report questionnaire scores and their correlations are depicted in Table 1.

Cognitive and affective switching tasks

For the cognitive switching task, results of the paired samples *t*-test showed that RTs on switch trials (M = 1446.2 ms, SD = 541.7 ms) were significantly greater than RTs on repeat trials (M = 1283.6 ms, SD = 410.5 ms), $t(82) = 6.58$, $p < .001$, $d = 1.45$. Similarly, using paired samples *t*-tests, greater RTs on switch trials (M = 1494.6 ms, SD = 324.2 ms) than on repeat trials (M = 1354.9 ms, SD = 292.3 ms), $t(81) = 12.1$, $p < .001$, $d = 2.62$, were found for the affective switching task.

The mean and *SD* of the different types of cognitive and affective switch costs as well as their correlations are presented in Table 1. A repeated measures analysis of variance with a Greenhouse-Geisser correction revealed a significant difference between the four types of affective switch costs, $F(2.59, 212.2) = 31.8$, $p < .001$. Post hoc analyses using the Bonferroni correction showed that mean SC negAtoN was significantly larger than mean SC posAtoN ($p = .001$), mean SC negNtoA ($p < .001$), and mean SC posNtoA ($p < .001$). In addition, mean SC negNtoA was significantly smaller than mean SC posAtoN ($p < .001$), mean SC negAtoN ($p < .001$), and mean SC posNtoA ($p < .01$). No significant difference was found between mean SC posAtoN and mean SC posNtoA ($p = .061$).

In line with previous studies using similar task-switching paradigms to assess CF and AF (Genet et al., 2013; Malooly et al., 2013; Meesters et al., 2019), weak to moderate correlations were found between the different switch costs, suggesting that these switch costs express distinct components of CF and AF. Table 1 also displays the correlations between the different types of switch costs and the self-report measures. All switch costs were unrelated to the self-report measure of CF.

CF and AF as predictors for pain threshold and pain tolerance

The relationship between the different types of cognitive and affective switch costs and all pain outcome variables was examined using Pearson's correlations (Table 1). Very weak to weak correlations were found between the different cognitive or affective switch costs at one hand and pain threshold or pain tolerance at the other hand.

Variance inflation factors (VIFs; range 1.00–1.27) were checked for each hierarchical multiple regression model and suggested no collinearity problems between predictors. A nonsignificant regression model was identified for pain threshold, $R^2 = .05$, $F(5, 76) =$

Table 1. Mean, *SD* and Pearson correlations for pain threshold, pain tolerance, subjective pain experience ratings, the self-report flexibility measures and the different types of cognitive and affective switch costs

Measure	*M* (*SD*)	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1. Pain threshold	46.00 (2.17)	-													
2. Pain tolerance	48.20 (1.35)	.83***	-												
Subjective pain experience ratings – threshold															
3. Pain intensity	54.52 (20.10)	.18	.09	-											
4. Pain unpleasantness	52.17 (22.27)	.22	.10	.89**	-										
5. Fear of pain	25.41 (18.76)	.20	.13	.52**	.51**	-									
Subjective pain experience ratings – tolerance															
6. Pain intensity	56.45 (15.85)	.02	.10	.69**	.60**	.53**	-								
7. Pain unpleasantness	57.44 (19.04)	.03	.07	.67**	.69**	.50**	.89**	-							
8. Fear of pain	47.81 (20.09)	.06	.09	.50**	.53**	.71**	.77**	.83**	-						
Self-report measure															
9. CFI	101.3 (13.05)	-.06	-.02	.02	.11	-.07	-.02	.08	.04	-					
Switch costs															
10. CF, general SC	159.3 (212.7)	.07	.13	.01	-.08	-.03	.06	.03	.02	-.19	-				
11. AF, general SC	141.3 (104.8)	.09	.13	.03	.02	.08	.11	.02	.02	.08	.36***	-			
12. AF, SC posAtoN	181.9 (221.7)	-.03	.06	.02	-.08	.06	.10	-.06	.06	.01	.07	.30**	-		
13. AF, SC negAtoN	299.2 (260.8)	-.15	-.01	-.02	-.01	.10	-.09	-.12	.08	.08	.19	.41***	.36	-	
14. AF, SC posNtoA	79.4 (238.8)	-.04	-.03	.10	.11	.06	.05	.04	.08	.04	.17	.48***	-.19	.10	-
15. AF, SC negNtoA	-42.4 (236.5)	.15	.17	.03	.11	.04	.05	.02	-.07	.03	.13	.33**	-.003	-.21	.14

N = 83 (18 men) for self-report measures and switch costs; N = 82 (18 men) for pain threshold and related subjective pain experience; N = 77 (15 men) for pain tolerance and related subjective pain experience; pain threshold, the average temperature (°C) across the last three threshold measurements; pain tolerance, the average temperature (°C) across the last three tolerance measurements; CFI, Cognitive Flexibility Inventory; CF, cognitive flexibility; SC, switch cost; AF, affective flexibility; SC posAtoN, switch cost for positive picture and affective-to-neutral trial; SC negAtoN, switch cost for negative picture and affective-to-neutral trial; SC posNtoA, switch cost for positive picture and neutral-to-affective trial; SC negNtoA, switch cost for negative picture and neutral-to-affective trial; M, mean; SD, standard deviation. ** $p < .01$; *** $p \leq .001$.

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.74, p = .60. On the contrary, a significant regression model for pain tolerance was found, R^2 = .17, F(6, 75) = 2.46, p < .05. Sex showed to be a significant predictor of pain tolerance, but not of pain threshold, indicating that men exhibited a higher pain tolerance than women. Similar results were obtained when the regression analyses were performed with the backward deletion procedure for both pain threshold, R^2 = .03, F(1, 80) = 2.54, p = .12, and pain tolerance, R^2 = .11, F(1, 80) = 10.0, p < .01.

CF and AF as predictors for retrospective pain experience ratings

Pearson's correlations did not reveal any significant associations between the cognitive or affective switch costs and the retrospective pain experience ratings neither for the threshold series (all ps ≥ .31, Table 1), nor for the tolerance series (all ps ≥ .32, Table 1). For each multiple regression model, VIFs (range 1.00–1.26) were checked and indicated no problems with collinearity between predictors. For the threshold series, nonsignificant regression models were identified for retrospective pain intensity, R^2 = .11, F(6, 75) = 1.59, p = .16, and fear of pain, R^2 = .10, F(6, 75) = 1.45, p = .21. Sex showed to be a significant predictor of both retrospective pain intensity (β = .33, p < .01) and fear of pain (β = .30, p = .01). The regression model for retrospective pain unpleasantness was significant, R^2 = .17, F(6, 75) = 2.60, p < .05, with sex as significant predictor (β = .38, p = .001), suggesting that men gave lower pain unpleasantness ratings than women. When applying backward deletion, significant regression models were identified for retrospective pain intensity, R^2 = .11, F(1, 80) = 9.88, p < .05, pain unpleasantness, R^2 = .13, F(1, 80) = 12, p = .001, and fear of pain, R^2 = .09, F(1, 80) = 7.48, p < .01, with sex as significant predictor in all models (pain intensity: β = .33, p < .01; pain unpleasantness: β = .36, p = .001; fear of pain: β = .92, p < .01).

For the tolerance series, analyses revealed no significant regression model for retrospective pain intensity, R^2 = .08, F(6, 70) = 1.03, p = .41, pain unpleasantness, R^2 = .05, F(6, 70) = .55, p = .77, and fear of pain, R^2 = .07, F(6, 70) = .92, p = .49. Sex was a significant predictor of retrospective fear of pain (β = .27, p < .05). Backward deletion yielded similar results for pain unpleasantness, R^2 = .03, F(1, 75) = 2.35, p = .29, but significant regression models for pain intensity, R^2 = .06, F(1, 75) = 4.32, p < .05, and fear of pain, R^2 = .07, F(1, 75) = 5.83, p < .05, with sex as significant predictor (pain intensity: β = .23, p < .05; fear of pain: β = .27, p < .05).

DISCUSSION

The purpose of the present study was to investigate the link between two specific types of flexibility (i.e., CF and AF) and pain sensitivity outcomes (i.e., pain threshold, pain tolerance, and retrospective pain experience ratings). Results showed no evidence for the hypothesis that increased levels of CF and AF would be related to lower pain experience.

Current results are in disagreement with previous findings suggesting a relationship between CF and pain experience (Attal et al., 2014; Bjekić et al., 2018; Moriarty et al., 2011; Oosterman et al., 2010). However, note that studies on the relation between CF and the experience of pain have predominantly focused on the effect of pain on cognitive switching performance, thereby demonstrating reduced switching performance when in pain (Boselie et al., 2014; Karp et al., 2006; Van Ryckeghem et al., 2012; Verdejo-García et al., 2009). Although CF has been proposed as a precursor of prolonged pain responses as well (for a review, see Moriarty et al., 2011), empirical evidence on the direct relation between CF and pain is sparse. Using a prospective study design, Attal et al. (2014) demonstrated low levels of CF to be predictive of the development of postsurgical chronic pain. The present, short-term thermal stimulation as pain induction method might not be sensitive enough to capture the influence of a similar effect of flexibility on heat pain tolerance. Furthermore, we included a college student sample with relatively low variability in CF.

In the current study, we adopted a task-switching paradigm to assess CF (Boselie et al., 2017). Note that the definition of CF includes the ability of switching between tasks in accordance to changing environmental demands, and thereby implies that CF not only requires task-switching ability but possibly also the ability to inhibit prepotent, automatic responses, that is, cognitive inhibition. Indeed, cognitive inhibition is closely associated with cognitive task-switching ability (Miyake et al., 2000). Contrasting the available evidence on the link between task switching performance and pain, several studies have reported better cognitive inhibition to be associated with reduced sensitivity for experimental pain (Bjekić et al., 2018; Karsdorp et al., 2014; Oosterman et al., 2010). It may be speculated that inhibition may be the component of CF that plays the most important role in pain perception (Miyake et al., 2000). Future research should therefore consider the use of different tasks specifically tapping into the inhibition and switching components of CF.

In line with earlier work (Meesters et al., 2019), we found no associations between AF and pain tolerance. The current study was designed to include a pain procedure that was better adapted to measure pain tolerance, because it has a smaller ceiling effect than the ischemic pain procedure in the previous study by Meesters et al. (2019). In addition, the use of thermal stimuli to induce pain also allowed a pain threshold measurement. However, we found no evidence for an association between AF and pain threshold, nor for retrospective pain experience ratings. So far, evidence only exists for an association between AF and recovery from ischemic pain with faster switches from neutral to positive contexts being beneficial for recovery (Meesters et al., 2019). We may therefore suggest that the link between AF and pain specifically applies to recovery from pain. Given the affective dimension of pain experience (e.g., Craig, 2003), recovery from pain entails recovery from an affective challenge. In other words, recovery involves a switch in affective contexts and hence may benefit from flexibility in attending to and disengaging from a painful stimulus. Also, flexibility involves faster and stronger responding to changing stimuli with a quicker return to baseline when the stimulus is not there anymore (e.g., Papousek et al., 2012), which seems to correspond to the warning function of pain to inform us about potential physical harm or illness as well as adaptive recovery when the painful stimulus has been removed. As AF is a relatively new concept, future studies seem necessary to aid understanding of AF and its relation to the experience of pain.

For the affective switching task, different switch costs could be calculated on the basis of the direction of the switch, that is, whether a switch was being made from the affective toward the neutral rule or vice versa. The current findings showed that individuals find it harder to switch away from processing negative information than from positive or neutral information. On the contrary, the fastest switches are made from processing neutral towards negative information. These results imply that the processing of negative information takes precedence over positive or neutral information.

Last, it should be noted that explorative correlational analyses showed zero to weak associations between the behavioral measure of CF and AF, and self-reported CF. This lack of an association is remarkable and hard to explain, especially given the conceptual overlap between the self-report and behavioral constructs of interest. One speculative explanation for the lack of correlations between the behavioral and self-report measure of flexibility might be sought in conceptual distinctiveness between the aspects of flexibility that are assessed by the instruments. Alternatively, resulting correlations might evidence a discrepancy between self-reported (explicit) and behavioral (implicit) flexibility measures (Fazio & Olson, 2003; Wilson et al., 2000). However, note that aforementioned explanations are speculative at best, and in need of further scrutiny.

Some potential study limitations should be discussed. First, the study sample consisted of healthy pain-free students who were mainly highly educated women generally scoring high on self-reported CF, resulting in decreased generalizability of our findings. Second, a significant proportion of participants reached the predetermined maximum tolerance level. Nevertheless, sensitivity analyses did not show any effects of tolerance maximum on hypothesized associations. Furthermore, sample size is relatively low for the multiple correlations. Given the assumption that flexibility may be a predictor of maladaptive pain behavior and cognitions, study designs with long-term follow up assessments and/or designs measuring flexibility in naturalistic settings to increase ecological validity may be more desirable. In addition, switch costs are widely distributed (Boselie et al., 2017, 2018; Meesters et al., 2019) and as a result may be less suitable for studying individual differences. We did not control for differences in general working memory ability which could have been important for switching task performance (Genet et al., 2013). Future studies should therefore control for general working memory ability.

We used heat stimulation to induce pain in the current study to more reliably assess pain threshold and tolerance. However, this prevented replication of the previously found association between AF and recovery from pain (Meesters et al., 2019). It remains elusive what the exact influence of the employment of different pain procedures in the current (i.e., heat stimulation) compared to the previous study (i.e., ischemic pain procedure; Meesters et al., 2019) may have been on study outcomes. Pain induced by heat stimulation is qualitatively different from pain induced by ischemic procedures. For instance, heat stimulation induces phasic pain, a short-lived type of pain with almost immediate recovery after stimulus removal. In contrast, ischemic procedures induce tonic pain - a relatively long-lasting type of pain – for which recovery typically takes longer as compared to phasic pain. Furthermore, the duration of the pain task in both studies (short vs. long) may be related to a difference in the need for coping, that is, pain of long duration may require more coping than phasic pain. Finally, the pain procedure allowed participants to terminate pain stimulation themselves, which might have induced a feeling of perceived control that affected pain sensitivity measures.

In conclusion, the present study did not find any evidence for the predictive value of CF and AF for heat pain threshold and tolerance. Furthermore, performance on both flexibility measures was not related to the subjective pain experience ratings (i.e., pain intensity, pain unpleasantness, and fear of pain for both pain threshold and tolerance series). Future research is necessary to further elucidate the role of flexibility as steering mechanism in pain. Unraveling what psychological factors play a role in the perception of pain is worthwhile, as both prevention and therapy of chronic pain would benefit of such knowledge.

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Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

All procedures performed in this study were in accordance with the standards of the Ethical Review Committee of the Faculty of Psychology and Neuroscience (ERCPN), Maastricht University. Informed consent was obtained from all individual participants included in the study.

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REFERENCES

Abbate-Daga, G., Buzzichelli, S., Amianto, F., Rocca, G., Marzola, E., McClintock, S. M., & Fassino, S. (2011). Cognitive flexibility in verbal and nonverbal domains and decision making in anorexia nervosa patients: a pilot study. *BMC Psychiatry, 11*(1), 162. https://doi.org/10.1186/1471-244x-11-162

Attal, N., Masselin-Dubois, A., Martinez, V., Jayr, C., Albi, A., Fermanian, J., Bouhassira, D., & Baudic, S. (2014). Does cognitive functioning predict chronic pain? Results from a prospective surgical cohort. *Brain, 137*(Pt 3), 904-917. https://doi.org/10.1093/brain/awt354

Attridge, N., Eccleston, C., Noonan, D., Wainwright, E., & Keogh, E. (2017). Headache impairs attentional performance: a conceptual replication and extension. *Journal of Pain, 18*(1), 29.

Attridge, N., Keogh, E., & Eccleston, C. (2016). The effect of pain on task switching: pain reduces accuracy and increases reaction times across multiple switching paradigms. *PAIN, 157*(10), 2179-2193. https://doi.org/10.1097/j.pain.0000000000000627

Bjekić, J., Živanović, M., Purić, D., Oosterman, J. M., & Filipović, S. R. (2018). Pain and executive functions: a unique relationship between Stroop task and experimentally induced pain. *Psychological Research, 82*(3), 580-589. https://doi.org/10.1007/s00426-016-0838-2

Bond, F. W., Hayes, S. C., Baer, R. A., Carpenter, K. M., Guenole, N., Orcutt, H. K., Waltz, T., & Zettle, R. D. (2011). Preliminary psychometric properties of the Acceptance and Action Questionnaire-II: a revised measure of psychological inflexibility and experiential avoidance. *Behav Ther, 42*(4), 676-688. https://doi.org/10.1016/j.beth.2011.03.007

Boselie, J. J. L. M., Vancleef, L. M. G., & Peters, M. L. (2017). Increasing Optimism Protects Against Pain-Induced Impairment in Task-Shifting Performance. *Journal of Pain, 18*(4), 446-455. https://doi.org/10.1016/j.jpain.2016.12.007

Boselie, J. J. L. M., Vancleef, L. M. G., & Peters, M. L. (2018). Filling the glass: Effects of a positive psychology intervention on executive task performance in chronic pain patients. *Eur J Pain, 22*(7), 1268-1280. https://doi.org/10.1002/ejp.1214

Boselie, J. J. L. M., Vancleef, L. M. G., Smeets, T., & Peters, M. L. (2014). Increasing optimism abolishes pain-induced impairments in executive task performance. *PAIN, 155*(2), 334-340. https://doi.org/10.1016/j.pain.2013.10.014

Campbell-Sills, L., & Stein, M. B. (2007). Psychometric analysis and refinement of the Connor-davidson Resilience Scale (CD-RISC): Validation of a 10-item measure of resilience. *J Trauma Stress, 20*(6), 1019-1028. https://doi.org/10.1002/jts.20271

Craig, A. D. (2003). A new view of pain as a homeostatic emotion. *Trends Neurosci, 26*(6), 303-307.

Dennis, J. P., & Vander Wal, J. S. (2010). The Cognitive Flexibility Inventory: Instrument Development and Estimates of Reliability and Validity. *Cognitive Therapy and Research, 34*(3), 241-253. https://doi.org/10.1007/s10608-009-9276-4

Eccleston, C. (1995). Chronic pain and distraction: an experimental investigation into the role of sustained and shifting attention in the processing of chronic persistent pain. *Behav Res Ther, 33*(4), 391-405. https://doi.org/10.1016/0005-7967(94)00057-q

Fazio, R., & Olson, M. (2003). Implicit Measures in Social Cognition Research: Their Meaning and Use. *Annual review of psychology, 54*, 297-327. https://doi.org/10.1146/annurev.psych.54.101601.145225

Fledderus, M., Oude Voshaar, M. A., Ten Klooster, P. M., & Bohlmeijer, E. T. (2012). Further evaluation of the psychometric properties of the Acceptance and Action Questionnaire-II. *Psychol Assess, 24*(4), 925-936. https://doi.org/10.1037/a0028200

Garnefski, N., & Kraaij, V. (2006). Cognitive emotion regulation questionnaire – development of a short 18-item version (CERQ-short). *Personality and Individual Differences, 41*(6), 1045-1053. https://doi.org/10.1016/j.paid.2006.04.010

Genet, J. J., Malooly, A. M., & Siemer, M. (2013). Flexibility is not always adaptive: affective flexibility and inflexibility predict rumination use in everyday life. *Cogn Emot, 27*(4), 685-695. https://doi.org/10.1080/02699931.2012.733351

Genet, J. J., & Siemer, M. (2011). Flexible control in processing affective and non-affective material predicts individual differences in trait resilience. *Cogn Emot, 25*(2), 380-388. https://doi.org/10.1080/02699931.2010.491647

Gratz, K. L., & Roemer, L. (2004). Multidimensional Assessment of Emotion Regulation and Dysregulation: Development, Factor Structure, and Initial Validation of the Difficulties in Emotion Regulation Scale. *Journal of Psychopathology and Behavioral Assessment, 26*(1), 41-54. https://doi.org/10.1023/b:joba.0000007455.08539.94

Grol, M., & De Raedt, R. (2018). The effect of positive mood on flexible processing of affective information. *Emotion, 18*(6), 819-833. https://doi.org/10.1037/emo0000355

Johnco, C., Wuthrich, V. M., & Rapee, R. M. (2014). Reliability and validity of two self-report measures of cognitive flexibility. *Psychol Assess, 26*(4), 1381-1387. https://doi.org/10.1037/a0038009

Karp, J. F., Reynolds, C. F., 3rd, Butters, M. A., Dew, M. A., Mazumdar, S., Begley, A. E., Lenze, E., & Weiner, D. K. (2006). The relationship between pain and mental flexibility in older adult pain clinic patients. *Pain Med, 7*(5), 444-452. https://doi.org/10.1111/j.1526-4637.2006.00212.x

Karsdorp, P. A., Geenen, R., & Vlaeyen, J. W. (2014). Response inhibition predicts painful task duration and performance in healthy individuals performing a cold pressor task in a motivational context. *Eur J Pain, 18*(1), 92-100. https://doi.org/10.1002/j.1532-2149.2013.00348.x

Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (1997). *International Affective Picture System (IAPS): Technical manual and affective ratings.* NIMH Center for the Study of Emotion and Attention, University of Florida.

Lee, R. S., Hermens, D. F., Porter, M. A., & Redoblado-Hodge, M. A. (2012). A meta-analysis of cognitive deficits in first-episode Major Depressive Disorder. *J Affect Disord, 140*(2), 113-124. https://doi.org/10.1016/j.jad.2011.10.023

Lezak, M. D. (1995). *Neuropsychological assessment* (3 ed.). Oxford University Press.

Mackinnon, A., Jorm, A. F., Christensen, H., Korten, A. E., Jacomb, P. A., & Rodgers, B. (1999). A short form of the Positive and Negative Affect Schedule: evaluation of factorial validity and invariance across demographic variables in a community sample. *Personality and Individual Differences, 27*(3), 405-416. https://doi.org/10.1016/S0191-8869(98)00251-7

Malooly, A. M., Genet, J. J., & Siemer, M. (2013). Individual differences in reappraisal effectiveness: the role of affective flexibility. *Emotion, 13*(2), 302-313. https://doi.org/10.1037/a0029980

Meesters, A., Vancleef, L. M. G., & Peters, M. L. (2019). Emotional flexibility and recovery from pain. *Motivation and Emotion*. https://doi.org/10.1007/s11031-018-9748-5

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The unity and diversity of executive functions and their contributions to complex "Frontal Lobe" tasks: a latent variable analysis. *Cognitive Psychology, 41*(1), 49-100. https://doi.org/10.1006/cogp.1999.0734

Moore, D. J., Keogh, E., & Eccleston, C. (2012). The interruptive effect of pain on attention. *Q J Exp Psychol (Hove)*, *65*(3), 565-586. https://doi.org/10.1080/17470218.2011.626865

Moriarty, O., McGuire, B. E., & Finn, D. P. (2011). The effect of pain on cognitive function: a review of clinical and preclinical research. *Prog Neurobiol, 93*(3), 385-404. https://doi.org/10.1016/j.pneurobio.2011.01.002

Oosterman, J. M., Dijkerman, H. C., Kessels, R. P., & Scherder, E. J. (2010). A unique association between cognitive inhibition and pain sensitivity in healthy participants. *Eur J Pain, 14*(10), 1046-1050. https://doi.org/10.1016/j.ejpain.2010.04.004

Papousek, I., Reiser, E. M., Weber, B., Freudenthaler, H. H., & Schulter, G. (2012). Frontal brain asymmetry and affective flexibility in an emotional contagion paradigm. *Psychophysiology, 49*(4), 489-498. https://doi.org/10.1111/j.1469-8986.2011.01324.x

Price, D. D., & Harkins, S. W. (1987). Combined Use of Experimental Pain and Visual Analogue Scales in Providing Standardized Measurement of Clinical Pain. *The Clinical Journal of Pain, 3*(1), 1-8.

Ruocco, A. C. (2005). The neuropsychology of borderline personality disorder: a meta-analysis and review. *Psychiatry Res, 137*(3), 191-202. https://doi.org/10.1016/j.psychres.2005.07.004

Sadock, B. J., & Sadock, V. A. (2007). *Synopsis of psychiatry* (10 ed.). Wolters Kluwer Business.

Scheier, M. F., Carver, C. S., & Bridges, M. W. (1994). Distinguishing optimism from neuroticism (and trait anxiety, self-mastery, and self-esteem): a reevaluation of the Life Orientation Test. *J Pers Soc Psychol, 67*(6), 1063-1078. https://doi.org/10.1037//0022-3514.67.6.1063

Spielberger, C. D., Gorsuch, R. L., Lushenne, R. E., Vagg, P. R., & Jacobs, G. A. (1983). *Manual for the Stait-Trait Anxiety Inventory*. Consulting Psychologists Press.

Sternheim, L., van der Burgh, M., Berkhout, L. J., Dekker, M. R., & Ruiter, C. (2014). Poor cognitive flexibility, and the experience thereof, in a subclinical sample of female students with obsessive-compulsive symptoms. *Scand J Psychol, 55*(6), 573-577. https://doi.org/10.1111/sjop.12163

Sullivan, M., Bishop, S. R., & Pivik, J. (1995). The Pain Catastrophizing Scale: Development and validation. *Psychological Assessment, 7*(4), 524-532. https://doi.org/10.1037/1040-3590.7.4.524

Van Ryckeghem, D. M., Crombez, G., Eccleston, C., Liefooghe, B., & Van Damme, S. (2012). The interruptive effect of pain in a multitask environment: an experimental investigation. *J Pain, 13*(2), 131-138. https://doi.org/10.1016/j.jpain.2011.09.003

Verdejo-García, A., López-Torrecillas, F., Calandre, E. P., Delgado-Rodríguez, A., & Bechara, A. (2009). Executive function and decision-making in women with fibromyalgia. *Arch Clin Neuropsychol, 24*(1), 113-122. https://doi.org/10.1093/arclin/acp014

Wilson, T. D., Lindsey, S., & Schooler, T. Y. (2000). A model of dual attitudes. *Psychol Rev, 107*(1), 101-126. https://doi.org/10.1037/0033-295x.107.1.101

CHAPTER 4

The effects of a brief mindfulness meditation exercise on pain experience and recovery

ABSTRACT

Mindfulness meditation (MM) has beneficial effects on pain outcomes in both clinical and experimental settings. However, the relation between MM and recovery from pain, as well as the mechanisms underlying the beneficial effects of MM, remain largely unknown. This study aimed to investigate the effect of a mindfulness exercise on pain experience and recovery, and the role of cognitive and affective flexibility in this relation. Thirty-three female students were randomly assigned to a mindfulness (n = 16) or a control condition (n = 17). Mindfulness was induced by means of a mindfulness exercise at the end of the first out of two lab sessions, by daily 20-min exercises in the week between the two lab sessions, and a final mindfulness exercise during the second lab session. During each lab visit, participants completed psychological questionnaires, and cognitive and affective flexibility were measured using task-switching paradigms with either neutral or affective stimuli, respectively. Participants provided pain intensity, pain unpleasantness and subjective stress ratings at semi-random time points during an ischemic pain task and 10-min recovery period. Pain tolerance was measured as the total time participants endured the pain task and time until recovery in terms of pain intensity and pain unpleasantness was registered. Although mindfulness was successfully induced, no effect was observed on pain tolerance, subjective stress ratings, and recovery in terms of pain intensity and pain unpleasantness, nor on cognitive and affective flexibility. Due to methodological issues, current findings should be carefully interpreted.

Keywords

mindfulness, tourniquet, pain, pain recovery, affective flexibility, cognitive flexibility

INTRODUCTION

Mindfulness-based interventions (MBIs) have been demonstrated to have beneficial effects on pain outcomes in clinical populations (e.g., Reiner et al., 2013; Veehof et al., 2011). Not only pain perception, but also recovery from pain seems to be affected by mindfulness (e.g., Chavez et al., 2020; Dowsey et al., 2019; Ratcliff, 2015). For instance, patients who completed a mindfulness-based stress reduction (MBSR) program prior to total joint arthroplasty showed greater improvements in pain and joint function 12 months after surgery than patients who received treatment as usual (Dowsey et al., 2019). In addition, guided meditation delivered before and during surgery speeded recovery in terms of anxiety levels in women undergoing stereotactic breast biopsy (Ratcliff, 2015). Making use of various experimental pain procedures, studies in healthy participants have found a similar link between mindfulness meditation (MM) and higher pain threshold (Reiner et al., 2016), higher pain tolerance (Choi et al., 2011; Kingston et al., 2007), and lower pain intensity and anxiety ratings (Zeidan, Gordan, Merchant, & Goolkasian, 2010). In addition, healthy female participants who followed a 2-week mindfulness self-training displayed a faster adaptation to tonic heat pain stimulation in terms of pain intensity ratings than control participants did (Reiner et al., 2016).

A variety of underlying mechanisms for the therapeutic effect of MM on psychological variables have been proposed (e.g., Gu et al., 2015; Holzel et al., 2011; Shapiro et al., 2006). One such working mechanism might be cognitive flexibility (CF) - the capacity to alter goals and to shift between mental sets or behaviors in line with situational demands (Miyake et al., 2000). Indeed, a recent systematic review and meta-analysis found evidence for CF as an explanatory mechanism for the beneficial effects of MM (Gu et al., 2015). Furthermore, it has repeatedly been demonstrated that MM can enhance CF-related processes (for a review, see Gallant, 2016). For example, Moynihan et al. (2013) have shown that older adults exhibited greater performance on a CF task after a MBSR program.

Research has demonstrated that the experience of acute experimental pain hinders CF (e.g., Boselie et al., 2014; Moore et al., 2012; Van Ryckeghem et al., 2012). Likewise, chronic pain has been linked to deficits in CF (for a review, see Moriarty et al., 2011). Conversely, a prospective study by Attal et al. (2014) has shown that CF was a protective factor against the development of chronic pain and reported pain severity six and 12 months after surgery. Moreover, CF has been related to higher cold pressor pain threshold and tolerance (Bjekic et al., 2018; Karsdorp et al., 2014). Taken together, these studies indicate the adaptive quality of CF and its involvement in pain perception and chronic pain.

A second mechanism proposed to underlie the beneficial effects of MM is affective flexibility (AF), a domain-specific instantiation of CF (Genet et al., 2013). AF refers to the ability to flexibly attend to and disengage from information in emotional contexts and thereby specifically concerns the flexible processing of affective information (Genet et al., 2013; Genet & Siemer, 2011; Malooly et al., 2013). AF is proposed to be important for adequate emotion regulation (Gross, 2007), and has been related to less rumination (Genet et al., 2013) and more use of reappraisal (Malooly et al., 2013). With respect to MM, Ortner et al. (2007) revealed in a two-part study that the level of mindfulness experience in meditators was related to a decrease in reactivity to both positive and negative stimuli, and that participants were faster in disengaging from negative stimuli after a 7-week mindfulness training. These findings suggest that people exhibiting higher levels of mindfulness may be better able to inhibit or disengage from (irrelevant) affective information and to shift more easily between processing stimuli of different emotional valence.

Recent research has started to examine the association between AF and pain (Meesters et al., 2019, 2021). According to Meesters et al. (2019), AF may play a role in the experience of pain, and in particular, recovery from pain. More specifically, AF was shown to be related to faster recovery in terms of pain intensity ratings. However, as these results were tentative, the exact relationship between AF and pain remains elusive.

The current study sought to examine the effect of MM on tolerance of, and recovery from ischemic pain, as well as the role of CF and AF in explaining this effect. To this end, mindfulness was induced in a convenience sample of female students. It was hypothesized that elevated pain tolerance and lower subjective stress ratings would be observed in participants receiving the MM induction as compared to control participants. Moreover, we expected that participants receiving the MM induction would show faster recovery in terms of pain intensity and pain unpleasantness. Because mindfulness is directed at changing the relation between the self and the experience (i.e., 'suffering'), instead of changing the sensory experience per se, the strongest effects were expected for pain unpleasantness and subjective stress ratings. Lastly, we also investigated the effect of the MM induction on CF and AF.

METHODS

Participants

Sixty-five female participants were recruited through the distribution of posters at Maastricht University, and advertisements on an electronic research participation system (SONA) and Facebook. Exclusion criteria were: prior experience with meditation practice, pregnancy, acute/chronic pain, injury or pain to the nondominant arm, (a history of) cardiovascular problems, severe medical diseases (e.g., diabetes), diagnosis of a psychiatric (e.g., depression, anxiety disorder) or neurological (e.g., epilepsy) disorder, the use of anxiolytics or antidepressants, cardiac arrhythmia, hyper/hypotension, the use of anticoagulants or the like, blood clotting problems, carrying an electronic implant, and impaired uncorrected vision.

Participants were tested by either one of two experimenters and randomly allocated to the MM or control group by means of an online randomization program (www.random.org). Participation requirements were checked at the start of the first lab session by means of self-report. Initially, 65 participants were included in the study, however, due to dropout of participants after the first lab session (n = 4) and insufficient protocol adherence by one of the experimenters (n = 27), 34 participants were left for analyses (mean age 23.6 years; *SD* = 4.68; range: 18 - 40 years). One participant reported concentration difficulties and was excluded from data analyses, resulting in a final study sample of 33 participants (mean age 23.7 years; *SD* = 4.75; range: 18 - 40 years) with 17 participants in the control group (mean age 24.2 years; *SD* = 5.93; range:18 – 40 years) and 16 in the MM group (mean age 23.1; *SD* = 3.16; range: 19 – 30 years).

Participants were asked to refrain from caffeine- and alcohol-containing beverages, smoking, and physical exertion for at least 30 min before each lab session. They were also instructed to not take any analgesic medication on the day of the experiment. The reward for partaking in the experiment was either course credits or a 37.5-euro gift voucher. Study approval was granted by the ethical review committee of the Faculty of Psychology and Neuroscience (ERCPN), Maastricht University.

Measures and materials

Mindfulness induction

The mindfulness induction consisted of various MM exercises. The first exercise was completed at the end of lab session 1. Next, participants in the MM group performed daily 20-min exercises in the week between the two lab sessions, which was followed up with the final mindfulness exercise in the second lab session. The MM exercises during lab session 1 and at home were offered to increase participants' understanding of mindfulness and to have them practice MM as to assure they would be able to perform the final mindfulness exercise during lab session 2.

Daily mindfulness home exercises

The mindfulness home exercises focused on cultivating awareness and acceptance of thoughts, feelings and bodily sensations and consisted of psychoeducation, standardized meditation practices of MBSR (Kabat-Zinn, 1982) and mindfulness-based cognitive therapy (Segal et al., 2002), performing routine activities with awareness, and short YouTube videos of a maximum duration of 4 min. An online self-training format was used to deliver the exercises over eight days (Qualtrics, Provo, UT). The daily invitation e-mails to the online environment included inspirational mindfulness-related quotes from mindfulness scholars (e.g., Thich Nhat Hanh or Buddha) as to inspire and motivate the participants to do the mindfulness exercises each day. All meditation exercises except the Eating with Awareness exercise were presented as pre-recorded audio-files. The YouTube videos covered different topics, including the positive effects of mindfulness on health (home exercise day 1; Salt et al., 2015), the transition from mindlessness to mindfulness (home exercise day 3; SmilingMind, 2016), the drawbacks of being concerned with goals (home exercise day 4; Watts, 2017), and observing thoughts without trying to change these (home exercise day 6; Gozenonline, 2017). A flowchart of the daily MM home exercises is provided in Figure 1.

Final mindfulness exercise

The eighth and final mindfulness exercise was again completed in the lab. It consisted of the 9-min seated meditation that the participants were already made familiar with during the first exercise in the lab and the fourth and seventh exercise at home. A 9-min excerpt of the audio book The Hobbit by J. R. R. Tolkien (BBC audiobooks, Ltd., 1997) was selected as neutral audio-file for the control group (Zeidan et al., 2010). The excerpt concerned the beginning of the story.

Mindfulness induction compliance

Compliance was measured at the end of each mindfulness home exercise by asking the participants to indicate the time (min) they had practiced MM that day. In addition, if

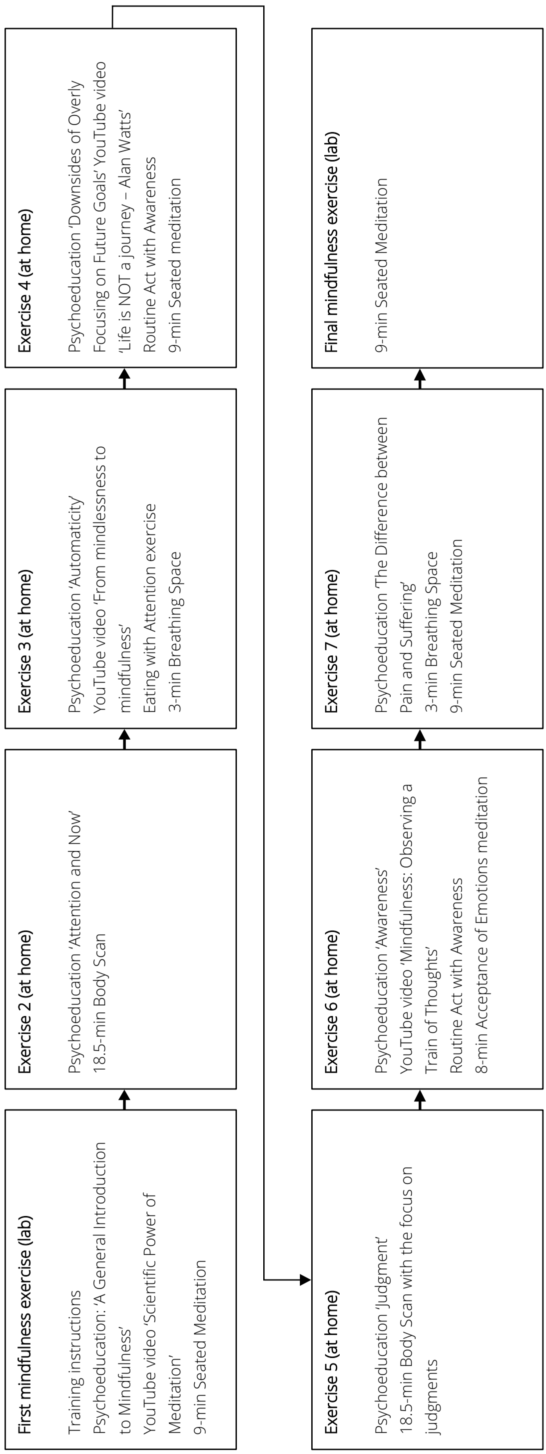

Figure 1. Flowchart of the mindfulness exercises

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applicable, they were also asked whether they had watched the educational YouTube videos, how many times they had practiced the 3-min breathing space exercise, how many times they had done a routine act with awareness, and whether they had done the audio-guided meditation exercise.

Pain induction procedure

Submaximum Effort Tourniquet Technique

Ischemic pain was induced using the Submaximum Effort Tourniquet Technique (SETT; Smith et al., 1966). The SETT is a tonic pain procedure inducing a deep aching pain, comparable in severity and duration to pathologic pain (Moore et al., 1979). Blood pressure was determined twice with an automatic Omron M3 Intellisense blood pressure monitor (OMRON Corporation, Kyoto, Japan) applied to the nondominant upper arm. In case the two measurements deviated to a great extent ($\Delta_{\text{systolic blood pressure}}$ > 10 mmHg), blood pressure was measured three times. Mean systolic blood pressure (SBP) was calculated across the two measurements or across the two of three values that were closest to one another. A Bremshey Sport® electronic hand dynamometer (Almere, The Netherlands) was utilized to measure the mean strength across two maximum handgrips with the nondominant hand in kg/lb.

For the SETT, an aneroid Minimus® II sphygmomanometer cuff (Riester, GmbH, Jungingen, Germany) was attached to the nondominant upper arm. The participant was requested to reach the arm towards the ceiling for 1 min in order to drain blood from the arm. The arm was then put to rest on the table and the cuff was inflated to 1.5 x the mean SBP as to obstruct blood flow. After 1 min, the participant squeezed a hand trainer at 70% of her maximum grip strength 12 times for 2 s with a 2-s break in between squeezes, with a digital metronome indicating the pace. The completion of the last squeeze marked the start of the pain induction. The cuff remained inflated and the subject was asked to rest her arm again until the experimenter would deflate the cuff, which was when pain tolerance was reached. The maximum time limit for pain tolerance was set at 20 min. SETT duration was not disclosed to participants. Recovery after cuff deflation was measured over a period of maximum 10 min (Meesters et al., 2019).

Pain outcomes

Pain-related experiences

Oral 0 to 10 numerical rating scales (NRSs) were employed for pain intensity (0 = "not painful at all"; 10 = "unbearably painful"), pain unpleasantness (0 = "not unpleasant at all"; 10 = "extremely unpleasant"), and subjective stress (0 = "no stress at all"; 10 = "an extreme amount of stress") ratings during the SETT and recovery period. A voice recorder was used to record the verbal ratings (Olympus® Digital Voice Recorder WS-812, Southend-on-Sea, SS2 5QH, UK). The timing of the ratings was indicated by a bell sound presented using Presentation® software (Version 18.0, Neurobehavioral Systems, Inc., Berkeley, CA), as described in more detail in the procedure section.

Pain tolerance, pain intensity recovery and pain unpleasantness recovery

Pain tolerance (s) was assessed as the time between the last squeeze with the hand trainer and the moment of SETT termination, which was when 1) pain intensity was maximally rated, 2) the participant wanted to end the task, or 3) at the limit of 20 min. Recovery in terms of pain intensity (s) and pain unpleasantness (s) was defined as the moment from SETT termination to the moment that pain intensity and pain unpleasantness ratings were 0, respectively. The corresponding variable names are pain intensity recovery and pain unpleasantness recovery.

The moment participants reached tolerance and total recovery was registered using the Presentation® software that also prompted the subjective pain ratings. That is, the experimenter had to press a space bar to indicate that pain tolerance was reached and this moment was registered by the software after which the recovery period immediately started.

Retrospective pain experience, cognitions, and coping strategies

Retrospective questions regarding pain experience, cognitions and coping strategies during the SETT and recovery period were administered after complete recovery and subsequent removal of the cuff. Included in this questionnaire were written visual analogue scales (VASs; 0 to 100) concerning the average experienced pain intensity, pain unpleasantness, and stress during the SETT, as well as threat, harmfulness, and fear of the SETT procedure (for the questions and answer scales, see Appendix A).

Participants also indicated the frequency of having certain negative cognitions and feelings during the SETT (5 items) and recovery period (5 items) (e.g., "Could this be harmful for my arm", "I am afraid that the pain will get worse") on a 5-point Likert scale with anchors at 1 ("almost never") to 5 ("almost all the time"). An average score across the items related to negative cognitions and feelings during the SETT and for the items concerning the recovery period was computed, since Cronbach's alphas were adequate to good (during SETT: $\alpha = .80$; during recovery period: $\alpha = .75$). Higher average scores indicate that participants had more negative cognitions and feelings during the SETT or recovery period. Coping strategies were assessed using an essay question and a question for which participants ranked nine strategies in the order of most to least frequently used strategy (e.g., ”I distracted myself”, ”I focused on my breath”).

Flexibility measures

Cognitive switching task

A task-switching paradigm based on the task of Schneider and Logan (2005) was administered in order to assess CF. In this task, participants have to categorize stimuli (numbers ranging from 1 to 9, excluding number 5) according to one of the following two sorting rules: 1) is the number odd or even (odd/even rule), or 2) is the number higher or lower than 5 (higher/lower rule). Responses are provided using the most left and right button on a 6-button response box. The participants had their left-hand index finger on the left button and their right-hand index finger on the right button of this response box.

Stimuli are presented one-by-one on a PC monitor. Each stimulus is preceded by a prime (500 ms) that indicates which sorting rule needs to be adopted in the upcoming trial (i.e., od/ev or hi/lo) (Kiesel et al., 2010). To remind participants of the answer categories, information about what answer option matches with which response key is simultaneously presented on screen with the stimulus. The stimulus stays onscreen till an answer is provided, whereupon the next prime is immediately shown. There are four versions of this task based on the mapping of the active categorization rule (odd/even or higher/lower) to the response keys (left or right), which were counterbalanced across participants.

The task entails 12 practice trials and 192 test trials. In the practice block, the first six stimuli have to be sorted according to the higher/lower rule, and the second series of six stimuli have to be sorted following the odd/even rule. The test block has two different trial types, namely trials on which the sorting rule changes from one trial to the next (switch trials) and trials on which the sorting rule is repeated (repeat trials). The test block consists of 96 trials of each type with switch and repeat trials in semi-randomized fixed order. Reaction times (RT; ms) and accuracy are registered. Switch costs (ms) are computed by subtracting RTs on repeat trials from RTs on switch trials. Higher switch costs are indicative for slower responses to switch than repeat trials and reflect less CF.

Affective switching task

The affective task-switching paradigm as developed by Genet et al. (2013) was employed to assess AF. In this task, participants sort affective pictures according to either an affective rule (i.e., is the picture positive or negative) or a neutral rule (i.e., does the picture contain one or no humans, or two or more). Responses are provided with the left-hand index finger on the left button, and the right-hand index finger on the right button on the same response box as for the cognitive switching task.

Task stimuli are 160 pictures from the International Affective Picture System (IAPS; Lang et al., 1997) that can be classified into four categories based on the two sorting rules. In each trail, the active categorization rule (the cue) is depicted simultaneously on the left and right side of the picture; "+" and "-" indicate positive and negative, "≤ 1" and "≥ 2" indicate one or no humans and two or more humans. The picture is presented against either a white or gray background with the color of the background matched to one of two cues. The picture category and cue are combined according to a pseudorandom order, resulting in eight task versions based on the mapping of the frame color (white or grey) to the active categorization rule (affective or neutral rule), and mapping of the response keys (left or right) to the categorization rule ("+" / "-" or "≤ 1" / "≥ 2").

The task consist of two 10-trial practice blocks in which one of two rules is practiced per block and two 160-trial test blocks in which both rules are presented randomly. RTs and accuracy (ms) are recorded and trials can either be switch or repeat. Switch trials are trials in which the categorization rule is alternated from one trial to another with picture valence remaining the same (e.g., switch from the affective to the neutral rule when the picture remains negative). A repeat trial is characterized by repetition of the categorization rule from one trial to the next with picture valence remaining the same (e.g., a repeat of the affective rule when the picture remains negative). Switch costs (ms) are calculated by subtracting RTs on repeat trials from RTs on switch trials. Four types of switch costs were computed. More specifically, switch costs from negative-to-neutral task sets were computed by subtracting RTs on negative-negative repeat trials from RTs on negative-to-neutral switch trials (SC negAtoN). This type of switch cost was analogously computed for positive pictures (SC posAtoN). In a similar vein, switch costs from neutral-to-negative task sets were calculated by subtracting RTs on neutral-neutral repeat trials when the picture was negative from RTs on neutral-to-negative switch trials (SC negNtoA). This computation was repeated for positive pictures (SC posNtoA). Lower switch costs (i.e., faster responses to switch tasks) reflect more AF.

Self-report measures

Demographics

Basic sociodemographic information (age, mother tongue, nationality, type and year of study) was obtained at the start of the survey during lab session 1.

Mindfulness

The 5-item state version of the Mindful Attention Awareness Scale (state-MAAS) assesses state mindfulness (Brown & Ryan, 2003). Respondents indicate to what degree they are having the experiences illustrated in the items at that very moment by rating the items on a 7-point Likert scale ranging from 0 ("not at all") to 6 ("very much"). Psychometric properties of this scale are excellent (Brown & Ryan, 2003). In this study, a Cronbach's alpha of .86 was obtained for lab session 1 for the state-MAAS.

The extended version of the Kentucky Inventory of Mindfulness Skills (KIMS-E) comprises 46 items that tap into five mindfulness skills (i.e., the factors Observing, Describing, Acting with Awareness, and Accepting without Judgments; Non-reactivity to Inner Experience; Raes et al., 2009). Items are scored on a 5-point Likert scale, ranging from 1 ("never or very rarely true") to 5 ("very often or always true"). Reliability and validity of the original KIMS-E has been found to be good (Raes et al., 2009). A Cronbach's alpha of .81 was obtained for the KIMS-E in the current study for lab session 1.

Acceptance

The Acceptance and Action Questionnaire-II (AAQ-II) assesses acceptance (Bond et al., 2011; Fledderus et al., 2012) via nine items scored on a 7-point Likert scale ranging from 1 ("never true") to 7 ("always true"). Reliability and validity have been found to be adequate (Bond et al., 2011). The Cronbach's alpha for the AAQ-II was .87 for lab session 1 in the current sample.

Subjective stress

Subjective stress during the previous week was measured using the Perceived Stress Scale (PSS; Cohen et al., 1983). Ten items inquire how often subjects have had the feeling during the preceding week that their daily life was uncontrollable, unpredictable, and overloading and are rated from 0 ("never") to 4 ("very often"). The PSS has adequate psychometric characteristics (Cohen & Williamson, 1988). In the present study, the internal consistency of the PSS was good for lab session 1 ($\alpha = .89$).

Rumination

Rumination was measured using the 12-item Rumination subscale (RRQ-RUM) of the Rumination-Reflection Questionnaire (RRQ; Trapnell & Campbell, 1999). The participants are asked to rate their agreement with the items on a 5-point Likert scale ranging from 1 ("strongly disagree") to 5 ("strongly agree"). Previous studies have demonstrated good reliability and validity for this subscale (Joireman et al., 2002; Trapnell & Campbell, 1999). Cronbach's alpha of .89 was obtained for the RRQ-RUM for lab session 1 in the present study.

Pain catastrophizing

Pain catastrophizing was assessed with the Pain Catastrophizing Scale (PCS; Sullivan et al., 1995). The PCS consists of 13 items corresponding to either three aspects of pain catastrophizing, namely rumination, magnification, and helplessness. Each item is scored on a 5-point Likert scale with anchors ranging from 0 ("not at all") to 4 ("all the time"). The whole scale as well as each subscale exhibit good reliability (Osman et al., 2000; Osman et al., 1997). Internal consistency of the PCS in this study was $\alpha = .87$ for lab session 1.

Positive and negative affect

The 10-item Positive and Negative Affect Schedule short form (I-PANAS-SF) consists of two 5-item subscales measuring either state positive affect (PA) or state negative affect (NA; Thompson, 2007). Items are rated on a 5-point Likert scale with anchors at 1 ("very slightly or not at all") to 5 ("extremely"). Validity and reliability of this scale have been found adequate (Thompson, 2007). Cronbach's alphas in this study were .69 for the positive subscale and .81 for the negative subscale for lab session 1.

In addition, two VAS scales ranging from 0 ("not positive / negative at all") to 100 ("extremely positive / negative") were administered assessing how positive or negative the feelings were that the participants were having at that particular moment, that is, immediately after doing the audio-guided seated mediation or listening to the neutral audiobook of The Hobbit. The corresponding variable names are momentary PA rating and momentary NA rating.

Exit questions

Questions concerning an evaluation of the audiobook or audio-guided seated meditation, the goal of the study and the two switching tasks (attention and motivation to perform the tasks) were included in an exit questionnaire. These questions were not further reported, as they were administered for exploratory purposes.

Procedure

The study consisted of two lab sessions separated by one week during which the MM group practiced mindfulness. Each lab session was of approximately 2.5 h duration. Figure 2 outlines the study's procedure per lab session.

Lab session 1

Upon arrival, study eligibility was verified and written informed consent was obtained. The volar surface of the nondominant arm was checked for (healing) wounds, as obstruction of the blood flow during the SETT may cause wounds to start bleeding again. If detected, the lab sessions were rescheduled to a later moment in time. After blood pressure and maximum handgrip strength measurement, participants filled in a psychological test battery including demographic questions, the KIMS-E, I-PANAS-SF, AAQ-II, PSS, PCS, and RRQ-RUM. All questionnaires in this study were presented via an online survey application (Qualtrics, Provo, UT). Next, to measure heart rate variability (HRV) a Polar® RS800CX (Polar CIC, USA) heart rate band was attached around the chest. However, HRV data could not be used due to too many artifacts in the recordings. Participants then carried out both switching tasks in counterbalanced order thereby taking into account the different versions of both tasks. The same order and versions were employed across lab sessions for each participant. Both tasks were preceded with detailed instructions presented on screen.

Next, blood pressure was measured for a second time and the SETT procedure was explained. Participants were told that it would be completely normal if their arm would turn white or become cold or numb during the SETT and that this would almost immediately disappear upon cuff deflation. Participants were not informed about the duration of the SETT: the task was ended by the experimenter when 20 min had passed, a maximum pain intensity score of 10 was given, or when the participant expressed the wish to stop. Participants were familiarized with the sound and pace of the digital metronome that indicated the speed at which the hand trainer had to be squeezed as well as with the bell sound indicating when ratings should be verbally given.

During the SETT and recovery period, participants rated pain intensity and pain unpleasantness. The difference between these two ratings was explained using a standardized written description of a sound analogy (for details, see Price & Harkins, 1987). The ratings were administered in immediate succession at 12 time points (0, 60, 150, 270, 330, 450, 540, 630, 690, 870, 1020, and 1200 s) after completion of the last squeeze. Fewer ratings were registered when earlier SETT termination took place due to a maximum pain score of 10 or the participant's wish to stop. In addition, pain intensity and pain unpleasantness ratings were administered at 0, 45, 105, 150, 210, 270, 330, 420, 510, and 600 s (10 min) after cuff deflation until both pain intensity and pain unpleasantness ratings of 0 were given. Additionally, subjective stress ratings were taken at three time points, namely 1) when the last squeeze was completed, 2) when tolerance was reached, and 3) when participants had completely recovered.

After recovery, participants filled in the retrospective questions. The MM group then received instructions for the mindfulness home exercises and completed the first mindfulness exercise in the lab, allowing them to ask questions and to familiarize with the online environment. They performed the mindfulness home exercises from home the next day until their return to the lab for session 2. An e-mail invitation was sent each morning at 7 a.m. containing a link to the online environment. Participants received a reminder e-mail at 7 p.m. if they had not yet performed the mindfulness exercise by then. Participants in the control group were offered the opportunity to complete the mindfulness exercises after they had finished lab session 2.

Lastly, participants answered the exit questions and were checked for experiencing lingering sensations caused by the SETT and if so, phoned the same evening by the experimenter to verify whether these sensations had worn off.

Lab session 2

The procedure for lab session 2 was almost identical to the procedure for session 1, with the exception of the final mindfulness exercise for participants in the MM group where they practiced audio-guided seated meditation. Control participants were instructed to listen to an audiobook ("The Hobbit") for the same amount of time while sitting quietly until the experimenter would return to the room. The KIMS-E was administered before the final mindfulness exercise/audiobook listening to examine the effects of the mindfulness home erxercises on trait mindfulness without confounding it by the eventual short-term effects of the final mindfulness exercise. To assess the effects of the final exercise itself, the state-MAAS was administered before and after the exercise/audiobook listening. In addition, momentary PA and NA ratings were administered after the final mindfulness exercise/audiobook listening, as to study how the meditation and audiobook were experienced. The remainder of the session followed the procedure of session 1. After the SETT recovery period, control subjects received instructions for the mindfulness home exercises and started the first mindfulness exercise, whereas the MM group was finished with the experiment. Before leaving the second lab session, participants were thanked, granted their reward for participation, received both oral and written debriefing, and were dismissed.

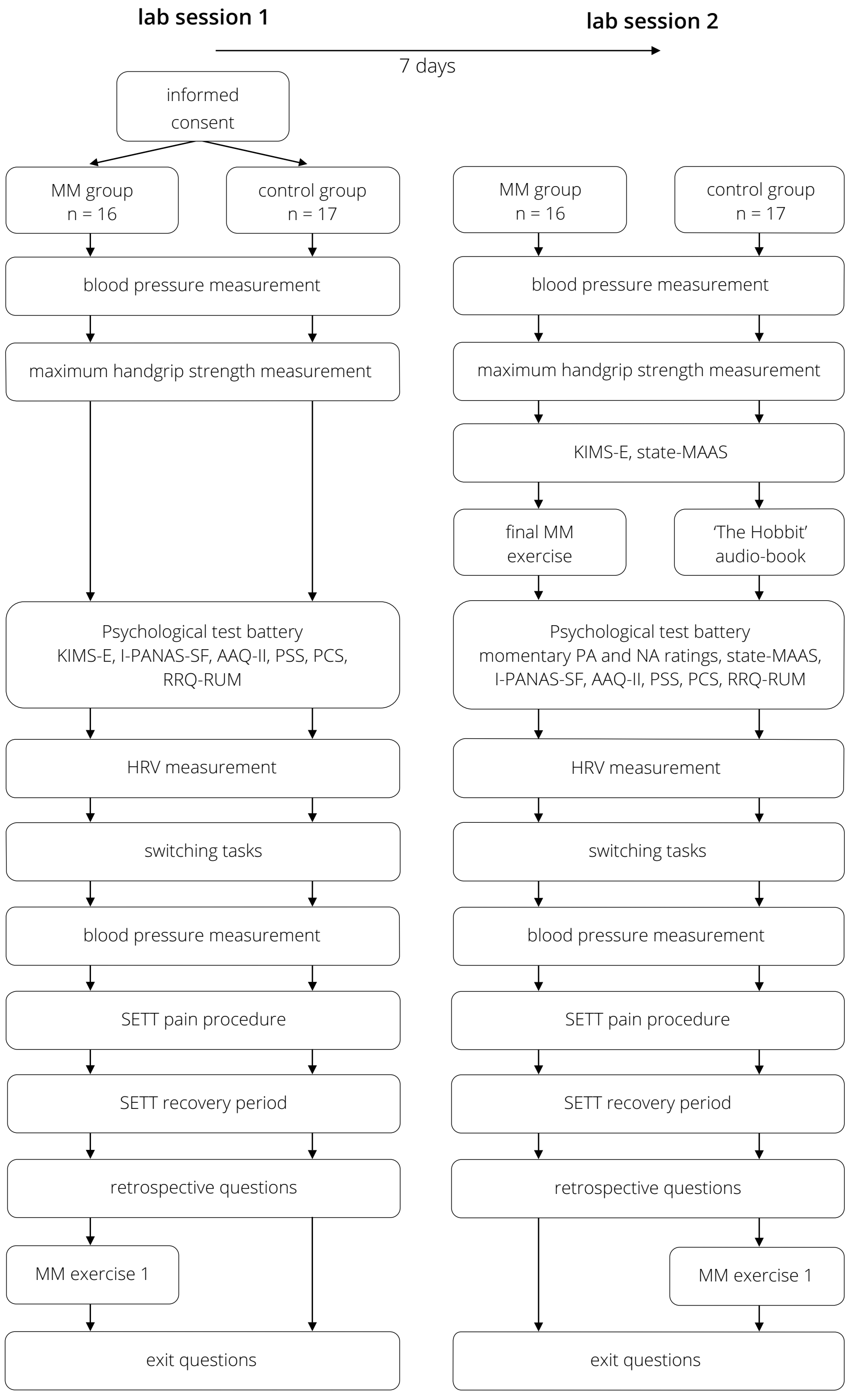
lab session 1
lab session 2
7 days
informed consent
MM group n = 16
control group n = 17
blood pressure measurement
maximum handgrip strength measurement
KIMS-E, state-MAAS
final MM exercise
'The Hobbit' audio-book
Psychological test battery
KIMS-E, I-PANAS-SF, AAQ-II, PSS, PCS, RRQ-RUM
Psychological test battery
momentary PA and NA ratings, state-MAAS, I-PANAS-SF, AAQ-II, PSS, PCS, RRQ-RUM
HRV measurement
switching tasks
blood pressure measurement
SETT pain procedure
SETT recovery period
retrospective questions
MM exercise 1
exit questions

Figure 2. Flowchart of the study procedure. *MM, mindfulness meditation group; KIMS-E, Kentucky Inventory of Mindfulness Skills extended version; state-MAAS, state version of the Mindful Attention Awareness Scale; I-PANAS-SF, Positive and Negative Affect Schedule short form; AAQ-II, Acceptance and Action Questionnaire-II; PSS, Perceived Stress Scale; PCS, Pain Catastrophizing Scale; RRQ-RUM, Rumination-Reflection Questionnaire – rumination subscale; momentary PA and NA ratings, visual analogue scales for positive and negative affect; HRV, heart rate variability; SETT, Submaximum Effort Tourniquet Technique.*

Statistical analyses

Statistical analyses were conducted using SPSS version 26 software (SPSS, Inc, IL, USA). Normality and homogeneity of variance were checked. The primary outcome variables were 1) pain experience (i.e., pain tolerance, pain intensity recovery, and pain unpleasantness recovery), 2) CF (i.e., cognitive switch cost), 3) AF (i.e., the four types of affective switch costs), and 4) subjective stress ratings. Secondary outcomes were 1) individual difference constructs (i.e., trait mindfulness (KIMS-E), rumination (RRQ-RUM), acceptance (AAQ-II), perceived stress (PSS), positive and negative affect (I-PANAS-SF), and pain catastrophizing (PCS), and 2) retrospective pain experience (i.e., retrospective pain intensity, pain unpleasantness, and stress during the SETT, threat, harmfulness, and fear of the SETT procedure). All analyses were two-tailed and results were regarded significant when $\alpha \leq .05$ for primary outcomes and - to correct for multiple testing – when $\alpha \leq .01$ for secondary outcomes.

Analyses for both switching tasks were performed on RTs. Incorrect responses (CF session 1: 6.3% of the trials; CF session 2: 4.4% of the trials; AF session 1: 7.7% of the trials; AF session 2: 5.7% of the trials) were excluded from the analyses. Following Genet et al. (2013), RTs of 250 ms and smaller were replaced with the value of 250 ms in order to limit the effect of individual outlying latencies (CF session 1: 0% of all trials; CF session 2: 0.14% of all trials; AF session 1: 0.20% of all trials; AF session 2: 0.02% of all trials). Furthermore, RTs larger than 2.5 *SD* above the individual mean RT were replaced with the individual mean RT plus 2.5 *SD*, in accordance with previous studies using the same task (Genet et al., 2013; Malooly et al., 2013) (CF session 1: 3.19% of the trials; CF session 2: 3.25% of the trials; AF session 1: 2.84% of the trials; AF session 2: 2.85% of the trials).

Descriptive statistics were retrieved and baseline differences between the MM and control group were checked using Chi-square tests for demographic characteristics (i.e., mother tongue, nationality, year and type of study) and independent samples *t*-tests for age, psychological questionnaire scores (i.e., KIMS-E, AAQ-II, PSS, PCS, I-PANAS-SF positive and negative affect, RRQ-RUM), and the different types of switch costs (i.e., SC CF, SC AF posAtoN, SC AF negAtoN, SC AF posNtoA, SC AF negNtoA).

For the manipulation check, a repeated measures analysis of variance (ANOVA) with condition (MM vs. control group) as between-subjects (BS) factor and time (before the start of the final mindfulness exercise/audiobook listening as PRE vs. after the final mindfulness exercise/audiobook listening as POST) as within-subjects (WS) factor was used to analyze whether the mindfulness induction successfully increased state-MAAS scores. In addition, to test the effect of the mindfulness induction during lab session 2 on momentary PA and NA ratings, independent samples *t*-tests were employed with condition (MM vs. control group) as independent variable.

A 2 x 2 repeated measures ANOVA was performed as our general statistical approach to test for effects of time (lab session 1 vs. lab session 2), group (MM vs. control goup), and group x time interactions on primary and secondary outcomes. Nonsignificant main effects of condition and time are not reported in the current paper, as we were primarily interested in group x time interactions. A 2 x 2 x 3 repeated measures ANOVA with condition as BS factor (MM vs. control group), time as WS factor (lab session 1 vs. lab session 2) and measurement time as WS factor (at the start of the SETT vs. moment of pain tolerance vs. at the end of the recovery period) was used to test the effect of the mindfulness induction on subjective stress ratings.

Because recovery time has been shown to be related to SETT duration (Meesters et al., 2019), the analyses of pain intensity recovery and pain unpleasantness recovery were controlled for pain tolerance time. Pearson's correlation analysis demonstrated that as expected, pain tolerance was associated with both pain intensity recovery and pain unpleasantness recovery in both lab sessions. Therefore, residualized recovery scores were calculated. First, pain intensity recovery and pain unpleasantness recovery were regressed on pain tolerance for lab session 1 or 2 separately. For each regression analyses, unstandardized residuals were saved and subsequently entered as dependent variable in repeated measures ANOVA to test the effect of the MM induction on pain intensity recovery and pain unpleasantness recovery.

Lastly, planned mediation analyses to test the mediating role of CF and AF in the effect of MM on pain experience and recovery from pain were not performed, as our results did not warrant testing such mediation.

RESULTS

Cognitive and affective switching task characteristics

Paired samples *t*-tests indicated that for both lab sessions RTs on switch trials (CF session 1: *M* = 1547.6 ms, *SD* = 566.5 ms; CF session 2: *M* = 1203.0 ms, *SD* = 410.4 ms; AF session 1: *M* = 1559.3 ms, *SD* = 357.1 ms; AF session 2: *M* = 1281.1 ms, *SD* = 306.0 ms) were significantly larger than RTs on repeat trials (CF session 1: *M* =1403.9 ms, *SD* = 503.0 ms; CF session 2: *M* =1075.7 ms, *SD* = 353.8 ms; AF session 1: *M* = 1397.7 ms, *SD* = 310.6 ms; AF session 2: *M* = 1163.0 ms, *SD* = 261.0 ms) for both the cognitive (session 1: $t(32) = 3.38$, $p = .002$, $d = 1.20$; session 2: $t(32) = 5.56$, $p < .001$, $d = 1.97$) and the affective switching task (session 1: $t(32) = 10.7$, $p < .001$, $d = 3.77$; session 2: $t(32) = 9.28$, p < 001, $d = 3.28$).

Pearson's correlations between the different types of cognitive and affective switch costs are presented for the entire sample in Table 1. A repeated measures ANOVA with a Greenhouse–Geisser correction revealed a significant difference between the four types of affective switch costs at lab session 1, $F(1.80, 57.6) = 15.9$, $p < .001$. Post hoc analyses using the Bonferroni correction showed that mean SC negAtoN was significantly larger than mean SC posAtoN ($p = .043$), mean SC negNtoA ($p < .001$), and mean SC posNtoA ($p = .008$). In addition, mean SC negNtoA was significantly smaller than mean SC posAtoN ($p = .001$) and mean SC posNtoA ($p = .015$). No significant difference was found between mean SC posAtoN and mean SC posNtoA ($p = .162$).

Descriptive statistics for lab session 1

Table 2 displays the means and *SD*s of pain outcomes, the different types of cognitive and affective switch costs, and questionnaire scores across the two lab sessions and conditions. If the SETT was not terminated before the time limit of 20 min, a pain tolerance score of 1200 s was registered. For the control group, this was the case for 10 (58.8%) of the 17 participants for lab session 1 and 9 (52.9%) for lab session 2. For the MM group, a pain tolerance score of 1200 s was registered for 9 (56.3%) of the 16 participants for lab session 1 and 7 (43.8%) of the 16 participants for lab session 2.

Table 1. Pearson's correlations for the different types of switch costs

		Lab session 1					Lab session 2				
Measure	**M (SD)**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
1. CF, general SC	143.8 (244.2)	-					-				
2. AF, general SC	161.7 (87.1)	.19	-				.09	-			
3. AF, SC posAtoN	246.8 (228.4)	.23	.41*	-			.15	.56***	-		
4. AF, SC negAtoN	357.9 (253.7)	-.19	.40	.58***	-		.18	.39*	.46**	-	
5. AF, SC posNtoA	84.4 (264.2)	.18	.24	-.33	-.49**	-	.23	.33	-.05	-.46**	-
6. AF, SC negNtoA	-84.7 (289.0)	.01	.01	-.50**	-.58***	.43*	-.14	.21	-.04	-.31	.33

N = 33. CF, cognitive flexibility; SC, switch cost; AF, affective flexibility; SC posAtoN, switch cost for positive picture and affective-to-neutral trial; SC negAtoN, switch cost for negative picture and affective-to-neutral trial; SC posNtoA, switch cost for positive picture and neutral-to-affective trial; SC negNtoA, switch cost for negative picture and neutral-to-affective trial. $^{*}p < .05$. $^{**}p < .01$. $^{***}p \leq .001$.

Demographics, self-report assessment and switch costs for lab session 1

Chi-square tests showed no significant differences between the MM and control group during lab session 1 in any demographic variables, including mother tongue, nationality and year and type of study (all *p*s ≥ .24). Results of independent samples *t*-tests neither revealed significant differences between the two conditions at lab session 1 in age, trait mindfulness (KIMS-E), PA and NA (I-PANAS-SF), and pain catastrophizing (PCS; all *p*s ≥ .04), nor in any type of cognitive or affective switch costs (all *p*s ≥ .034) (Table 2).

The effectiveness of the MM induction

Results showed that the final MM exercise was effective in inducing state mindfulness in the MM group compared to the control group. More specifically, repeated measures ANOVA showed a significant interaction effect between group and time on state-MAAS scores, $F(1, 31) = 4.58$, $p = .040$, $\eta p^2 = .13$. Studying the simple effects using independent samples *t*-test indicated a significant difference in state-MAAS scores between the two conditions POST the mindfulness induction in session two, $t(31) = -2.75$, $p = .010$, $d = -.99$, but not PRE the induction, $t(31) = -.98$, $p = .34$, $d = -.35$ (control group: $M = 3.85$, $SD = 1.21$; MM group: $M = 4.24$, $SD = 1.07$). Participants in the MM group scored significantly higher on state-MAAS at POST ($M = 4.73$, $SD = .96$) than participants in the control group ($M = 3.62$, $SD = 1.31$).

Table 2. Means (*SD*) of primary and secondary outcome variables across lab sessions and conditions

	control (n = 17)		MM (n = 16)	
	lab session 1	**lab session 2**	**lab session 1**	**lab session 2**
pain outcomes				
pain tolerance	1003.4 (306.4)	983.8 (311.0)	926.9(330.3)	870.0 (363.1)
pain intensity recovery	291.2 (174.4)	276.18 (199.4)	296.3 (178.8)	247.5 (185.3)
pain unpleasantness recovery	434.1 (162.6)	399.7 (159.0)	346.9 (161.0)	272.8 (197.9)
switch costs				
CF, SC	174.0 (311.5)	169.2 (159.9)	111.6 (146.8)	82.7 (74.1)
AF, SC posAtoN	327.1 (262.4)	302.1 (168.2)	161.5 (150.9)	136.0 (184.6)
AF, SC negAtoN	384.4 (285.8)	371.5 (300.0)	329.7 (220.3)	258.2 (151.5)
AF, SC posNtoA	22.9 (273.5)	-.99 (257.4)	149.7 (245.4)	92.7 (210.9)
AF, SC negNtoA	-169.7 (305.0)	-50.3 (197.3)	5.62 (249.2)	-17.4 (151.5)
questionnaire scores				
KIMS-E	138.3 (12.5)	137.6 (12.5)	147.3 (11.3)	152.1 (15.1)
AAQ-II	46.2 (10.7)	44.2 (10.9)	50.8 (6.96)	51.3 (8.23)
PSS	18.5 (6.47)	20.8 (6.25)	15.4 (7.18)	14.4 (7.31)
PCS	18.3 (8.43)	22.6 (8.65)	19.0 (7.79)	20.3 (11.3)
I-PANAS-SF PA	13.1 (4.16)	12.9 (4.55)	13.0 (2.61)	12.2 (3.23)
I-PANAS-SF NA	8.24 (2.88)	8.65 (3.77)	6.44 (2.94)	7.13 (2.68)
RRQ-RUM	3.53 (.64)	3.58 (.72)	3.60 (.62)	3.23 (.57)

N = 33. MM, mindfulness meditation group; pain intensity recovery, time until total recovery in terms of pain intensity (s); pain unpleasantness recovery, time until total recovery in terms of pain unpleasantness (s); CF, cognitive flexibility; SC, switch cost; AF, affective flexibility; SC posAtoN, switch costs for positive picture and affective-to-neutral trial; SC negAtoN, switch costs for negative picture and affective-to-neutral trial; SC posNtoA, switch costs for positive picture and neutral-to-affective trial; SC negNtoA, switch costs for negative picture and neutral-to-affective trial; KIMS-E, Kentucky Inventory of Mindfulness Skills extended version; AAQ-II, Acceptance and Action Questionnaire-II; PSS, Perceived Stress Scale; PCS, Pain Catastrophizing Scale; I-PANAS-SF PA, positive affect; I-PANAS-SF NA, negative affect; RRQ-RUM, Rumination-Reflection Questionnaire – rumination subscale.

4

In a similar vein, results of an independent samples *t*-test revealed that after the brief mindfulness exercise in the lab, the momentary PA rating was higher in the MM group (M = 74.1, SD = 12.1) than in the control group (M = 61.9, SD = 8.60), $t(31) = -3.36$, $p = .002$, $d = 1.19$. No significant difference between the conditions in momentary NA rating was found, $t(31) = .87$, $p = .39$, $d = .31$ (MM group: M = 20.1, SD = 19.1; control group; M = 25.9, SD = 19.8).

Primary study outcomes

Pain outcomes

For pain tolerance, no significant group x time interaction was observed, $F(1, 31) = .16$, $p = .69$, $\eta p^2 = .005$. At both lab session 1 and 2, Pearson's correlation coefficients demonstrated a moderate to strong relationship between pain tolerance and pain intensity recovery (lab session 1: $r(31) = .32$, $p = .068$; lab session 2: $r(31) = .56$, $p = .001$), as well as between pain tolerance and pain unpleasantness recovery (lab session 1: $r(31) = .44$, $p = .011$; lab session 2: $r(31) = .51$, $p = .002$). Repeated measures ANOVA neither revealed a significant group x time interaction for pain intensity recovery, $F(1, 31) = .23$, $p = .63$, $\eta p^2 = .007$, nor for pain unpleasantness recovery, $F(1, 31) = .73$, $p = .40$, $\eta p^2 = .023$.

Cognitive and affective switch costs

Repeated measures ANOVA demonstrated no significant group x time interaction effect on SC CF, $F(1, 31) = .15$, $p = .70$, $\eta p^2 = .005$. There were also no group x time interactions for any of the affective switch costs (AF SC posAtoN: $F(1, 31) = .00$, $p = .995$, $\eta p^2 = .000$; AF SC negAtoN: $F(1, 31) = .38$, $p = .54$, $\eta p^2 = .012$; AF SC posNtoA: $F(1, 31) = .14$, $p = .71$, $\eta p^2 = .004$; AF SC negNtoA: $F(1, 31) = 2.78$, $p = .11$, $\eta p^2 = .082$). The main effect of condition on AF SC posAtoN reached significance, $F(1, 31) = 8.72$, $p = 006$, $\eta p^2 = .22$, indicating that across lab sessions participants in the MM group had significantly smaller AF SC posAtoN than participants in the control group (see Table 2).

Subjective stress ratings

Table 3 presents the means and *SD*s of lab session 1 and 2 subjective stress ratings per condition and measurement time (i.e., at the start of the SETT, at pain tolerance, and at the end of the recovery period). A 2 x 2 x 3 repeated measures ANOVA demonstrated no significant three- or two-way interactions (all ps $\geq .23$). A significant effect of time on subjective stress was observed, $F(1, 31) = 5.72$, $p = .023$, $\eta p^2 = .16$, indicating that subjective stress ratings in both groups across all 3 time points significantly decreased from lab session 1 to lab session 2 (EMM difference (SE): -.75 (.31), 95% CI [.11, 1.38]). The main effect of measurement time was also significant, $F(2, 62) = 85.7$, $p < .001$, $\eta p^2 = .73$. Paired comparisons with Bonferroni correction showed that across both lab sessions in both groups subjective stress ratings were significantly higher at the moment of pain tolerance than at both the start of the SETT (EMM difference (SE): 2.92 (.34), 95% CI [-3.77, -2.07], $p < .001$) and the end of the recovery period (EMM difference (SE): -4.32 (.38), 95% CI [-5.27, -3.37], $p < .001$). In addition, participants in both groups had significantly smaller subjective stress ratings at the end of the recovery period as compared to the start of the SETT across both lab sessions (EMM difference (SE): -.1.41 (.29), 95% CI [-2.15, -.66], $p < .001$).

Table 3. Means (*SD*) of subjective stress per measurement time, condition and lab session

	control (n = 17)		**MM (n = 16)**	
	lab session 1	**lab session 2**	**lab session 1**	**lab session 2**
subjective stress				
at the start of the SETT	2.91 (2.25)	1.47 (1.50)	2.44 (1.97)	2.44 (2.42)
at pain tolerance	5.53 (2.85)	4.27 (3.23)	6.13 (2.22)	5.00 (3.03)
at total recovery	.79 (1.47)	.62(1.08)	1.34 (1.60)	.88 (1.09)

N = 33. MM, mindfulness meditation group; SETT, Submaximum Effort Tourniquet Technique.

Secondary study outcomes

Self-report assessment

We explored the effects of the mindfulness induction on secondary outcomes, including KIMS-E, RRQ-RUM, AAQ-II, PSS, I-PANAS-SF PA, I-PANAS-SF NA, and PCS scores. Results of repeated measures ANOVA showed no significant group x time interaction for KIMS-E scores, $F(1, 31) = 3.13$, $p = .087$, $\eta p^2 = .092$. The main effect of condition on KIMS-E scores was significant, $F(1, 31) = 7.77$, $p = .009$, $\eta p^2 = .20$, indicating that participants in the MM condition scored higher on KIMS-E across both lab sessions than participants in the control condition. A significant group x time interaction effect was found on RRQ-RUM scores, $F(1, 31) = 15.09$, $p = .001$, $\eta p^2 = .33$. A paired samples *t*-test showed a significant effect of time in the MM group, $t(15) = 4.60$, $p < .001$, $d = .63$, indicating that participants in the MM group displayed a significant decrease in rumination from lab session 1 to 2 (Table 2). No significant group x time interaction effect was found on AAQ-II, $F(1, 31) = 1.72$, $p = .20$, $\eta p^2 = .053$, PSS, $F(1, 31) = 2.17$, $p = .15$, $\eta p^2 = .066$, I-PANAS-SF PA, $F(1, 31) = .23$, $p = .64$, $\eta p^2 = .007$, I-PANAS-SF NA, $F(1, 31) = .79$, $\eta p^2 = .002$, and PCS scores, $F(1, 31) = 1.59$, $p = .22$, $\eta p^2 = .049$.

Retrospective pain experience

Results of several repeated measures ANOVAs revealed no significant group (MM vs. control group) x time (lab session 1 vs. lab session 2) interaction for retrospective pain intensity, pain unpleasantness, stress during the SETT, and fear (all *p*s ≥ .38; Table 4). The interaction between group and time reached borderline significance for both retrospective threat, $F(1, 31) = 3.19$, $p = .084$, $\eta p^2 = .093$ (see Figure 3A), and harmfulness, $F(1, 31) = 3.78$, $p = .061$, $\eta p^2 = .11$ (see Figure 3B). Simple effect analyses revealed a significant decrease from lab session 1 to 2 in retrospective threat, $t(15) = 3.73$, $p = .002$, $d = .997$; (Figure 3A), and harmfulness ratings, $t(15) = 2.73$, $p = .015$, $d = .54$ (Figure 3B). The main effect of time on retrospective pain unpleasantness was marginally significant, $F(1, 31) = 4.01$, $p = .054$, $\eta p^2 = .12$, indicating that participants in both groups gave significantly lower ratings at lab session 2 than at lab session 1.

Retrospective pain experience

Results of several repeated measures ANOVAs revealed no significant group (MM vs. control group) x time (lab session 1 vs. lab session 2) interaction for retrospective pain intensity, pain unpleasantness, stress during the SETT, and fear (all *p*s ≥ .38; Table 4). The interaction between group and time reached borderline significance for both retrospective threat, $F(1, 31) = 3.19$, $p = .084$, $\eta p^2 = .093$ (see Figure 3A), and harmfulness, $F(1, 31) = 3.78$, $p = .061$, $\eta p^2 = .11$ (see Figure 3B). Simple effect analyses revealed a significant decrease from lab session 1 to 2 in retrospective threat, $t(15) = 3.73$, $p = .002$, $d = .997$; (Figure 3A), and harmfulness ratings, $t(15) = 2.73$, $p = .015$, $d = .54$ (Figure 3B). The main effect of time on retrospective pain unpleasantness was marginally significant, $F(1, 31) = 4.01$, $p = .054$, $\eta p^2 = .12$, indicating that participants in both groups gave significantly lower ratings at lab session 2 than at lab session 1.

Table 4. Means and *SD*s of retrospective pain experience and cognitions and emotions across lab sessions and conditions

	control (n = 17)		MM (n = 16)	
	lab session 1	**lab session 2**	**lab session 1**	**lab session 2**
retrospective pain experience				
pain intensity	67.9 (17.3)	62.0 (22.09)	65.9 (21.4)	65.7 (18.7)
pain unpleasantness	80.9 (17.8)	77.2 (18.5)	85.1 (15.6)	75.1 (24.5)
stress	42.2 (28.1)	34.8 (28.3)	49.2 (26.8)	43.1 (29.4)
threat	42.3 (27.1)	37.1 (28.5)	53.3 (21.1)	31.3 (23.0)
harmfulness	27.2 (27.9)	28.4 (28.5)	30.4 (24.8)	18.4 (19.2)
fear	34.4 (27.4)	30.4 (26.3)	40.0 (29.3)	36.6 (23.3)
cognitions and emotions				
during SETT	2.45 (.80)	2.04 (.72)	2.48 (.85)	1.90 (.81)
during recovery	1.51 (.58)	1.45 (.58)	1.49 (.58)	1.23 (.23)

N = 33. MM, mindfulness meditation group.

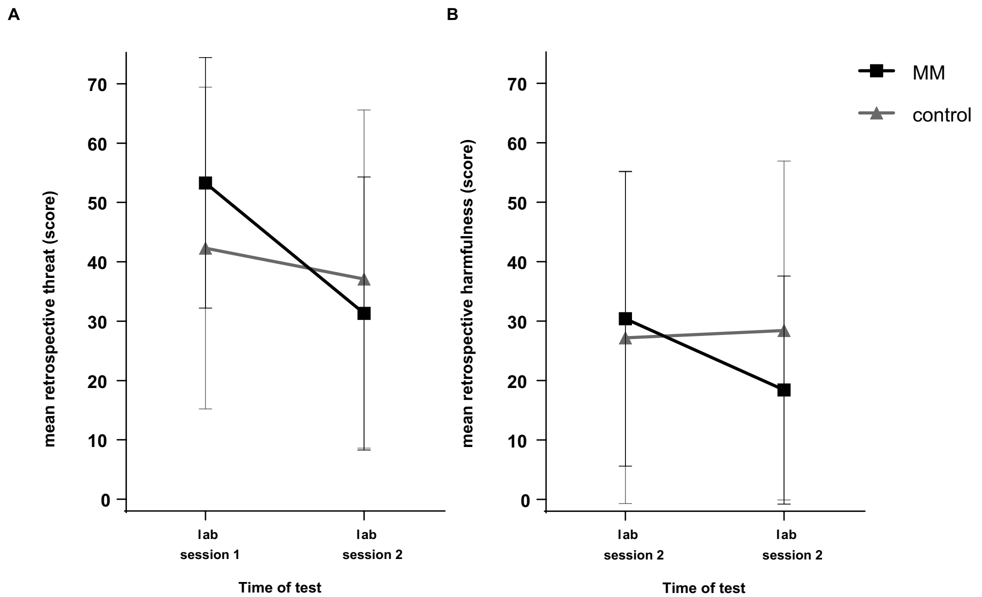

Figure 3. Lab session 1 to lab session 2 changes in retrospective threat (A) and harmfulness ratings (B). *Raw means and SDs are presented. n = 17 for the control group and n = 16 for the MM group. MM, mindfulness meditation group.*

Study experience

Cognitions and coping strategies

No significant group x time interaction on retrospective cognitions and emotions during the SETT, $F(1, 31) = .37$, $p = .55$, $\eta p^2 = .012$, or during the recovery period, $F(1, 31) = 1.19$, $p = .28$, $\eta p^2 = .037$ were found. There was a significant effect of time on the experience of negative cognitions and emotions during the SETT, $F(1, 31) = 13.5$, $p = .001$, $\eta p^2 = .30$. Participants in both groups reported to have experienced fewer negative cognitions and emotions during the SETT at lab session 2 than at lab session 1 (Table 4).

Mindfulness homework compliance

The 16 participants in the MM group completed a median of 6 of a total of 6 home exercise sessions over one week (range 1-6) with the majority of participants (15 participants, 93.7%) having done a total of five or six home exercise sessions. Participants reported to have spent an average of 21.0 min/training session. Thirteen (81.3%) of 16 participants reported to have practiced the audio-guided meditation exercise during home exercise 2 and 4, 14 participants (87.5%) during home exercise 5, and 15 participants during both home exercise 6 and 7 (93.8%).

DISCUSSION

This study examined whether a mindfulness induction could improve tolerance for, and recovery from an acute pain experience in a healthy female student population. CF and AF were studied as possible underlying mechanisms and measured by using switching tasks with either neutral (Boselie et al., 2017; Hildebrandt et al., 2016) or affective stimuli (Genet et al., 2013; Malooly et al., 2013), respectively. Results indicated no significant effects of the mindfulness induction on pain tolerance, subjective stress, and recovery from pain in terms of pain intensity and pain unpleasantness ratings. Likewise, no significant differences were found between the MM and control group in any type of cognitive and affective switch costs. However, our secondary analyses suggested a decrease in retrospective threat and harmfulness ratings in the MM group compared to the control group. All in all, this study did not find support for the beneficial effects of MM on pain experience and recovery, or on CF and AF.

A Tourniquet pain procedure (i.e., the SETT, originally developed to test the effects of analgesics on experimental pain in humans) was employed to induce ischemic pain (Smith et al., 1966). The SETT thereby functioned as a laboratory analogue of pain recovery, as this pain induction technique has been reported to allow the measurement of prolonged recovery to baseline periods in comparison to other pain induction techniques including the cold pressor task and electrocutaneous stimulation. Moreover, it induces tonic pain that is believed to be comparable to prolonged annoying pain reported in real life by pain patients (Moore et al., 1979; Sinke et al., 2015). Also, in the present study the SETT procedure caused subjective stress levels to rise with a peak at pain tolerance, followed by a decrease in stress levels when participants had recovered from the pain. These findings corroborate the appropriateness of the SETT for the assessment of pain experience and recovery. However, the maximum SETT duration of 20 min appeared to be too short to reach pain tolerance in most participants, and consequently, resulted in decreased reliability of our pain tolerance measurement. In order to avoid a ceiling effect, future studies employing the SETT should consider to extend the maximum duration of the task.

As MM is believed to require practice in order to be applied effectively (e.g., Goldberg et al., 2020), we opted for an induction of mindfulness in the lab (i.e., lab session 2) that was preceded by daily mindfulness home exercises for one week that included psychoeducation and the practice of MM. Supporting the effectiveness of the MM lab induction, results showed that immediately after the induction participants in the MM group scored higher on state mindfulness than participants in the control group, as was also the case for momentary PA ratings. In other words, the MM induction proved effective in increasing state mindfulness and momentary PA as compared to listening to a neutral audio-file (i.e., 9-min excerpt of the audio book The Hobbit by J. R. R. Tolkien). The effect of practice was not observed on trait mindfulness scores as assessed at the very beginning of lab session 2. Both groups showed relatively high initial scores in trait mindfulness that even increased slightly towards the second lab session. A 7-day period might have been too short to robustly increase differential effects of the additional practice in trait scores. However, results were apparent after the MM induction in the lab session, though it cannot be derived from current results to what extent additional practice contributed to this effect. Interestingly, the present results correspond to previous research reporting reduced rumination levels after an 8-week mindfulness meditation course in a sample of healthy students (Meesters et al., 2017), as evidenced by a decrease in rumination from lab session 1 to lab session 2 after performing the daily mindfulness home assignments.

Practicing MM with the purpose of pain relief is directed at promoting the capacity to parse between the sensory experience of pain and the subjective (mostly negative) judgment one attaches to the pain (i.e., the "suffering"). Awareness of the sensation of pain devoid of subjective judgment ultimately leads to the attenuation of pain. Consequently, we predicted that MM would primarily affect pain unpleasantness and subjective stress ratings. Although current findings provide no evidence for this hypothesis, the results of our secondary analyses suggest that the mindfulness induction might have an effect on subjective retrospective pain experience, as evidenced by borderline significant decreases with medium effect sizes (Richardson, 2011) in retrospective threat and harmfulness ratings in the MM group compared to the control group. Although the effect did not reach the conventional level of significance of alpha < .05, the effect sizes were of moderate magnitude. Therefore, future research into the effects of MM on pain may particularly focus on retrospective pain experience.

A growing body of research has concentrated on studying cognitive processes such as executive functioning and CF as potential underlying mechanisms by which MM may provide mental health benefits (Gu et al., 2015; Zeidan et al., 2012). We therefore hypothesized that MM would improve performance on both types of switching tasks measuring CF and AF. However, no effect of the MM induction on either CF or AF was observed, and subsequent mediation analyses were not performed. Some previous studies have also provided inconclusive evidence for the effect of MM on CF (Gill et al., 2020). A possible explanation for these mixed findings may be the various methodologies employed in these studies including the use of different performance-based measures for CF, thereby complicating the comparison of study results. Also of importance here, is the current study's small sample size that could have had a negative impact on the reliability of the switching tasks. Another possible explanation for the absence of a link between MM and flexibility would be that the brief mindfulness exercise used for the MM induction in this study was not robust enough to significantly affect CF and AF. Taken together, whether MM can really enhance CF remains elusive.

Some possible limitations to the present study should be acknowledged. Despite an a priori power calculation, the sample size was small, which may have led to the lack of significant results. Moreover, the small sample size hindered the scope of data interpretation and made in-depth data analyses impossible. The reason for the small sample size was the exclusion of participants tested by one of the experimenters who insufficiently adhered to the protocol. In addition, the sample consisted of healthy female university students aged 18 to 40, thereby limiting generalizability of study results. As aforementioned, another limitation involves the 20 min ceiling in the SETT, which decreased the reliability of the pain tolerance measurement. Also, participants completed both switching tasks in anticipation of a potentially painful task, which may have interfered with switching task performance (e.g., Van Damme et al., 2004).

By offering daily mindfulness home exercises in the week between lab session 1 and 2, we aimed to optimize the MM induction. However, some possible drawbacks to these home exercises should be noted. For instance, contrary to the MM group, participants in the control group did not receive any exercises during this period. Moreover, a consequence of the one-week period between lab sessions was that we did not have full control over other factors that might have had an influence on CF, AF, and pain experience. However, the present findings did not demonstrate a significant difference in trait mindfulness between the MM and control condition.

In conclusion, the current results did not support the hypothesis that a MM induction could improve pain perception and recovery from pain, or CF and AF. It should be borne in mind that due to the small sample size, the scope of current data interpretation was hindered, as well as in-depth analysis of the results. Despite the null findings, the present study provides grounds for continuing the study of individual differences in the effect of MM on pain experience, pain recovery, CF, and AF.

REFERENCES

Attal, N., Masselin-Dubois, A., Martinez, V., Jayr, C., Albi, A., Fermanian, J., Bouhassira, D., & Baudic, S. (2014). Does cognitive functioning predict chronic pain? Results from a prospective surgical cohort. *Brain, 137*(Pt 3), 904-917. https://doi.org/10.1093/brain/awt354

Bjekic, J., Zivanovic, M., Puric, D., Oosterman, J. M., & Filipovic, S. R. (2018). Pain and executive functions: a unique relationship between Stroop task and experimentally induced pain. *Psychol Res, 82*(3), 580-589. https://doi.org/10.1007/s00426-016-0838-2

Bond, F. W., Hayes, S. C., Baer, R. A., Carpenter, K. M., Guenole, N., Orcutt, H. K., Waltz, T., & Zettle, R. D. (2011). Preliminary psychometric properties of the Acceptance and Action Questionnaire-II: a revised measure of psychological inflexibility and experiential avoidance. *Behav Ther, 42*(4), 676-688. https://doi.org/10.1016/j.beth.2011.03.007

Boselie, J. J. L. M., Vancleef, L. M. G., & Peters, M. L. (2017). Increasing Optimism Protects Against Pain-Induced Impairment in Task-Shifting Performance. *J Pain, 18*(4), 446-455. https://doi.org/10.1016/j.jpain.2016.12.007

Boselie, J. J. L. M., Vancleef, L. M. G., Smeets, T., & Peters, M. L. (2014). Increasing optimism abolishes pain-induced impairments in executive task performance. *PAIN, 155*(2), 334-340. https://doi.org/10.1016/j.pain.2013.10.014

Brown, K. W., & Ryan, R. M. (2003). The benefits of being present: mindfulness and its role in psychological well-being. *J Pers Soc Psychol, 84*(4), 822-848.

Chavez, J. L., Porucznik, C. A., Gren, L. H., Guan, J., Joyce, E., Brodke, D. S., Dailey, A. T., Mahan, M. A., Hood, R. S., Lawrence, B. D., Spiker, W. R., Spina, N. T., & Bisson, E. F. (2020). The Impact of Preoperative Mindfulness-Based Stress Reduction on Postoperative Outcomes in Lumbar Spine Degenerative Disease: 3-Month and 12-Month Results of a Pilot Study. *World Neurosurg, 139*, e230-e236. https://doi.org/10.1016/j.wneu.2020.03.186

Choi, K. E., Rampp, T., Saha, F. J., Dobos, G. J., & Musial, F. (2011). Pain modulation by meditation and electroacupuncture in experimental submaximum effort tourniquet technique (SETT). *Explore (NY), 7*(4), 239-245. https://doi.org/10.1016/j.explore.2011.04.004

Cohen, S., Kamarck, T., & Mermelstein, R. (1983). A global measure of perceived stress. *J Health Soc Behav, 24*(4), 385-396.

Cohen, S., & Williamson, G. M. (1988). *Perceived stress in a probability sample of the United States.* (Spacapan S. & Oskamp S., Eds.). Sage.

Dowsey, M., Castle, D., Knowles, S., Monshat, K., Salzberg, M., Nelson, E., Dunin, A., Dunin, J., Spelman, T., & Choong, P. (2019). The effect of mindfulness training prior to total joint arthroplasty on post-operative pain and physical function: A randomised controlled trial. *Complementary Therapies in Medicine, 46*, 195-201. https://doi.org/10.1016/j.ctim.2019.08.010

Fledderus, M., Oude Voshaar, M. A., Ten Klooster, P. M., & Bohlmeijer, E. T. (2012). Further evaluation of the psychometric properties of the Acceptance and Action Questionnaire-II. *Psychol Assess, 24*(4), 925-936. https://doi.org/10.1037/a0028200

Gallant, S. N. (2016). Mindfulness meditation practice and executive functioning: Breaking down the benefit. *Conscious Cogn, 40*, 116-130. https://doi.org/10.1016/j.concog.2016.01.005

Genet, J. J., Malooly, A. M., & Siemer, M. (2013). Flexibility is not always adaptive: affective flexibility and inflexibility predict rumination use in everyday life. *Cogn Emot, 27*(4), 685-695. https://doi.org/10.1080/02699931.2012.733351

Genet, J. J., & Siemer, M. (2011). Flexible control in processing affective and non-affective material predicts individual differences in trait resilience. *Cogn Emot, 25*(2), 380-388. https://doi.org/10.1080/02699931.2010.491647

Gill, L. N., Renault, R., Campbell, E., Rainville, P., & Khoury, B. (2020). Mindfulness induction and cognition: A systematic review and meta-analysis. *Consciousness and Cognition, 84*, 102991. https://doi.org/10.1016/j.concog.2020.102991

Goldberg, S. B., Knoeppel, C., Davidson, R. J., & Flook, L. (2020). Does practice quality mediate the relationship between practice time and outcome in mindfulness-based stress reduction? *Journal of Counseling Psychology, 67*(1), 115-122. https://doi.org/10.1037/cou0000369

Gozenonline. (2017). *Mindfulness: Observing a Train of Thoughts [Video File].* https://www.youtube.com/watch?v=F0SWMICwtm0

Gross, J. J. (2007). *Handbook of emotion regulation*. Guilford Press.

Gu, J., Strauss, C., Bond, R., & Cavanagh, K. (2015). How do mindfulness-based cognitive therapy and mindfulness-based stress reduction improve mental health and wellbeing? A systematic review and meta-analysis of mediation studies. *Clin Psychol Rev, 37*, 1-12. https://doi.org/10.1016/j.cpr.2015.01.006

Hildebrandt, L. K., McCall, C., Engen, H. G., & Singer, T. (2016). Cognitive flexibility, heart rate variability, and resilience predict fine-grained regulation of arousal during prolonged threat. *Psychophysiology, 53*(6), 880-890. https://doi.org/10.1111/psyp.12632

Holzel, B. K., Lazar, S. W., Gard, T., Schuman-Olivier, Z., Vago, D. R., & Ott, U. (2011). How Does Mindfulness Meditation Work? Proposing Mechanisms of Action From a Conceptual and Neural Perspective. *Perspect Psychol Sci, 6*(6), 537-559. https://doi.org/10.1177/1745691611419671

Joireman, J. A., Parrott, L., & Hammersla, J. (2002). Empathy and the self-absorption paradox: Support for the distinction between self-rumination and self-reflection. *Self Identity, 1*, 53-65.

Kabat-Zinn, J. (1982). An outpatient program in behavioral medicine for chronic pain patients based on the practice of mindfulness meditation: theoretical considerations and preliminary results. *Gen Hosp Psychiatry, 4*(1), 33-47.

Karsdorp, P. A., Geenen, R., & Vlaeyen, J. W. (2014). Response inhibition predicts painful task duration and performance in healthy individuals performing a cold pressor task in a motivational context. *Eur J Pain, 18*(1), 92-100. https://doi.org/10.1002/j.1532-2149.2013.00348.x

Kiesel, A., Steinhauser, M., Wendt, M., Falkenstein, M., Jost, K., Philipp, A. M., & Koch, I. (2010). Control and interference in task switching - a review. *Psychol Bull, 136*(5), 849-874. https://doi.org/10.1037/a0019842

Kingston, J., Chadwick, P., Meron, D., & Skinner, T. C. (2007). A pilot randomized control trial investigating the effect of mindfulness practice on pain tolerance, psychological well-being, and physiological activity. *J Psychosom Res, 62*(3), 297-300. https://doi.org/10.1016/j.jpsychores.2006.10.007

Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (1997). *International Affective Picture System (IAPS): Technical manual and affective ratings*. NIMH Center for the Study of Emotion and Attention, University of Florida.

Malooly, A. M., Genet, J. J., & Siemer, M. (2013). Individual differences in reappraisal effectiveness: the role of affective flexibility. *Emotion, 13*(2), 302-313. https://doi.org/10.1037/a0029980

Meesters, A., den Bosch-Meevissen, Y., Weijzen, C. A. H., Buurman, W. A., Losen, M., Schepers, J., Thissen, M., Alberts, H., Schalkwijk, C. G., & Peters, M. L. (2017). The effect of Mindfulness-Based Stress Reduction on wound healing: a preliminary study. *J Behav Med*. https://doi.org/10.1007/s10865-017-9901-8

Meesters, A., Vancleef, L. M. G., & Peters, M. L. (2019). Emotional flexibility and recovery from pain. *Motivation and Emotion, 43*(3), 493-504. https://doi.org/10.1007/s11031-018-9748-5

Meesters, A., Vancleef, L. M. G., & Peters, M. L. (2021). The role of cognitive and affective flexibility in individual differences in the experience of experimentally induced heat pain. *Journal of Experimental Psychopathology, 12*(2), 20438087211018447. https://doi.org/10.1177/20438087211018447

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The unity and diversity of executive functions and their contributions to complex "Frontal Lobe" tasks: a latent variable analysis. *Cogn Psychol, 41*(1), 49-100. https://doi.org/10.1006/cogp.1999.0734

Moore, D. J., Keogh, E., & Eccleston, C. (2012). The interruptive effect of pain on attention. *Q J Exp Psychol (Hove)*, *65*(3), 565-586. https://doi.org/10.1080/17470218.2011.626865

Moore, P. A., Duncan, G. H., Scott, D. S., Gregg, J. M., & Ghia, J. N. (1979). The submaximal effort tourniquet test: its use in evaluating experimental and chronic pain. *PAIN, 6*(3), 375-382.

Moriarty, O., McGuire, B. E., & Finn, D. P. (2011). The effect of pain on cognitive function: a review of clinical and preclinical research. *Prog Neurobiol, 93*(3), 385-404. https://doi.org/10.1016/j.pneurobio.2011.01.002

Moynihan, J. A., Chapman, B. P., Klorman, R., Krasner, M. S., Duberstein, P. R., Brown, K. W., & Talbot, N. L. (2013). Mindfulness-based stress reduction for older adults: effects on executive function, frontal alpha asymmetry and immune function. *Neuropsychobiology, 68*(1), 34-43. https://doi.org/10.1159/000350949

Ortner, C. N. M., Kilner, S. J., & Zelazo, P. D. (2007). Mindfulness meditation and reduced emotional interference on a cognitive task. *Motivation and Emotion, 31*(4), 271-283. https://doi.org/10.1007/s11031-007-9076-7

Osman, A., Barrios, F. X., Gutierrez, P. M., Kopper, B. A., Merrifield, T., & Grittmann, L. (2000). The Pain Catastrophizing Scale: further psychometric evaluation with adult samples. *J Behav Med, 23*(4), 351-365. https://doi.org/10.1023/a:1005548801037

Osman, A., Barrios, F. X., Kopper, B. A., Hauptmann, W., Jones, J., & O'Neill, E. (1997). Factor structure, reliability, and validity of the Pain Catastrophizing Scale. *J Behav Med, 20*(6), 589-605. https://doi.org/10.1023/a:1025570508954

Price, D. D., & Harkins, S. W. (1987). Combined Use of Experimental Pain and Visual Analogue Scales in Providing Standardized Measurement of Clinical Pain. *Clin J Pain, 3*(1), 1-8.

Raes, F., Dewulf, D., Van Heeringen, C., & Williams, J. M. (2009). Mindfulness and reduced cognitive reactivity to sad mood: evidence from a correlational study and a non-randomized waiting list controlled study. *Behav Res Ther, 47*(7), 623-627. https://doi.org/10.1016/j.brat.2009.03.007

Ratcliff, C. G. (2015). *Brief Guided Mindfulness Meditation for Women Undergoing Stereotactic Breast Biopsy: Effects on Patient Self-Report, EEG Activity, and Physiological Measures* [Unpublished doctoral dissertation]. University of Houston, Houston, Texas.

Reiner, K., Granot, M., Soffer, E., & Lipsitz, J. D. (2016). A Brief Mindfulness Meditation Training Increases Pain Threshold and Accelerates Modulation of Response to Tonic Pain in an Experimental Study. *Pain Med, 17*(4), 628-635. https://doi.org/10.1111/pme.12883

Reiner, K., Tibi, L., & Lipsitz, J. D. (2013). Do Mindfulness-Based Interventions Reduce Pain Intensity? A Critical Review of the Literature. *Pain Medicine, 14*(2), 230-242. https://doi.org/10.1111/pme.12006

Richardson, J. T. E. (2011). Eta squared and partial eta squared as measures of effect size in educational research. *Educational Research Review, 6*(2), 135-147. https://doi.org/10.1016/j.edurev.2010.12.001

Salt, R., Brown, G., Moffit, M., & [AsapSCIENCE]. (2015). *The Scientific Power of Meditation [Video File]*. https://www.youtube.com/watch?v=Aw71zanwMnY

Schneider, D. W., & Logan, G. D. (2005). Modeling task switching without switching tasks: a short-term priming account of explicitly cued performance. *J Exp Psychol Gen, 134*(3), 343-367. https://doi.org/10.1037/0096-3445.134.3.343

Segal, Z., Williams, M. R., & Teasdale, J. (2002). *Mindfulness-based cognitive therapy for depression: A new approach to preventing relapse.* Guilford Press.

Shapiro, S. L., Carlson, L. E., Astin, J. A., & Freedman, B. (2006). Mechanisms of mindfulness. *J Clin Psychol, 62*(3), 373-386. https://doi.org/10.1002/jclp.20237

Sinke, C., Schmidt, K., Forkmann, K., & Bingel, U. (2015). Phasic and tonic pain differentially impact the interruptive function of pain. *PloS one, 10*(2), e0118363-e0118363. https://doi.org/10.1371/journal.pone.0118363

SmilingMind. (2016). *From mindlessness to mindfulness [Video File]*. https://www.youtube.com/watch?v=4WD9KCf5sIY

Smith, G. M., Egbert, L. D., Markowitz, R. A., Mosteller, F., & Beecher, H. K. (1966). An experimental pain method sensitive to morphine in man: the submaximum effort tourniquet technique. *J Pharmacol Exp Ther, 154*(2), 324-332.

Sullivan, M. J., Bishop, S. R., & Pivik, J. (1995). The Pain Catastrophizing Scale: development and validation. *Psychological Assessment, 7*, 524–532.

Thompson, E. R. (2007). Development and validation of an internationally reliable short-form of the Positive and Negative Affect Schedule (PANAS). *Journal of Cross-Cultural Psychology, 38*, 227–242. https://doi.org/10.1177/0022022106297301

Trapnell, P. D., & Campbell, J. D. (1999). Private self-consciousness and the five-factor model of personality: distinguishing rumination from reflection. *J Pers Soc Psychol, 76*(2), 284-304. https://doi.org/10.1037//0022-3514.76.2.284

Van Ryckeghem, D. M., Crombez, G., Eccleston, C., Liefooghe, B., & Van Damme, S. (2012). The interruptive effect of pain in a multitask environment: an experimental investigation. *J Pain, 13*(2), 131-138. https://doi.org/10.1016/j.jpain.2011.09.003

Veehof, M. M., Oskam, M. J., Schreurs, K. M., & Bohlmeijer, E. T. (2011). Acceptance-based interventions for the treatment of chronic pain: a systematic review and meta-analysis. *PAIN, 152*(3), 533-542. https://doi.org/10.1016/j.pain.2010.11.002

Watts, A. (2017). *Life is NOT a Journey - Alan Watts [Video File]*. http://www.youtube.com/watch?v=rBpaUICxEhk

Zeidan, F., Grant, J. A., Brown, C. A., McHaffie, J. G., & Coghill, R. C. (2012). Mindfulness meditation-related pain relief: Evidence for unique brain mechanisms in the regulation of pain. *Neuroscience Letters, 520*(2), 165-173. https://doi.org/10.1016/j.neulet.2012.03.082

Zeidan, F., Johnson, S. K., Diamond, B. J., David, Z., & Goolkasian, P. (2010). Mindfulness meditation improves cognition: evidence of brief mental training. *Conscious Cogn, 19*(2), 597-605. https://doi.org/10.1016/j.concog.2010.03.014

CHAPTER 5

The effect of Mindfulness-Based Stress Reduction on wound healing: a preliminary study

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ABSTRACT

Psychological factors have been shown to influence the process of wound healing. This study examined the effect of Mindfulness-Based Stress Reduction (MBSR) on the speed of wound healing. The local production of pro-inflammatory cytokines and growth factors was studied as potential underlying mechanism. Forty-nine adults were randomly allocated to a waiting-list control group (n = 26) or an 8-week MBSR group (n = 23). Pre- and post-intervention/waiting period assessment for both groups consisted of questionnaires. Standardized skin wounds were induced on the forearm using a suction blister method. Primary outcomes were skin permeability and reduction in wound size monitored once a day at day 3, 4, 5, 6, 7, and 10 after injury. Secondary outcomes were cytokines and growth factors and were measured in wound exudates obtained at 3, 6, and 22 h after wounding. Although there was no overall condition effect on skin permeability or wound size, post hoc analyses indicated that larger increases in mindfulness were related to greater reductions in skin permeability 3 and 4 days after wound induction. In addition, MBSR was associated with lower levels of interleukin (IL)-8, and placental growth factor (PlGF) in the wound fluid 22 h after wound induction. These outcomes suggest that increasing mindfulness by MBSR might have beneficial effects on early stages of wound healing.

Trial Registration NTR3652, http://www.trialregister.com

Keywords

wound healing, mindfulness, intervention, inflammation, cytokine, growth factor

INTRODUCTION

Over the past decades studies have repeatedly shown that psychological factors can influence the process of wound healing (e.g., Broadbent & Koschwanez, 2012; House, 2015). Most of these studies focused on the effects of psychosocial distress on wound healing and consistently reported impaired wound healing across different wound models and different stressors (Bosch et al., 2007; Cole-King & Harding, 2001; Ebrecht et al., 2004; Garg et al., 2001; Kiecolt-Glaser et al., 2005; Maple et al., 2015). A meta-analysis revealed a robust association between stress and impaired healing (Walburn et al., 2009). The effects of stress on wound healing can be mediated by multiple immune and neuroendocrine pathways and may affect various stages of the healing process (Christian et al., 2006; Gouin & Kiecolt-Glaser, 2011).

Pro-inflammatory cytokines such as interleukin (IL)-1α, IL-1β, IL-6, IL-8 and tumor necrosis factor (TNF)-α are crucial during the early phases of the healing process, and thus for successful resolution of wounds. Their function is to remove damaged tissue, limit infection and to stimulate tissue repair (Lowry, 1993). Consequently, upregulation of pro-inflammatory cytokines at the wound site is seen during the inflammatory phase of healing (Werner & Grose, 2003). A potential mechanism responsible for the effect of stress on the healing process may consist of the suppression of pro-inflammatory cytokine activity at the wound site. Using an experimental wound induction procedure, Glaser et al. (1999) and Kiecolt-Glaser et al. (2005) have found lower levels in wound fluid of respectively the pro-inflammatory cytokines IL-1α and IL-8 at 5 and 24 h and IL-6, IL-1β, and TNF-α at 22 h after wound induction in participants reporting high stress levels or after stress induction. Broadbent et al. (2003) studied surgical wounds and found that pre-operative stress was related to lower levels of IL-1β in the wound fluid. However, there may not be a simple linear association between the expression of pro-inflammatory cytokines and the healing process. Adequate wound healing depends on the delicate balance between pro- and anti-inflammatory effects. Excessive inflammation delays wound healing; indeed higher concentrations of pro-inflammatory cytokines have been found in chronic wounds (Beidler et al., 2009).

In addition to cytokines, growth factors such as vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) are important for wound repair (Failla et al., 2000; Johnson & Wilgus, 2014). The role of VEGF in particular is well documented (Johnson & Wilgus, 2014) and considered important in stimulating the formation of new blood vessels (i.e., angiogenesis), which is imperative for tissue restoration. Animal and human studies have shown that low levels of VEGF are related to impaired healing

(Johnson & Wilgus, 2014). On the other hand, stress could delay wound healing through decreasing growth factors at the wound site. Glucocorticoid up-regulation has been shown to negatively affect angiogenesis by down-regulating VEGF expression in vitro (Nauck et al., 1998). Moreover, preliminary evidence exists demonstrating a stress-induced delay in wound healing accompanied by decreased VEGF expression in an animal model of wound healing (Pyter et al., 2014).

If stress can negatively affect wound healing, then reducing stress may have positive effects on the speed and quality of wound healing. Psychological interventions such as relaxation and disclosure writing have indeed been found to improve healing of surgical wounds (Broadbent et al., 2012), wounds induced by skin biopsy (Robinson et al., 2016; Weinman et al., 2008), and to speed recovery of skin permeability after mild injury induced by tape-stripping (Robinson et al., 2015).

Mindfulness-Based Stress Reduction (MBSR) is another intervention that might positively affect wound healing. MBSR is a type of meditation practice that is directed at promoting a controlled, nonjudgmental, and non-evaluative awareness of moment-to-moment experiences (Kabat-Zinn, 1990). A recent meta-analysis showed that MBSR can effectively reduce stress, anxiety and depression and enhance quality of life in healthy individuals (Khoury et al., 2015). Rosenkranz et al. (2013) examined the effects of MBSR on the level of IL-8 and TNF-α in skin blisters in response to a laboratory stressor and capsaicin exposure. No main effect of the intervention was found but more intensive MBSR practice was associated with a decrease in TNF-α level from pre- to post-training in response to psychosocial stress and an inflammatory stimulus.

The current study examined the effect of an 8-week MBSR intervention on the healing of blister skin wounds in healthy adults. Participants were not specifically selected for elevated stress levels to ensure comparability with previous studies investigating the effects of psychological interventions on wound healing in healthy participants (e.g., Koschwanez et al., 2013; Robinson et al., 2015; Robinson et al., 2016; Weinman et al., 2008). In addition, MBSR has been found to reduce stress in healthy populations not selected for elevated stress levels (Khoury et al., 2015). Trans-epidermal water loss (TEWL) – an index for skin permeability – and wound size were the primary outcomes and assessed until 10 days after injury. Secondary outcomes were pro-inflammatory cytokines IL-1β, IL-6, IL-8 and TNF-α, the growth factors VEGF, PlGF and the soluble Fms-like tyrosine kinase-1 (sFlt-1) and were measured at 3, 6 and 22 h post injury. We hypothesized that individuals receiving the MBSR training would display a faster decrease in TEWL and wound size over the course of 10 days. In subsequent exploratory analyses, we examined the effects of MBSR on pro-inflammatory cytokine and growth factor levels in wound fluid.

MATERIALS AND METHODS

Participants

Participants were 49 healthy adults aged 19-28 years (mean age 22.1 +/- 2.1 years; 8 men) recruited through pamphlets and posters at Maastricht University and Maastricht University Medical Centre. They were rewarded with a MBSR training and an additional financial compensation of 100 euro. Individuals were screened over the telephone followed by a dermatologist's visit. They were excluded if they documented health problems (e.g., diabetes mellitus, cancer, auto-immune diseases, hypo/hyperthyroidism, etc.) and/or medication use (e.g., psychotropic drugs, blood pressure regulators, immunosuppressive drugs, steroids, etc.). Also excluded were individuals who: smoked; consumed more than 10 caffeinated foods or drinks per day; consumed more than 20 (men) or 10 (women) alcoholic drinks per week; had a body mass index ≤ 18 or ≥ 30; experienced intensely stressful events in the last three months; received psychological treatment within the last six months; or reported experience with meditation practice. Additional exclusion criteria included having a blood and/or needle phobia, previous allergic responses to adhesives, bandages, tapes, or silicones, or dermal dysfunctions such as vitiligo, psoriasis, atopic dermatitis, and multiple moles. Written informed consent was obtained from all individual participants included in this study. The study was approved by the Medical Ethical Committee of Maastricht University Medical Centre.

Measures

Questionnaires

The Kentucky Inventory of Mindfulness Skills (KIMS) was used as manipulation check for the mindfulness intervention (Baer et al., 2004). This instrument measures four mindfulness skills: observing, describing, acting with awareness, and accepting without judgment. Internal consistency of the KIMS in the current sample was $\alpha = .82$ at pre- and $\alpha = .88$ at post-intervention. Additional questionnaires were administered to measure the effects of the mindfulness intervention on dispositional mindfulness (Mindfulness Attention Awareness Scale; MAAS; Brown & Ryan, 2003), dispositional optimism (the revised Life Orientation Test; LOT-R; Scheier et al., 1994), and rumination and reflection (the Rumination-Reflection Questionnaire; RRQ; Trapnell & Campbell, 1999). Cronbach's alpha for the MAAS in this sample was .85 and .80 at pre- and post-intervention, respectively. Similarly, the internal consistency of the LOT-R was good at both pre- (α

= .82) and post-intervention (α = .89). Lastly, in the current sample, Cronbach's alpha was .89 at both pre- and post-intervention for the rumination subscale and .90 at pre- and .93 at post-intervention for the reflection subscale. Pre- and post-intervention questionnaire data were not available for 3 and 5 participants, respectively.

Intervention

Participants were randomly assigned to either a waiting-list control group (WLC; n = 26; 5 men) or a MBSR group (n = 23; 3 men). The MBSR intervention followed a standardized 8-week MBSR protocol (Kabat-Zinn, 1982) with some elements from Mindfulness-Based Cognitive Therapy (Segal et al., 2002) taught by an experienced trainer. Two successive groups of 15 people each were conducted. Three individuals in the MBSR group received advice from the dermatologist not to participate in the wound healing part of the study and were therefore excluded. Another four individuals were excluded because they did not complete the MBSR training due to a lack of time. The duration of each session was 2.5 h and comprised sharing and reflecting on past week's experiences, meditation exercises, and presentations providing theoretical insight. Participants were encouraged to practice meditation exercises at home on a daily basis (30-60 min) and implement various smaller mindfulness exercises in their daily routine. Participants in the WLC condition were invited to complete the MBSR training at the end of the study.

Suction blister model

In order to induce wounds, a standardized procedure for suction blisters was adopted as previously described (Glaser et al., 1999; Kiecolt-Glaser et al., 2005; Zimmerli & Gallin, 1987). In short, a trained assistant created eight 8-mm diameter blister wounds. Prior to wound induction a mild depilatory cream was applied to the skin in order to remove hair at the wound site. An acrylic template with eight holes was attached to the disinfected volar surface of the nondominant forearm at 2 cm from the elbow joint, after which a mild constant 350 mmHg suction with a vacuum pump (Neuro probe, Cabin John, MD, ISA) was applied via the holes until blisters developed (1 - 1.5 h). During the whole procedure a 250 W infrared lamp was placed at 30 cm from the suction site in order to increase the rate of blister formation, simultaneously ensuring that the temperature above the skin did not exceed 37°C. Next, the epidermis of each blister was removed using a sterile surgical knife, and a plastic sterile 8-well template was attached over the blister wounds. Each well was filled with 1.0 mL of sterile saline solution (0.9% Sodium Chloride, NaCl) and sealed off sterile. At 3, 6, and 22 h after wound induction, wound fluid was taken from the wells with a sterile syringe. Wound fluid samples were centrifuged at 5000G for 5 min at 4°C in order to obtain undiluted supernatant which was then aliquoted over three samples of 200 μl each and stored at -80°C. Exudate was taken from three wells at 3 and 6 h post wound induction and from the remaining two wells at 22 h post wound induction. The well plate was left in place until the last sample of wound fluid was taken (around 8 AM on the next day), after which the wound site was covered with a large sterile water-resistant bandage. The assistant inducing the wounds was blind to group status. Participants were requested to refrain from strenuous physical exercise, sugar, caffeine, and alcohol consumption, or the use of recreational drugs for 22 h after wound induction (DeRijk et al., 1997).

Wound healing

Participants briefly revisited the research unit on day 3, 4, 5, 6, 7, and 10 between 10 AM and 12 AM to monitor the progress of wound healing related to TEWL and wound surface area measurements.

Trans-epidermal water loss

TEWL was used as an index for wound permeability. TEWL measures the evaporation rate in the air layer adjacent to the skin, which increases when the skin is damaged and decreases as the barrier function of the skin recovers (e.g., Altemus et al., 2001). An evaporimeter (VapoMeter, Delfin Technologies, Stamford, CT, USA), was used to determine TEWL above the wound site. Room temperature was maintained at 20 - 22°C. Upon arrival participants relaxed for 10 min to control for any preceding physical exertion. The mean TEWL of two measurements of the two most proximal blisters to the elbow was obtained daily from 3 to 7 days and at 10 days post wound induction in addition to control values measured at two sites on the contralateral arm. The average control values per day were then subtracted from TEWL values above the wound site to control for normal variations in TEWL. Due to unavailability of participants or technical difficulties, 21 participants had available data for each day, 18 for five days, nine for four days, and one for one day.

Wound surface area

Wound surface area was determined by taking digital images of the wound site. The participant's arm was positioned at 28 cm from the camera's lens and built-in camera lights controlled the lighting. For calibration purposes an 8-mm diameter circle sticker was placed next to the wound site. ImageJ software (version 1.44, NIH, Bestheda, MD, USA) was used to map the surface areas of each blister. After calibration of the photograph, the wound area of each blister was assessed in mm^2 within a hand-drawn delineated area, including the scab but excluding erythema and scar tissue. Two trained raters blind to the experimental conditions analyzed each photograph. Inter-rater difference was computed for each wound surface area as percent deviation of rater A from rater B. Surface area measurements corresponding to inter-rater differences of > 20% and an absolute difference of at least 2 mm^2 were assessed again by a third rater (rater C, 1.66% of measurements). Mean wound surface area was calculated by averaging the values of rater A and B, or in case of a third rater, across the value of rater C and the value of rater A or B that was closest to rater C. A two-way random effect model with absolute agreement intra-class correlation coefficient (ICC) was then performed to test interrater reliability for each time point and blister. All ICC (2,2) values were > .95. Due to limited availability of participants and technical difficulties on some days, wound surface area data was incomplete. Surface area data was collected for each day for 18 participants, five days for 20 participants, four days for eight participants, three days for one participant, and one day for one participant.

Cytokines and growth factors

Wound exudate was analysed for IL-1β, IL-6, IL-8 and TNF-α, VEGF, sFlt-1, and PlGF by a multi-array detection system based on electrochemiluminescence technology (MesoScale Discovery SECTOR Imager 2400, Gaithersburg, MD, USA). The intra- and inter-assay coefficients of variation (CVs) were 6.9% and 8.7% for IL-6, 3.5% and 4.1% for IL-8, 5.9% and 8.6% for TNF-α, 4.7% and 7.0% for PlGF, 6.2% and 3.3% for sFlt-1, and 5.3% and 2.8% for VEGF, respectively. Because IL-1β was measured using one kit, only an intra-assay CV of 10.7% could be computed. Cytokines were measured in the 3, 6, and 22 h samples, whereas growth factors were only measured in the 22 h samples. This was because it has been shown that these growth factors only start to increase in concentration approximately one day post injury (Johnson & Wilgus, 2014). One participant had missing cytokine and growth factor data at 3 and 6 h, and nine participants at 22 h due to unavailability of the participant or leakage of the well template, leaving 39 participants with data for all three time points.

Procedure

The KIMS, MAAS, LOT-R, and RRQ were administered four days before the start of the intervention through an online questionnaire program. During the next eight weeks participants followed a MBSR program or started a waiting period. Thereafter, participants completed the same set of questionnaires to assess the effect of the intervention on these variables. Participants were then individually invited to the research unit for the wound induction procedure within one month after completion of the MBSR intervention. Participants were asked to continue practicing mindfulness in the intervening period. The day of the wound induction began at 8 AM with the suction blister procedure. During suction which took approximately 75 min, participants were provided with breakfast and filled in some questionnaires (not further reported). Participants remained in the lab until 6 h had transpired. During this time they performed a few computer tasks and spent the rest of the time doing personal activities (e.g., reading, work). At 3 and 6 h post wound induction wound fluid was collected. The next day, participants returned to the lab at 8 AM to provide the final samples of wound exudate and to have the well template removed. Participants briefly revisited the research unit on day 3 to 7 and day 10 post wound induction between 10 AM and 12 AM to measure TEWL and to have a photograph taken of the blisters. During the intervening periods, the wound site remained covered with sterile adhesive bandage.

Statistical analysis

All statistical analyses were performed using SPSS 22.0. Descriptive statistics were computed and independent samples *t* tests and a chi-square test were used to check whether randomization was successful. Two-way analyses of variance (ANOVAs) with condition (WLC vs. MBSR) and sex (men vs. women) as independent variables were performed to check baseline differences in questionnaire scores. Random intercept mixed regression analyses were performed for all outcome measures. Sex was included as factor, as it is known that men and women exhibit distinct physiological properties of the skin (Gilliver et al., 2007). We started testing saturated models including all predictors and their interactions and continued with stepwise exclusion of non-significant interaction terms. Primary outcome measures were TEWL and wound surface area and secondary outcomes were cytokines (IL-1β, IL-6, IL-8 and TNF-α) and growth factors (VEGF, PlGF, and sFlt-1). Statistical significance was assumed to exist at $\alpha \leq .05$ for primary outcomes and at an adjusted $\alpha \leq .01$ for secondary outcomes in order to correct for multiple testing.

Mixed regression analyses with time (pre- vs. post-intervention) as level 1 (within-subjects) factor and condition (WLC vs. MBSR) and sex (men vs. women) as level 2 (between-subjects) factors were conducted in order to test the effect of MBSR on change in KIMS, MAAS, LOT-R, RRQ-reflection, and RRQ-rumination from pre- to post-intervention. To examine the effect of MBSR on TEWL, wound surface area, cytokine and growth factor levels, mixed regression analyses with blister (blister 1 to 8) as level 1 (within-subjects) predictor, time (day 3 to 7 and 10 post wound induction) as level 2 (within-subjects) predictor, and condition (WLC vs. MBSR) and sex (men vs. women) as level 3 (between-subjects) predictors were performed for TEWL and wound surface area. In these models, blisters were nested within time and time was nested within individuals.

In the models analyzing cytokine data, time (3, 6, and 22 h post wound induction) was defined as level 1 (within-subjects) factor and condition (WLC vs. MBSR) and sex (men vs. women) as level 2 (between-subjects) factors. Only one level was specified for the models analyzing growth factors, namely condition (WLC vs. MBSR) and sex (men vs. women) as level 1 (between-subjects) variables.

RESULTS

Baseline statistics

Two-way ANOVAs with condition and sex as independent variables revealed no significant differences between the conditions and sexes at baseline in mindfulness, optimism, rumination and reflection (Table 1). Participants in the two conditions neither differed significantly in age ($t(47) = -.50$, $p = .62$), nor sex ($\chi^2(1) = .34$, $p = .71$).

Table 1. Means (*SD*) of pre- and post-intervention questionnaire scores for both conditions

	Pre-intervention		**Post-intervention**	
	WLC (n = 25)	**MBSR (n = 21)**	**WLC (n = 22)**	**MBSR (n = 22)**
1. KIMS	126 (12.4)	121 (14.2)	125 (13.2)	134 (15.5)
2. MAAS	3.77 (0.71)	3.63 (0.60)	3.68 (0.54)	3.87 (0.60)
3. LOT-R	21.4 (4.05)	20.3 (3.86)	22.7 (5.31)	22.5 (4.13)
4. RRQ-rum	3.54 (0.76)	3.71 (0.57)	3.50 (0.62)	3.24 (0.57)
5. RRQ-refl	3.32 (0.65)	3.52 (0.66)	3.31 (0.82)	3.60 (0.65)

WLC = waiting-list control group; MBSR = Mindfulness-Based Stress Reduction group; KIMS = Kentucky Inventory of Mindfulness Skills; MAAS = Mindfulness Attention Awareness Scale; LOT-R = Life Orientation Test Revised; RRQ-rum = Rumination-Reflection Questionnaire – rumination subscale; RRQ-refl = Rumination-Reflection Questionnaire – reflection subscale.

Self-report assessment

Multilevel random intercept modeling was conducted to test the effect of MBSR on change in KIMS, MAAS, LOT-R, RRQ-reflection, and RRQ-rumination from pre- to post-intervention. A significant time x condition x sex interaction for KIMS was found ($F(1, 39.5) = 8.53$, $p = .006$). Testing multilevel models with a time x condition interaction term for both sexes separately revealed a significant time x condition interaction for KIMS in women ($F(1, 34.4) = 8.34$, $p = .006$) and men ($F(1, 5.30) = 14.5$, $p = .011$). Participants in the MBSR condition improved more in terms of KIMS than WLC subjects. This improvement was larger for men than for women. The time x condition x sex interaction also reached significance for rumination ($F(1, 39.5) = 4.79$, $p = .035$). Separate multilevel models tested the time x condition interaction for both sexes and showed a significant time x condition interaction for rumination in men ($F(1, 4.95) = 7.87$, $p = .038$), but not in women ($F(1, 35.0) = 1.99$, $p = .17$); rumination decreased more in male participants in the MBSR condition than in the WLC condition. For the MAAS, LOT-R and RRQ-reflection no time x condition x sex or time x condition interactions were detected.

5

Wound healing

Trans-epidermal water loss

None of the interactions with blister were significant in the multilevel models for TEWL and therefore excluded. Because a significant time x condition x sex interaction was observed ($F(5, 439) = 4.89$, $p < .001$) separate analyses for women and men were performed. For women no significant time x condition interaction was found ($F(5, 382) = .20$, $p = .96$), but it did reach significance for men ($F(5, 59) = 8.94$, $p < .001$; Table 2). Exploring the simple effects of condition per time point in men demonstrated a significant effect of condition at day 3 ($b = 104$, $p = .001$) and day 4 post wound induction ($b = 83$, $p = .001$). TEWL was lower in the MBSR than the WLC condition at 3 and 4 days after wounding. Figure 1A displays the estimated marginal means for TEWL across sex and condition.

Wound surface area

After excluding all non-significant four- and three-way interactions, multilevel modeling revealed a significant blister x condition x sex interaction ($F(7, 1784) = 5.49$, $p < .001$) and time x condition x sex interaction ($F(5, 1793) = 3.72$, $p = .002$) for wound surface area. The significant blister x condition x sex interaction was not of interest for the present

Table 2. Parameter estimates for the final multilevel models for trans-epidermal water loss and wound surface area across women and men

	TEWL								**Wound surface area**							
	Women (n = 41)				**Men (n = 8)**				**Women (n = 40)**				**Men (n = 8)**			
Simple effects	**b**	**SE**	***t***	***p***	**b**	**SE**	***t***	***p***	**b**	**SE**	***t***	***p***	**b**	**SE**	***t***	***p***
Condition effect on day 3	4.37	9.29	0.47	.64	104	15.23	6.80	< .001	-1.20	1.54	-0.78	.44	6.02	2.16	2.78	.010
Condition effect on day 4	7.02	9.61	0.73	.47	83.3	21.9	3.80	< .001	-1.03	1.54	-0.67	.51	3.89	2.51	1.55	.13
Condition effect on day 5	2.52	9.78	0.26	.80	25.9	18.0	1.44	.16	-1.12	1.56	-0.71	.48	2.25	2.30	0.98	.34
Condition effect on day 6	3.84	9.98	0.39	.70	11.9	16.2	.73	.47	-1.14	1.56	-0.73	.47	1.24	2.21	0.56	.58
Condition effect on day 7	-1.34	9.70	-0.14	.89	-2.81	15.2	-0.18	.86	-1.33	1.55	-0.86	.39	-0.27	2.16	-0.12	.90
Condition effect on day 10	-1.35	10.0	-0.14	.89	1.37	14.6	0.094	.93	1.98	1.56	1.27	.21	2.34	2.12	1.10	.28

b = estimate; SE = standard error; TEWL = trans-epidermal water loss.

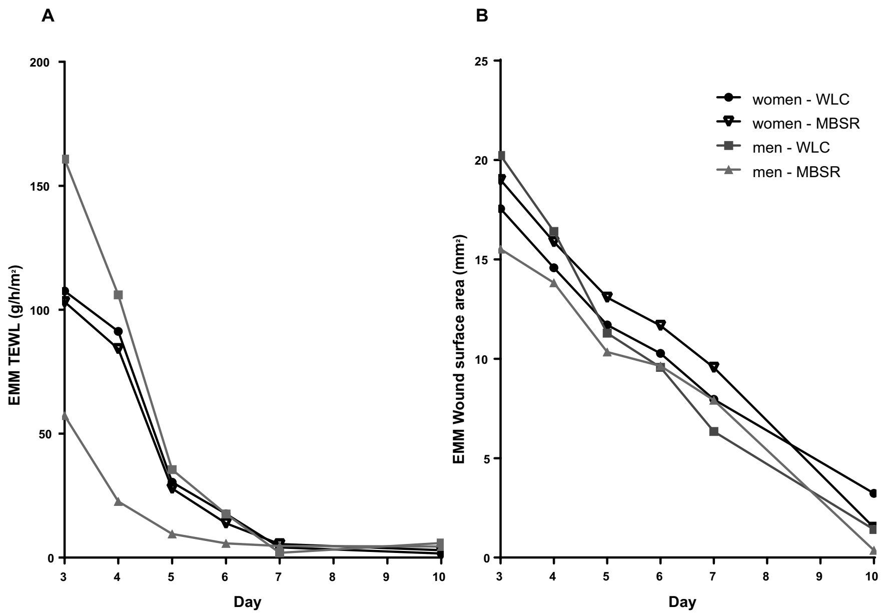

Figure 1. Estimated marginal means for TEWL (A) and wound surface area scores (B) for men and women. *WLC = waiting-list control group; MBSR = Mindfulness-Based Stress Reduction group; EMM = estimated marginal means; TEWL = trans-epidermal water loss.*

study, but was retained in the model during subsequent testing. Multilevel models for women and men separately revealed significant time x condition interaction effects in both women ($F(5, 1550) = 4.90$, $p < .001$) and men ($F(5, 275) = 3.82$, $p = .002$). The wound surface area scores as estimated by the final multilevel models are presented in Figure 1B. For women, the simple effect of condition was not significant on any time point (see Table 2). In men, the simple effect of condition on day 3 was significant ($b = 6.02$, $p = .010$, see Table 2). The simple effects of condition on subsequent days were not significant.[1]

Biological markers

Table S1 displays the absolute cytokine and growth factor concentrations as determined by the multi-array platform across condition and sex (Appendix B).

[1] All wounds healed normally but five participants experienced post-inflammatory hyperpigmentation for longer than six months.

Pro-inflammatory cytokines

The time x condition x sex interaction did not reach significance for any of the cytokines. Consequently, these interaction terms were excluded from the multilevel models. For IL-8, the time x condition interaction ($F(2, 286) = 5.96$, $p = .003$) and time x sex interaction ($F(2, 292) = 21.8$, $p < .001$) were significant. Simple effect analyses per time point revealed significant effects at 22 h post wound induction for condition ($b = 1014$, $p < .001$) and sex ($b = 3059$, $p < .001$). Levels of IL-8 were higher in the WLC group relative to the MBSR group and higher in men compared to women (see Figure 2). For IL-1β, IL-6 and TNF-α, only the time x sex interactions reached significance (IL-1β: $F(2, 290) = 31$, $p < .001$; IL-6: $F(2, 290) = 7.19$, $p = .001$; TNF-α: $F(2, 299) = 27.0$, $p < .001$). At 22 h after wounding, men displayed higher levels of IL-1β ($b = 3751$, $p < .001$), IL-6 ($b = 3369$, $p < .001$) and TNF-α ($b = 3684$, $p < .001$) than women.

Growth factors

For PlGF a significant main effect of condition ($F(1, 36) = 7.38$, $p = .010$) was found. At 22 h post wound induction the WLC group exhibited higher levels of PlGF relative to the mindfulness group ($b = 7.74$, $p = .010$) (see Figure 2). A significant condition x sex interaction was observed for VEGF ($F(1, 37.6) = 15.5$, $p < .001$) and sFlt-1 ($F(1, 36.7) = 15.6$, $p < .001$). Simple effect analyses showed that the effect of condition was only significant for men 22 h after injury (VEGF: $b = 2617$, $p < .001$; sFlt-1: $b = 4002$, $p < .001$) with participants in the mindfulness condition displaying lower levels of both VEGF and sFlt-1 than participants in the WLC condition.

Post hoc analyses

Because not everyone profited from the MBSR intervention to the same degree, we examined post hoc whether the increase in mindfulness levels after the intervention was related to TEWL, wound surface area, cytokine and growth factor levels. Similar multilevel models were built with the increase in mindfulness (diffKIMS) as predictor instead of condition. For TEWL, a significant time x diffKIMS interaction was found ($F(5, 399) = 10.45$, $p < .001$). The effect of diffKIMS on day 3 ($b = -1.86$, $p < .001$) and day 4 after wound induction ($b = -2.11$, $p < .001$) was significant, showing that larger increases in mindfulness were related to greater decreases in TEWL, irrespective of sex (see Figure 3). When the analysis was repeated for women only, this also revealed a significant time x diffKIMS interaction ($F(5, 331.5) = 6.36$, $p < .001$). The effect of diffKIMS was significant at day 3 ($b = -1.46$, $p = 0.004$) and at day 4 after injury ($b = -2.45$, $p < .001$). For wound

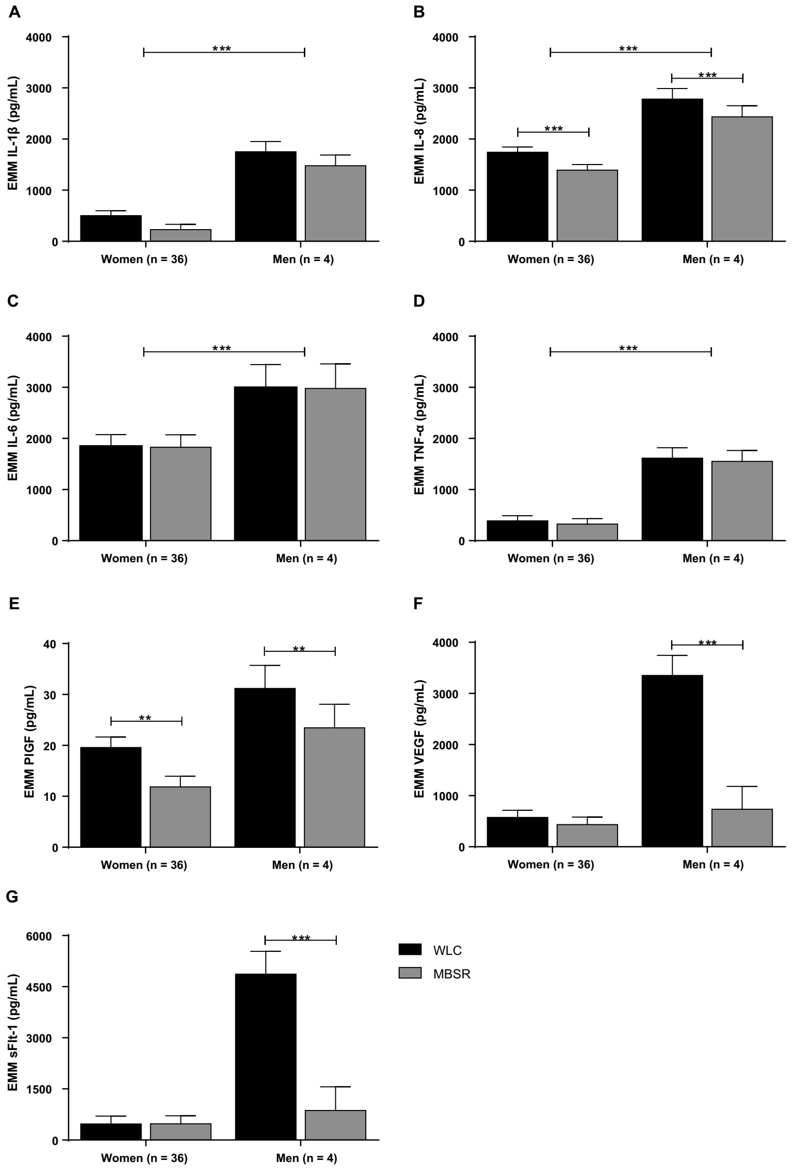

Figure 2. Estimated marginal means and standard error of means for IL-1β (A), IL-8 (B), IL-6 (C), TNF-α (D), PlGF (E), VEGF (F), and sFlt-1 (G) at 22 h post wound induction. *WLC = waiting-list control group; MBSR = Mindfulness-Based Stress Reduction group; EMM = estimated marginal means; IL = interleukin; TNF-α = tumor necrosis factor α; PlGF = placental growth factor; VEGF = vascular endothelial growth factor; sFlt-1 = soluble Fms-like tyrosine kinase-1. ** $p \leq .01$; *** $p \leq .001$.*

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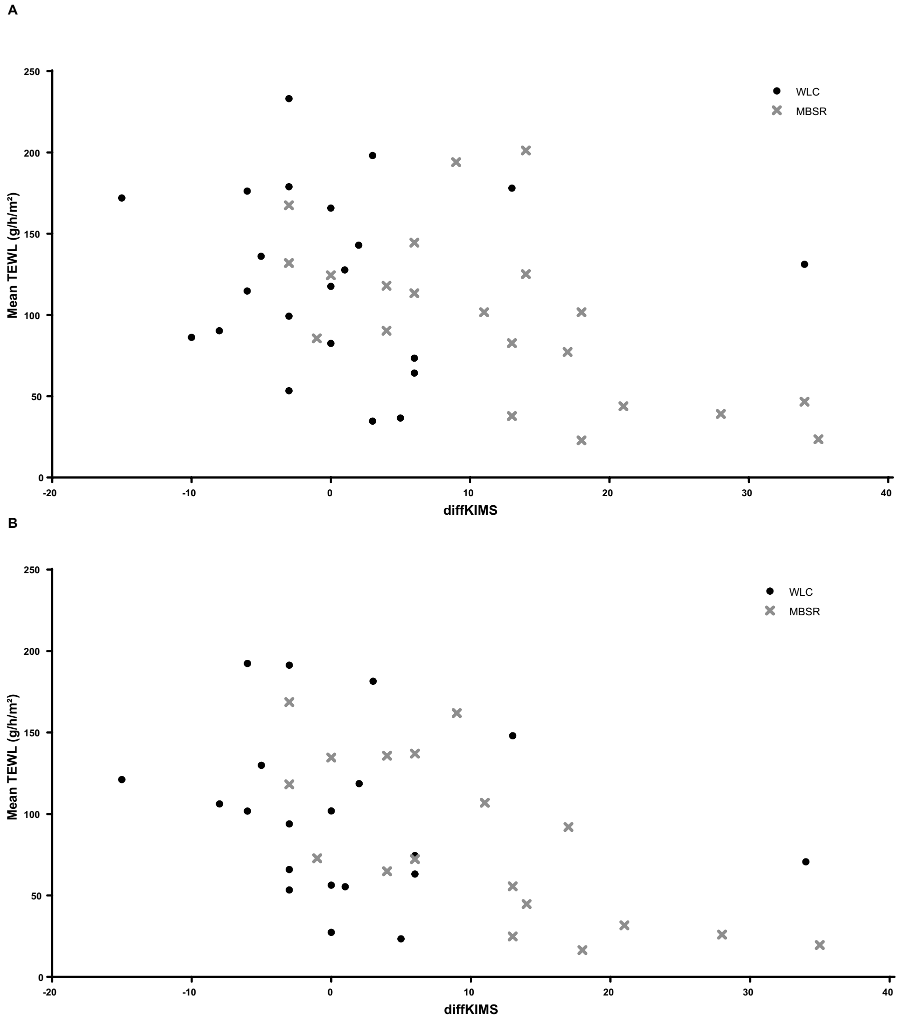

Figure 3. Scatterplots displaying the relationship between mean trans-epidermal water loss scores and diffKIMS for the WLC and MBSR group at day 3 (A) and day 4 (B) post wound induction. *WLC = waiting-list control group; MBSR = Mindfulness-Based Stress Reduction group; TEWL = trans-epidermal water loss; diffKIMS = amount of increase in mindfulness levels after the MBSR intervention.*

surface area, a significant time x diffKIMS x sex interaction was found (*F*(5, 1589) = 4.80, *p* < .001). However, simple effect analyses per time point did not reveal any significant diffKIMS effects for men or women. The post hoc analyses also indicated significant time x diffKIMS interactions for IL-1β (*F*(2, 252) = 5.34, *p* = .005) and IL-8 (*F*(2, 254) = 7.31, *p* = .001). Larger increases in mindfulness were associated with lower levels of IL-1β (*b* =

-46.0, $p < .001$) and IL-8 ($b = -51.7$, $p < .001$) at 22 h after wounding. The diffKIMS x sex interaction was significant for VEGF ($F(1, 38.1) = 9.19$, $p = .004$) and sFlt-1 ($F(1, 33.6) = 7.86$, $p = .008$), with higher levels of diffKIMS related to lower levels of VEGF ($b = -75.6$, $p = .001$) and sFlt-1 ($b = -118.6$, $p = .001$) in men at 22 h after wounding.

DISCUSSION

This study examined the effect of an 8-week MBSR intervention on wound healing. Because our analyses indicated an interaction of condition with sex, separate analyses for men and women were performed. Although for men significant effects on TEWL and wound size seemed to be present, we cannot reliably interpret these findings as only three men had received the MBSR intervention. For women, no differences in wound healing were found between participants in the MBSR and WLC condition; there were no effects on TEWL, and although a significant time x condition effect was found for wound surface area, none of the single time points significantly differed between the conditions. Thus, the hypothesis that receiving a MBSR training would lead to faster wound healing was not supported.

Since not everybody benefited to the same extent of the MBSR intervention, we examined, post hoc, whether the actual improvement in mindfulness was predictive for the speed of wound healing. This analysis showed that larger increases in mindfulness scores were related to greater decreases in TEWL, but not wound size, at day 3 and 4. Because men showed the largest increases in mindfulness after MBSR this may possibly have contributed to the fact that the condition effect on TEWL and wound size was found to be significant in men. Nevertheless, the association between the actual change in mindfulness and speed of wound healing was also apparent when analyses were repeated for women only. The finding that the participants who improved most in mindfulness skills benefitted most in terms of wound healing is consistent with a study demonstrating that the amount of practice completed by the participants in the MBSR condition determined its effect on a healing-related process. Specifically, Rosenkranz et al. (2013) found that total time practicing MBSR was negatively related to TNF-α level in skin blisters in response to psychological stress and capsaicin exposure. We did not measure practicing time but it could be hypothesized that those who practice most also gain the most benefit from the intervention.

This study adds to current knowledge by investigating the role of local pro-inflammatory cytokine and growth factor release as potential underlying mechanisms of improved wound healing. We found that compared to WLC participants, both men and women in the MBSR condition had lower levels of IL-8 and PlGF at the wound site 22 h after wounding. Post hoc analyses also showed that greater increases in mindfulness were related to larger decreases in IL-1β and IL-8 22 h after wounding. The finding that pro-inflammatory cytokine levels in wound fluid are lower in participants in the MBSR condition is consistent with the results of one earlier study on the effect of MBSR on local cytokine expression (Rosenkranz et al., 2013). However, the result is contrary to studies that found that cytokine levels were suppressed by stress (Broadbent et al., 2003; Glaser et al., 1999; Kiecolt-Glaser et al., 2005). It is probably an oversimplification to assume that an increased inflammatory response in the early phase of healing is always beneficial. For example, elevated inflammatory responses can actually impede healing, as illustrated by the finding of heightened cytokine levels in chronic wounds (Beidler et al., 2009). An adequate balance between pro- and anti-inflammatory forces is quintessential for optimal wound healing (e.g., Eming et al., 2007). Whether increases or decreases in cytokines are beneficial, may among other issues, depend on the base level within a certain individual. It should be borne in mind that we studied a healthy sample, not specifically selected for elevated stress level, and/or compromised wound healing. In these participants decreased local cytokine production might be adaptive, especially in case of small blister wounds, as a greater inflammatory response may impede the subsequent proliferation and remodeling phase and thereby the overall healing process (Mustoe et al., 2006). Further, since only limited tissue destruction is present in suction wounds and microbial contamination is minimal, there may be little need for a pro-inflammatory response. Future research would therefore benefit from examining subjects selected for elevated stress levels to investigate whether MBSR could diminish stress-induced delays in wound healing.

Growth factors, such as VEGF and PlGF, play an essential role in wound healing by performing multiple functions such as stimulating angiogenesis and the proliferation of fibroblasts and endothelial cells. Growth factors are expressed at low levels in the skin, but start to increase at about one day after injury (Johnson & Wilgus, 2014). VEGF and PlGF levels were clearly detectable 22 h after blistering. Contrary to expectations, MBSR was associated with lower levels of PlGF in wound fluid after 22 h. This finding is puzzling given previous research showing the importance of an up-regulation of PlGF for wound angiogenesis and thereby tissue repair. For instance, a deficiency in angiogenesis has been demonstrated to cause compromised wound healing in PlGF knock-out mice (Carmeliet et al., 2001). The functional significance of growth factors depends on the availability of receptors which they can bind to. The VEGF receptor family consists of three types of which one is important for wound healing and also binds PlGF: Fms-like tyrosine kinase-1 (Flt-1). There exist two forms of this receptor, namely one functional full length receptor (Flt-1) and a soluble decoy receptor (sFlt-1) that suppresses both VEGF and PlGF activity upon binding. The balance between the availability of the full length and the soluble receptor determines the net effect of VEGF and PlGF on wound healing (Shibuya, 2015). Although we measured the level of sFlt-1, we did not assess availability of Flt-1, making it difficult to draw conclusions about the effects of decreases in PlGF on wound healing. It therefore remains unclear what the exact role of PlGF is as a potential mediator of MBSR on wound healing.

Some limitations of this study should be mentioned. First, only few male participants were included and the numbers were even smaller for cytokine and growth factor data due to missing data. Further, although we did not include a measure of perceived stress, we did assess rumination at pre- and post-intervention and found that MBSR significantly reduced rumination levels in men. Men also scored highest on rumination before the intervention. When taking rumination as a proxy for stress susceptibility, MBSR seemed to have benefited participants most in need of stress reduction. Indeed, post hoc examination revealed that larger decreases in rumination from pre- to post-intervention were associated with greater decreases in TEWL at day 3 and 4 in men. In addition, in the overall sample the effect of condition on TEWL was mediated by rumination (data not shown). Possibly, when selecting participants for high stress and rumination levels, we may observe an overall MBSR effect on wound healing. Therefore, research is warranted to further elucidate whether the effect of MBSR is mediated by reduced stress levels. Another limitation was that it was not possible to monitor wound size and TEWL from the moment of wound induction onwards, due to the attached well plate that was used for collecting wound fluid. It would have been valuable to examine healing from the moment of wound induction onwards to study early stages of healing. Additionally, although interrater reliability was excellent, assessment of wound surface area using digital images is not without problems. Determining the margin of the wounds is sometimes difficult, especially during later days when scabs start to develop. Moreover, photography only assesses healing at the surface level, whereas areas deep within the wound are equally important for the healing process (Dyson et al., 2003). However, TEWL was our primary outcome and there was good concordance between these assessments. Lastly, the experimental wounds were small and future research into the clinical effects of MBSR on wound healing would benefit from examining various degrees of surgical and chronic wounds.

To conclude, the current outcomes provide preliminary evidence that MBSR can affect the early stages of wound healing. To our knowledge, this study was the first to examine the effects of a psychological intervention on the levels of growth factors in wound fluid and should therefore be replicated and extended to other relevant factors.

Future research into the exact mechanisms underlying improved wound healing by psychological factors is highly warranted.

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Compliance with ethical standards

Conflict of interest

Astrid Meesters, Yvo M. C. In den BoschMeevissen, Chantal A. H. Weijzen, Wim A. Buurman, Mario Losen, Jan Schepers, Monique R. T. M. Thissen, Hugo J. E. M. Alberts, Casper G. Schalkwijk, and Madelon L. Peters declare that they have no conflict of interest.

Human and animal rights and Informed consent

All procedures followed were in accordance with ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

REFERENCES

Altemus, M., Rao, B., Dhabhar, F. S., Ding, W., & Granstein, R. D. (2001). Stress-induced changes in skin barrier function in healthy women. *Journal of Investigative Dermatology, 117*(2), 309-317. https://doi.org/10.1046/j.1523-1747.2001.01373.x

Baer, R. A., Smith, G. T., & Allen, K. B. (2004). Assessment of mindfulness by self-report: the Kentucky inventory of mindfulness skills. *Assessment, 11*(3), 191-206. https://doi.org/10.1177/1073191104268029

Beidler, S. K., Douillet, C. D., Berndt, D. F., Keagy, B. A., Rich, P. B., & Marston, W. A. (2009). Inflammatory cytokine levels in chronic venous insufficiency ulcer tissue before and after compression therapy. *Journal of Vascular Surgery, 49*(4), 1013-1020. https://doi.org/10.1016/j.jvs.2008.11.049

Bosch, J. A., Engeland, C. G., Cacioppo, J. T., & Marucha, P. T. (2007). Depressive symptoms predict mucosal wound healing. *Psychosomatic Medicine, 69*(7), 597-605. https://doi.org/10.1097/PSY.0b013e318148c682

Broadbent, E., Kahokehr, A., Booth, R. J., Thomas, J., Windsor, J. A., Buchanan, C. M., Wheeler, B. R., Sammour, T., & Hill, A. G. (2012). A brief relaxation intervention reduces stress and improves surgical wound healing response: a randomised trial. *Brain, Behavior, and Immunity, 26*(2), 212-217. https://doi.org/10.1016/j.bbi.2011.06.014

Broadbent, E., & Koschwanez, H. E. (2012). The psychology of wound healing. *Current Opinion in Psychiatry, 25*(2), 135-140. https://doi.org/10.1097/YCO.0b013e32834e1424

Broadbent, E., Petrie, K. J., Alley, P. G., & Booth, R. J. (2003). Psychological stress impairs early wound repair following surgery. *Psychosomatic Medicine, 65*(5), 865-869. https://doi.org/10.1097/01.PSY.0000088589.92699.30

Brown, K. W., & Ryan, R. M. (2003). The benefits of being present: mindfulness and its role in psychological well-being. *J Pers Soc Psychol, 84*(4), 822-848.

Carmeliet, P., Moons, L., Luttun, A., Vincenti, V., Compernolle, V., De Mol, M., Wu, Y., Bono, F., Devy, L., Beck, H., Scholz, D., Acker, T., DiPalma, T., Dewerchin, M., Noel, A., Stalmans, I., Barra, A., Blacher, S., VandenDriessche, T., Ponten, A., Eriksson, U., Plate, K. H., Foidart, J., Schaper, W., Charnock-Jones, D. S., Hicklin, D. J., Herbert, J., Collen, D., & Persico, M. G. (2001). Synergism between vascular endothelial growth factor and placental growth factor contributes to angiogenesis and plasma extravasation in pathological conditions. *Nature Medicine, 7*(5), 575-583. https://doi.org/10.1038/87904

Christian, L. M., Graham, J. E., Padgett, D. A., Glaser, R., & Kiecolt-Glaser, J. K. (2006). Stress and wound healing. *Neuroimmunomodulation, 13*(5-6), 337-346. https://doi.org/10.1159/000104862

Cole-King, A., & Harding, K. G. (2001). Psychological factors and delayed healing in chronic wounds. *Psychosomatic Medicine, 63*(2), 216-220. https://doi.org/10.1097/00006842-200103000-00004

DeRijk, R., Michelson, D., Karp, B., Petrides, J., Galliven, E., Deuster, P., Paciotti, G., Gold, P. W., & Sternberg, E. M. (1997). Exercise and circadian rhythm-induced variations in plasma cortisol differentially regulate interleukin-1 beta (IL-1 beta), IL-6, and tumor necrosis factor-alpha (TNF alpha) production in humans: high sensitivity of TNF alpha and resistance of IL-6. *Journal of Clinical Endocrinology and Metabolism, 82*(7), 2182-2191. https://doi.org/10.1210/jcem.82.7.4041

Dyson, M., Moodley, S., Verjee, L., Verling, W., Weinman, J., & Wilson, P. (2003). Wound healing assessment using 20 MHz ultrasound and photography. *Skin Research and Technology, 9*(2), 116-121. https://doi.org/10.1034/j.1600-0846.2003.00020.x

Ebrecht, M., Hextall, J., Kirtley, L. G., Taylor, A., Dyson, M., & Weinman, J. (2004). Perceived stress and cortisol levels predict speed of wound healing in healthy male adults. *Psychoneuroendocrinology, 29*(6), 798-809. https://doi.org/10.1016/s0306-4530(03)00144-6

Eming, S. A., Krieg, T., & Davidson, J. M. (2007). Inflammation in wound repair: molecular and cellular mechanisms. *Journal of Investigative Dermatology, 127*(3), 514-525. https://doi.org/10.1038/sj.jid.5700701

Failla, C. M., Odorisio, T., Cianfarani, F., Schietroma, C., Puddu, P., & Zambruno, G. (2000). Placenta growth factor is induced in human keratinocytes during wound healing. *Journal of Investigative Dermatology, 115*(3), 388-395. https://doi.org/10.1046/j.1523-1747.2000.00085.x

Garg, A., Chren, M. M., Sands, L. P., Matsui, M. S., Marenus, K. D., Feingold, K. R., & Elias, P. M. (2001). Psychological stress perturbs epidermal permeability barrier homeostasis: implications for the pathogenesis of stress-associated skin disorders. *Archives of Dermatology, 137*(1), 53-59. https://doi.org/10.1001/archderm.137.1.53.

Gilliver, S. C., Ashworth, J. J., & Ashcroft, G. S. (2007). The hormonal regulation of cutaneous wound healing. *Clinics in Dermatology, 25*(1), 56-62. https://doi.org/10.1016/j.clindermatol.2006.09.012

Glaser, R., Kiecolt-Glaser, J. K., Marucha, P. T., MacCallum, R. C., Laskowski, B. F., & Malarkey, W. B. (1999). Stress-related changes in proinflammatory cytokine production in wounds. *Archives of General Psychiatry, 56*(5), 450-456. https://doi.org/10.1001/archpsyc.56.5.450

Gouin, J. P., & Kiecolt-Glaser, J. K. (2011). The impact of psychological stress on wound healing: methods and mechanisms. *Immunology and Allergy Clinics of North America, 31*(1), 81-93. https://doi.org/10.1016/j.iac.2010.09.010

House, S. L. (2015). Psychological distress and its impact on wound healing: an integrative review. *Journal of Wound, Ostomy and Continence Nursing, 42*(1), 38-41. https://doi.org/10.1097/won.0000000000000080

Johnson, K. E., & Wilgus, T. A. (2014). Vascular Endothelial Growth Factor and Angiogenesis in the Regulation of Cutaneous Wound Repair. *Advances in Wound Care, 3*(10), 647-661. https://doi.org/10.1089/wound.2013.0517

Kabat-Zinn, J. (1982). An outpatient program in behavioral medicine for chronic pain patients based on the practice of mindfulness meditation: theoretical considerations and preliminary results. *Gen Hosp Psychiatry, 4*(1), 33-47.

Kabat-Zinn, J. (1990). *Full Catastrophe Living.* Delacorte.

Khoury, B., Sharma, M., Rush, S. E., & Fournier, C. (2015). Mindfulness-based stress reduction for healthy individuals: A meta-analysis. *Journal of Psychosomatic Research, 78*(6), 519-528. https://doi.org/10.1016/j.jpsychores.2015.03.009

Kiecolt-Glaser, J. K., Loving, T. J., Stowell, J. R., Malarkey, W. B., Lemeshow, S., Dickinson, S. L., & Glaser, R. (2005). Hostile marital interactions, proinflammatory cytokine production, and wound healing. *Archives of General Psychiatry, 62*(12), 1377-1384. https://doi.org/10.1001/archpsyc.62.12.1377

Koschwanez, H. E., Kerse, N., Darragh, M., Jarrett, P., Booth, R. J., & Broadbent, E. (2013). Expressive writing and wound healing in older adults: a randomized controlled trial. *Psychosomatic Medicine, 75*(6), 581-590. https://doi.org/10.1097/PSY.0b013e31829b7b2e

Lowry, S. F. (1993). Cytokine mediators of immunity and inflammation. *Archives of Surgery, 128*(11), 1235-1241. https://doi.org/10.1001/archsurg.1993.01420230063010

Maple, H., Chilcot, J., Lee, V., Simmonds, S., Weinman, J., & Mamode, N. (2015). Stress predicts the trajectory of wound healing in living kidney donors as measured by high-resolution ultrasound. *Brain, Behavior, and Immunity, 43*, 19-26. https://doi.org/10.1016/j.bbi.2014.06.012

Mustoe, T. A., O'Shaughnessy, K., & Kloeters, O. (2006). Chronic wound pathogenesis and current treatment strategies: a unifying hypothesis. *Plastic and Reconstructive Surgery, 117*(7 Suppl), 35S-41S. https://doi.org/10.1097/01.prs.0000225431.63010.1b

Nauck, M., Karakiulakis, G., Perruchoud, A. P., Papakonstantinou, E., & Roth, M. (1998). Corticosteroids inhibit the expression of the vascular endothelial growth factor gene in human vascular smooth muscle cells. *European Journal of Pharmacology, 341*(2), 309-315. https://doi.org/10.1016/S0014-2999(97)01464-7

Pyter, L. M., Yang, L., da Rocha, J. M., & Engeland, C. G. (2014). The effects of social isolation on wound healing mechanisms in female mice. *Physiology and Behavior, 127*, 64-70. https://doi.org/10.1016/j.physbeh.2014.01.008

Robinson, H., Jarrett, P., & Broadbent, E. (2015). The Effects of Relaxation Before or After Skin Damage on Skin Barrier Recovery: A Preliminary Study. *Psychosomatic Medicine, 77*(8), 844-852. https://doi.org/10.1097/psy.0000000000000222

Robinson, H., Jarrett, P., Vedhara, K., & Broadbent, E. (2016). The effects of expressive writing before or after punch biopsy on wound healing. *Brain, Behavior, and Immunity*. https://doi.org/10.1016/j.bbi.2016.11.025

Rosenkranz, M. A., Davidson, R. J., Maccoon, D. G., Sheridan, J. F., Kalin, N. H., & Lutz, A. (2013). A comparison of mindfulness-based stress reduction and an active control in modulation of neurogenic inflammation. *Brain, Behavior, and Immunity, 27*(1), 174-184. https://doi.org/10.1016/j.bbi.2012.10.013

Scheier, M. F., Carver, C. S., & Bridges, M. W. (1994). Distinguishing optimism from neuroticism (and trait anxiety, self-mastery, and self-esteem): a reevaluation of the Life Orientation Test. *J Pers Soc Psychol, 67*(6), 1063-1078. https://doi.org/10.1037//0022-3514.67.6.1063

Segal, Z. V., Williams, J. M. G., & Teasdale, J. D. (2002). *Mindfulness-based Cognitive Therapy for Depression*. Guilford Press.

Shibuya, M. (2015). VEGF-VEGFR System as a Target for Suppressing Inflammation and other Diseases. *Endocrine, Metabolic & Immune Disorders Drug Targets, 15*(2), 135-144. https://doi.org/10.2174/1871530315666150316121956#sthash.LwXMiAy4.dpuf

Trapnell, P. D., & Campbell, J. D. (1999). Private self-consciousness and the five-factor model of personality: distinguishing rumination from reflection. *Journal of Personality and Social Psychology, 76*(2), 284-304. https://doi.org/10.1037/0022-3514.76.2.284

Walburn, J., Vedhara, K., Hankins, M., Rixon, L., & Weinman, J. (2009). Psychological stress and wound healing in humans: a systematic review and meta-analysis. *J Psychosom Res, 67*(3), 253-271. https://doi.org/10.1016/j.jpsychores.2009.04.002

Weinman, J., Ebrecht, M., Scott, S., Walburn, J., & Dyson, M. (2008). Enhanced wound healing after emotional disclosure intervention. *British Journal of Health Psychology, 13*(Pt 1), 95-102. https://doi.org/10.1348/135910707x251207

Werner, S., & Grose, R. (2003). Regulation of wound healing by growth factors and cytokines. *Physiol Rev, 83*(3), 835-870. https://doi.org/10.1152/physrev.2003.83.3.835

Zimmerli, W., & Gallin, J. I. (1987). Monocytes accumulate on Rebuck skin window coverslips but not in skin chamber fluid. A comparative evaluation of two in vivo migration models. *Journal of Immunological Methods, 96*(1), 11-17. https://doi.org/10.1016/0022-1759(87)90361-9

CHAPTER 6

General discussion

GENERAL DISCUSSION

The sensation of pain serves a crucial protective role, as it warns the body about potential physical harm or illness. However, when acute pain develops into chronic pain, it loses its adaptive function and becomes detrimental. Various psychosocial factors influence pain perception and the transition from acute to chronic pain. When we study protective factors next to risk factors, we can come to a comprehensive theoretical framework for the understanding of pain experience and chronicity.

The main aim of this dissertation was to examine psychological flexibility and mindfulness in relation to the experience of pain, and to the recovery of pain and wounds. Concretely, a series of experimental studies was set up to examine the protective value of two specific types of flexibility (i.e., emotional and cognitive flexibility) and mindfulness on increased pain experience and slow recovery. After a general introduction in **chapter 1**, we investigated whether flexible emotional responsiveness and affective flexibility – both aspects of emotional flexibility – predict tolerance for, and recovery from, experimentally induced pain (**chapter 2**). Second, the additive value of affective flexibility in explaining the experience of pain beyond that of general cognitive flexibility was tested in **chapter 3**. Third, in **chapter 4** and **5** we studied the effect of mindfulness on the experience of pain and its contribution to recovery. More specifically, we examined whether the effect of mindfulness on recovery was mediated by 1) affective and/or cognitive flexibility (**chapter 4**), and by 2) physiological wound healing processes (**chapter 5**). This final **chapter 6** provides a summary of the main findings of the studies as part of this dissertation, followed by a discussion of these findings. Future research recommendations are proposed throughout the chapter. Lastly, implications and methodological issues are described.

SUMMARY OF THE MAIN FINDINGS

Flexibility, pain, and recovery

Being flexible reflects the capacity to adjust or respond to a changing environment (Block & Block, 1980; Kashdan & Rottenberg, 2010), with higher levels of psychological flexibility predicting psychological well-being (e.g., Al-Jabari, 2012; Pyszkowska & Rönnlund, 2021; Ramaci et al., 2019). The majority of studies on flexibility has primarily focused on behavioral and cognitive flexibility, rather than focusing on emotional flexibility. In the field of pain, a link between psychological flexibility and chronic and experimentally induced acute pain has been put forward (Feinstein et al., 2011; Feldner et al., 2006; McCracken, 1998; McCracken & Velleman, 2010; Talaei-Khoei et al., 2017), yet at the start of this dissertation no studies were available on emotional flexibility and pain responses. In an attempt to address this gap, we adopted two operationalizations of emotional flexibility, either tapping into flexible emotional responsiveness or affective flexibility, and examined their associations with the experience of experimentally induced pain (pain threshold, pain tolerance, and retrospective pain intensity, pain unpleasantness and fear of pain ratings) and recovery from pain (pain intensity and pain unpleasantness ratings) (**chapter 2** and **chapter 3**).

In **chapter 2**, participants were subjected to an ischemic pain task and three pain outcomes were assessed, namely pain tolerance and recovery in terms of pain intensity and pain unpleasantness ratings. To measure aspects of emotional flexibility, both flexible emotional responsiveness and affective flexibility were assessed using computer tasks. Findings demonstrated a link between emotional flexibility and recovery from pain. More precisely, results showed that participants who exhibited higher levels of flexible emotional responding reflected in more distinct facial expressions (i.e., corrugator muscle activity, responsible for frowning) in response to changing positive and negative stimuli, were more likely to recover faster in terms of pain unpleasantness ratings. This study also found evidence in support of a link between more flexibility in switching between affective contexts and faster recovery from pain. More specifically, individuals who were better able to switch from processing neutral to affective information when the stimulus was positive were more likely to recover faster from pain in terms of pain intensity ratings. Contrary to our expectations, results indicated that none of the emotional flexibility measures were related to pain tolerance. These findings shed light on emotional flexibility as possible explanatory factor for individual differences in recovery from pain.

As our first study did not contain a non-affective measure of general cognitive flexibility, we aimed to examine the additive value of affective flexibility in explaining the experience of pain above and beyond that of cognitive flexibility (**chapter 3**). To this end, affective and cognitive flexibility were measured using two task-switching paradigms with either emotional (positive and negative pictures) or neutral stimuli (numbers ranging from 1 to 9, excluding 5), correspondingly. At the same time, this second study allowed methodological modifications, such as the inclusion of a pain threshold measurement by the use of thermal heat as pain stimulus, and the confinement of a ceiling effect in the pain tolerance measurement observed in the first study (i.e., 30% of the participants did not reach pain tolerance before the maximum duration of the ischemic pain task). Heat pain stimuli were administered to determine pain threshold, pain tolerance, and retrospective pain experience. In disagreement with our hypotheses, no associations were found between affective and/or cognitive flexibility, and pain sensitivity.

Mindfulness, pain, and recovery

A considerable amount of research has indicated the beneficial effects of mindfulness on pain and recovery (Chavez et al., 2020; Chiesa & Serretti, 2011; Dowsey et al., 2019; Garland et al., 2019; Ratcliff, 2015; Veehof et al., 2016). However, the underlying mechanisms of mindfulness remain largely unknown. Therefore, we investigated the effect of mindfulness on pain tolerance and recovery (pain intensity ratings, pain unpleasantness ratings, and recovery speed of skin wounds) and whether this effect was mediated by flexibility (affective and cognitive flexibility), and/or by physiological wound healing processes (**chapter 4** and **5**).

In **chapter 4**, we studied whether mindfulness could improve pain experience and recovery, and whether improvements in affective and/or cognitive flexibility could account for such effects. The study consisted of two lab sessions separated by one week during which participants in the mindfulness condition completed brief daily mindfulness assignments. Pre- and post-measures were affective and cognitive flexibility, both measured using task-switching paradigms, and the experience of and recovery from experimentally induced pain (ischemic pain task). It was hypothesized that participants in the mindfulness condition would exhibit a higher pain tolerance and reduced subjective stress ratings than participants in the wait-list control (WLC) condition. Also, faster recovery in terms of pain intensity and pain unpleasantness ratings was expected in participants in the mindfulness condition. In addition, mindfulness was predicted to improve both cognitive and affective flexibility, and their mediating role in the effect of mindfulness on pain outcomes was explored. We did not find support for any of our hypotheses. That is, findings showed that mindfulness was successfully induced, yet, no effect was observed on pain tolerance, subjective stress ratings, and recovery of pain intensity and pain unpleasantness ratings, nor on cognitive and affective flexibility.

Similar to chapter 4, the study presented in **chapter 5** examined the effects of mindfulness on recovery, only this time we focused on the recovery speed of skin wounds and examined physiological wound healing processes as potential underlying mechanisms. In this study, participants were randomly assigned to an 8-week Mindfulness-Based Stress Reduction (MBSR) or a WLC group. Standardized skin blisters were induced on the forearm using a suction method and trans-epidermal water loss (TEWL), and wound size were determined once daily at day 3, 4, 5, 6, 7, and 10 after wounding. To study potential underlying mechanisms of healing, cytokines (i.e., interleukin (IL)-1β, IL-6, IL-8 and tumor necrosis factor (TNF)-α), growth factors (i.e., vascular endothelial growth factor (VEGF) and placental growth factor (PlGF)) and the soluble Fms-like tyrosine kinase-1 receptor were measured in wound exudates taken at 3, 6, and 22 h after injury. We hypothesized a faster decrease in TEWL and wound size over the course of 10 days in the MBSR group as compared to the WLC group. Results showed no evidence for the hypothesis that MBSR would improve the healing speed of skin wounds. However, post hoc analyses showed that greater improvements in mindfulness were related to larger reductions in TEWL at day 3 and 4. Further, results showed that MBSR participants exhibited lower levels of IL-8 and PlGF in wound fluid after 22 h as compared to WLC participants. Post hoc findings demonstrated that larger improvements in mindfulness were associated to greater decreases in IL-1β and IL-8 22 h after blistering. Whether an increase or decrease in pro-inflammatory cytokines in the early phase of healing is beneficial remains elusive, given inconsistent results of previous studies (e.g., Broadbent et al., 2003; Glaser et al., 1999; Kiecolt-Glaser et al., 2005; Rosenkranz et al., 2013). To sum up, this study provided preliminary evidence of the influence of MBSR on early stages of wound healing, and of local pro-inflammatory cytokine and growth factor levels in wound fluid as mediators of recovery.

GENERAL DISCUSSION AND DIRECTIONS FOR FUTURE RESEARCH

Studying experimental pain and recovery

Experimental pain can be induced by the application of noxious stimuli of different modalities, such as ischemic, electrical, thermal (i.e., heat and cold), and chemical stimulation (Reddy et al., 2012). An important difference between the study presented in **chapter 3**, and the studies discussed in **chapter 2** and **4** is the way in which pain was experimentally induced. Not only did we use two different types of painful stimuli across studies (ischemic vs. thermal heat), also the length of painful stimulation differed (tonic vs. phasic). In **chapter 2** and **4**, ischemic pain was induced using the Submaximum Effort Tourniquet Technique (SETT), whereby long tonic painful stimulation was applied (Smith et al., 1966). In **chapter 3**, on the other hand, we administered thermal heat stimuli, thereby inducing a short phasic type of pain. Tonic pain stimuli resemble pain of pathologic origin in terms of duration and severity more closely than phasic pain stimuli (Moore et al., 1979; Sinke et al., 2015). Based on the finding of a moderate to strong positive relationship between total SETT duration and the length of the recovery period in both studies (**chapter 2** and **4**), one may speculate that longer painful stimulation is accompanied by longer recovery periods, making longer tonic pain procedures such as the SETT appropriate for measuring subsequent recovery. In addition, the duration of painful stimulation (long/tonic vs. short/phasic) may be associated to a different need for coping. In other words, painful stimulation of long duration may call for more coping than pain of short duration. A direction for future research is to study whether the modality and temporal characteristics of the painful stimulus have an effect on the relationship between flexibility and pain experience and recovery.

In **chapter 2** and **4**, recovery from pain was measured on the basis of subjective pain intensity and pain unpleasantness ratings. In **chapter 5**, the focus was on physiological recovery, which we measured as the healing speed of skin blisters in terms of TEWL and wound size. Faster healing of physical injuries or surgical incisions might imply faster recovery of the pain and restoration of functional capacities, as injury and pain are two strongly interrelated processes. In response to injury and pain, pro- and anti-inflammatory cytokines are produced by various types of cells local to the injury, as well as in the dorsal horn of the spinal cord and brain (Swift, 2018). After injury, the pro-inflammatory cytokines TNF-α and IL-1β promote the production of pain neurotransmitters in the spinal cord, and simultaneously inhibit the activity of pain suppressive cells thereby amplifying pain (Swift, 2018). As tissue repair progresses, the painful sensation ebbs away, unless acute pain transitions into chronic pain. Therefore, studying physiological recovery in terms of wound healing is a valuable addition to the study of pain in order to come to a comprehensive model for the understanding of pain experience and (non-)recovery.

The definition and assessment of emotional flexibility

Effective adjustment to alternating emotional events requires emotional flexibility, here conceptualized as the ability to regulate emotions flexibly and well matched to situational demands, including the flexible selection of emotion regulation strategies (Aldao et al., 2015; Westphal et al., 2010). As such, emotional flexibility not only entails flexible emotional responding to fluctuating positive and negative events, but also implies appropriate recovery from the primary emotional response in case of changing contexts (Beshai et al., 2018). Context sensitivity is one of the core characteristics of emotional flexibility (Coifman & Summers, 2019). Emotional flexibility is considered adaptive when it increases the opportunity to attain personal relevant goals (Aldao et al., 2015). Because of the multi-faceted nature of emotional flexibility, various methodological approaches are available regarding its assessment, ranging from simple self-report measures to complex task-based paradigms. In this dissertation, we opted for two distinct operationalizations of emotional flexibility, namely flexible emotional responsiveness and affective flexibility.

Flexible emotional responsiveness

In **chapter 2**, we utilized a task measuring flexible emotional responsiveness to changing positive and negative pictures across multiple modalities, including self-reported affect, facial expressions using electromyography (EMG) over the zygomatic major and the corrugator supercilii muscles, and defensive motivation as indexed by eye blink startle amplitude. In brief, trials consisted of three pictures of the same valence shown in succession. During the presentation of the second picture of a trial, acoustic startle probes were administered on a random 60% of the trials. Participants rated their current affect continuously throughout the entire task using a rating dial and received the instructions to turn the rating dial as often as their feelings changed throughout the task. Affect ratings in response to the first picture of each series were registered for further analyses. In addition, facial muscle activity was continuously assessed using EMG over the zygomatic major (an index of positive emotions) and the corrugator supercilii muscles (an index of negative emotions), and startle responses were recorded over the orbicularis oculi. In this task, greater differential responses to positive versus negative stimuli across multiple modalities are considered to be an index of the distinct brief responses that are characteristic for emotional flexibility (Papousek et al., 2012). In other words, greater difference scores reflect larger responses that are congruent to picture valence (e.g., higher zygomatic activity in response to positive trials, higher corrugator activity in response to negative trials), and therewith reflect greater flexible emotional responsiveness.

An advantage of context-sensitive paradigms such as this task is that participants are not instructed to regulate their emotional responses using specific strategies so that responses are spontaneous, implicit and deliberate, reflecting a complex multi-faceted perspective of emotional flexibility (Coifman & Summers, 2019). Both explicit (i.e., self-reported affect) and more implicit (i.e., psychophysiological responses) measures of emotional responses are assessed in this task. Although we found significant differences between responses to positive versus negative trials in zygomatic, corrugator and startle responses, results did not show this for affect ratings. A possible explanation for the lack of such a difference may be that participants did not comply with the task instruction to provide a rating for each individual picture shown in the task. Participants were found to only turn the rating dial on a small percentage of the trials and indicated to have experienced the task as relatively boring and long in duration. Alternatively, participants may have found it difficult to assign these ratings explicitly. However, the exact reason behind the lack of distinct self-reported affective responses remains unclear, and the absence of such relation is not in accordance with Waugh et al. (2011) who reported that participants rated their affect during current positive picture trials as more positive as compared to current negative picture trials. Nevertheless, and in line with Waugh et al. (2011), we did find differential physiological responses to positive versus negative trials, demonstrating that these type of responses are more automatic and not sensitive to (a lack of) motivation and other top-down processes.

Affective flexibility

Switching between stimuli varying in emotional valence is inherent to daily life. In **chapter 2**, **3** and **4**, an affective switching task was employed assessing the ability of task switching in an affective context (Genet et al., 2013). While following the set-up of the classical task switching paradigm for the assessment of affectively neutral switch costs (i.e., cognitive flexibility), the affective task-switching paradigm requires participants to switch attention between affective and non-affective features of emotional stimuli. In brief, participants viewed positively and negatively valanced pictures and categorized these according to either an affective rule (determining whether the picture content is positive or negative) or a neutral rule (determining whether the picture contains one or none, or two or more humans). Reaction times (RTs) were registered and trials were either switch (trial on which the sorting rule changes) or repeat (trials on which the same sorting rule is repeated). Note that the valence of the pictures never changed in the switch trials, it was only the categorization rule that alternated. Four types of switch costs were computer by subtracting RTs on repeat trials from RTs on switch trials, with lower switch costs (i.e., faster responses to switch trials) indicating greater affective flexibility. More specifically, switch costs were computed for 1) affective-to-neutral task sets separately for i) positive and ii) negative pictures, and 2) neutral-to-affective task sets separately for i) positive and ii) negative pictures. Hence, whereas the classical non-affective task-switching paradigms provide a non-affective measure for set shifting ability, the affective switching task allows to measure the ability of task switching in an affective context. A first study on the psychometric properties of an affective switching paradigm rather similar to our affective switching task demonstrated that response time-based affective switch costs exhibit excellent internal consistency and good test-retest reliability (Eckart et al., 2021). These first reliability results imply that affective switch costs are suitable for studying individual differences in affective flexibility. A drawback of this task is that it does not allow studying all possible types of switches, as it only allows the calculation of switch costs for switches from an affective (positive or negative) towards a neutral context and vice versa, while this is not possible for switches from positive towards negative contexts and vice versa. With the aim to solve this methodological limitation, Biro et al. (2021) recently developed an affective switching task that allows the computation of switch costs for direct switches between positive and negative pictures. It would be interesting to extend our line of research with this novel affective switching task to study how switches between positive and negative emotional valences relate to pain experience and recovery and whether the direction of the switch is of importance.

In addition to the paradigms implemented in this dissertation, various other methodological approaches exist capturing one or more aspects of emotional flexibility of which we would like to discuss a few. First, to the best of our knowledge, only one research team has developed a self-report measure for the direct assessment of emotional flexibility. Fu et al. (2018) designed the 10-item Emotional Flexibility Scale that assesses the capability to regulate positive and negative emotional responses flexibly to internal and external events. However, the scale has been developed for Chinese adolescents who have faced disasters such as earth quakes, thereby limiting its applicability in Western participant samples not having experienced disasters. A future research direction is to develop a self-report measure for emotional flexibility, as it would afford a simple measure that is brief and easier to administer and score than task-based paradigms, facilitating the study of associations with other psychological constructs in and outside controlled laboratory research environments.

Second, ecological momentary assessment (EMA), also known as experience-sampling technique, is a promising approach to the study of emotional flexibility, in which current emotional experiences are sampled in real time and across various contexts in the participant's natural environment (e.g., Feldman Barrett & Barrett, 2001). This technique is therefore characterized by high ecological validity (e.g., Shiffman et al., 2008). Another advantage of EMA is the reduced risk of memory bias (Coifman & Summers, 2019). EMA is particularly useful for studying flexible context-appropriate emotional responding. However, because EMA studies take place outside the laboratory, disadvantages of this method compared to studies that take place in the laboratory may lie in the fact that experimenters can exert less control (e.g., over specific emotional events taking place), as well as in potentially higher attrition rates (e.g., Feldman Barrett & Barrett, 2001).

General affective switching performance versus specific types of affective switch costs

Affective flexibility is a domain-specific instantiation of cognitive flexibility and conceptualized as the flexible processing of emotional information by switching attention between the affective and neutral information of the environment (Genet et al., 2013; Genet & Siemer, 2011; Malooly et al., 2013). Both cognitive and affective flexibility rely on executive functioning, which thereby creates conditions for flexibility (Miyake et al., 2000). As a result, impairments in executive functioning may be translated into deficits in general cognitive flexibility as well as affective flexibility, ultimately contributing to psychopathology and maladaptive pain responses in particular (e.g., Abbate-Daga et al., 2011; Sternheim et al., 2014). Given the emotional dimension of pain (e.g., Craig, 2003), we proposed affective flexibility to be an important explanatory factor in individual differences in the experience of, and recovery from pain. Affective flexibility in the context of pain is reflected in the ability to switch between the neutral, sensory aspects (e.g., location, type of pain, pain intensity) and the affective, evaluative aspects (e.g., unpleasantness) of the pain experience.

One general and four specific types of affective switch costs can be derived from the affective flexibility task. Although we only studied the different types of affective switch costs in relation to pain experience and recovery (**chapter 2**, **3** and **4**), one might advocate that examining the link between general affective switch cost and pain would have been worthwhile instead. The general affective switch cost does not take the direction of the switch being made (i.e., processing affective towards neutral aspects of emotional pictures and vice versa) into account, and therefore reflects a measure of general switching ability, i.e., general cognitive flexibility. However, the general affective switch cost does not equal cognitive switching ability, as the former takes place in an affective context. The moderate positive correlations between the general affective switch cost and cognitive switch cost found in **chapter 3** and **4** corroborate this. The studies presented in this dissertation found a consistent pattern of correlations between the different types of affective switch costs, ranging from weak to moderate (**chapter 2**, **3**, and **4**), thereby confirming previous study results (Genet et al., 2013; Grol & De Raedt, 2020, 2021; Malooly et al., 2013; Twivy et al., 2021; Wen & Yoon, 2019) indicating that the different types of affective switch costs tap into different components of affective flexibility. These studies showed different types of affective switch costs to be related to specific emotion regulation strategies (Genet et al., 2013; Grol & De Raedt, 2021; Malooly et al., 2013), vagally mediated heart rate variability (HRV; Grol & De Raedt, 2020), future anxiety and worry (Twivy et al., 2021), and depressive symptoms (Wen &

Yoon, 2019).

Malooly et al. (2013) were the first to use the affective switching task and showed that *less* efficient switches (decreased flexibility) away from processing the affective sorting rule towards the non-affective rule when the picture was negative were related to decreased use of reappraisal for the down-regulation of sad emotions in response to a sad movie clip. In later studies, less efficient switches of this specific type were also found related to increased use of rumination in daily life (Genet et al., 2013) and to higher levels of future depressive symptoms when affective flexibility was measured before a stressor (Wen & Yoon, 2019). Based on these findings, less efficient switching of attention from affective to non-affective information of negative pictures (i.e., difficulties in letting go of attention to affective aspects of negative pictures) seems to be associated with maladaptive outcomes. However, there are exceptions to this, as *more* efficient switches (greater flexibility) away from processing affective toward non-affective aspects of negative pictures (i.e., avoidance of affective aspects of negative pictures) was related to lower resting heart rate variability (Grol & De Raedt, 2020), and predicted more anxiety and worry over time (Twivy et al., 2021). The authors explained these findings in the light of the avoidance theory of worry and anxiety, positing that greater flexibility promotes attentional avoidance of negative information (Borkovec, 2004). This theory and scientific evidence suggest that anxious individuals exhibit attentional avoidance of negative information that is presented for longer durations (Borkovec, 2004; Cisler & Koster, 2010), here reflected by more efficient switching of attention from affective toward non-affective aspects of negative pictures. Taken together, depending on the situation more efficient switching of attention (greater flexibility) from affective toward non-affective aspects of negative pictures can either be adaptive or maladaptive. Considering positive pictures, more efficient switches away from processing non-affective towards affective aspects were predictive for reappraisal ability (Malooly et al., 2013), and smaller increases in anxiety over time (Twivy et al., 2021). In addition, slower switches away from the affective towards the non-affective aspects of positive pictures were associated with decreased use of rumination (Genet et al., 2013) and maladaptive emotion regulation strategies (Grol & De Raedt, 2021). Overall, findings regarding positive information are more consistent than findings related to negative pictures, indicating that more attention for the affective aspects of positive pictures is generally adaptive.

Results presented in **chapter 3** and **4** demonstrated that participants experienced more difficulties when switching attention away from processing the emotional meaning of negative pictures than from the emotional meaning of positive or neutral material. In contrast, in these chapters the most efficient switches were observed when shifting attention away from neutral toward affective aspects of negative information. These findings suggest that the processing of negative aspects of emotional material has priority over positive or neutral aspects. In addition, the affective character of the pictures appears to change the implicit salience of the categorization rules that are competing for attentional resources (Eckart et al., 2021), which is reflected by the asymmetric pattern of switch costs (i.e., small switch costs for switches from the non-affective towards the affective rule vs. large switch costs for switches from the affective towards the non-affective rule, see **chapter 2**, **3,** and **4**). The implicit salience is greater for the affective rule (deciding whether the picture content is positive or negative) than for the non-affective rule (determining whether the picture contains one or none, or two or more humans). In other words, the affective task set is attentionally dominant over the non-affective task set, thereby requiring more inhibition efforts when switching away from processing the affective towards the non-affective aspects of emotional pictures. This again implies that the affective task switching paradigm is more than a mere version of the cognitive task-switching paradigm using different stimuli, and hence, warrants to be examined in more detail.

To conclude, it can be suggested that studying affective flexibility as a specific instantiation of cognitive flexibility is worthwhile, and that the *direction of the affective switch* – whether a switch is being made from the affective toward the neutral rule or vice versa – and *stimulus valence* are crucial when predicting or determining psychological outcomes. Next to examining switches between affective and neutral information, it would be interesting for future research to also study direct switches between positively and negatively valenced information. We therefore stress the additive value of examining different types of affective switch costs rather than a global affective switch cost in relation to psychological outcomes.

Affective complexity as a sign of emotional flexibility

A growing body of research suggests that emotional flexibility is a feature of resilience (e.g., Folkman & Moskowitz, 2000; Fredrickson et al., 2003; Waugh et al., 2008). Here, resilience is defined as the successful adjustment to major and minor life challenges (Block & Kremen, 1996). Resilient individuals have been shown to be able to experience both positive and negative affect in response to stressful events (Folkman & Moskowitz, 2000; Fredrickson et al., 2003). For instance, Fredrickson et al. (2003) have found that the experience of both positive (e.g., love and gratitude) and negative affect (e.g., anger and fear) after the 9/11 terrorist attacks was observed in those participants who reported the fewest depressive symptoms. In other words, resilient people seem to exhibit the capacity to experience positive and negative affect as relatively independent affective experiences. This independence of positive and negative affect has been referred to as affective complexity.

An interesting complementary approach to the study of emotional flexibility in relation to pain may be provided by the Dynamic Model of Affect (DMA; Davis et al., 2004). This model posits that the state-like relationship between positive and negative affect is subject to fluctuations in stress (Davis et al., 2004). According to DMA, stressors such as (chronic) pain have an impact on the level of dependency between positive and negative affect, varying from being less inversely related or relatively independent affective states (i.e., two distinct affective dimensions) during safe and non-stressful periods to becoming more strongly inversely associated under conditions of stress (i.e., one bipolar affective dimension) (Davis et al., 2004). In other words, the DMA suggests that affective complexity is greater during non-stressful periods (Coifman et al., 2007). The DMA has received compelling support from numerous studies performed in experimental as well as naturalistic settings (e.g., Zautra et al., 2000), examining different types of stress, including acute (Zautra et al., 2000), chronic (e.g., Davis et al., 2004), and daily life stress (e.g., Zautra et al., 2002). All these studies indicated a shift in the level of dependency between positive and negative affect from low stress to stressful situations. From this perspective, and given that emotionally flexible people are able to experience both positive and negative affect at times of stress (Folkman & Moskowitz, 2000; Fredrickson et al., 2003), it may be speculated that greater affective independency or complexity during stress is a sign of emotional flexibility.

Future research should be directed at investigating the within-subject covariance between positive and negative affect in everyday life, for example by means of EMA designs, and how affective (in)dependency during stress is linked to pain and recovery. To examine the dynamics of positive and negative affect, we recently conducted a diary study (data analyses in progress) not included in this thesis. Specifically, in this study we aim to examine to what extent the dynamics of positive and negative affect as a function of stress are related to pain tolerance and recovery in terms of pain intensity and pain unpleasantness. An ischemic pain procedure in the lab was used to induce pain, after which participants kept a daily end-of-day diary at home for seven successive days as to determine fluctuations in positive affect, negative affect, and stress levels. First, we hypothesize that the relationship between positive and negative affect will become stronger at times of stress. Second, this relationship between positive affect and negative affect will be used as a predictor for pain tolerance and recovery from pain. Following the DMA, we predict that individuals who display low pain levels and fast recovery will be more likely to exhibit a larger independence (weaker associations) between positive and negative affect under stress (i.e., more emotional flexibility) as compared to individuals who experience higher pain levels and impaired recovery rates.

Mindfulness, recovery, and flexibility

Enhancements in psychological flexibility (Duarte & Pinto-Gouveia, 2017; Labelle et al., 2015; Marais et al., 2020) and its subcomponents affective flexibility (Zeidan et al., 2012; Zeidan & Vago, 2016) and cognitive flexibility (Gu et al., 2015; Zeidan et al., 2012) are among the mechanisms that have been proposed to underlie the analgesic effects of mindfulness. This dissertation did not provide evidence for an effect of mindfulness on affective or cognitive flexibility (**chapter 4**). Due to the exclusion of participants tested by one of the student experimenters who insufficiently adhered to the protocol, in-depth data analysis was seriously hindered, making it impossible to test whether flexibility was an underlying mechanism of the effect of mindfulness on pain and recovery. Therefore, a future research direction is to repeat this experiment with a large enough sample size per experimental condition, thereby enabling mediation analyses.

In **chapter 5**, we studied the effects of mindfulness on recovery speed of skin wounds and examined physiological wound healing processes as potential underlying mechanisms. Because findings showed an interaction between condition and sex, we performed analyses for men and women separately. For men, significant effects on TEWL and wound surface area were found, but results could not be reliably interpreted due to the very small sample size of men receiving MBSR (i.e., three men). For women, wound healing did not differ between MBSR and WLC participants. More specifically, no effects on TEWL were observed, and despite a significant condition x time interaction effect on wound size, no significant differences between the experimental groups on any of the single time points were found. Overall, results showed no evidence for the hypothesis that MBSR would improve the healing speed of skin wounds. Men displayed the largest improvements in mindfulness after receiving MBSR, which may explain the significant condition effect on TEWL and wound size in men. Post hoc analyses showed that greater improvements in mindfulness were related to larger reductions in TEWL at day 3 and 4. When repeating the analyses for women only, a similar link between the actual improvement in mindfulness and wound healing rate became evident. The finding of a positive link between improvements in mindfulness and speed of wound healing is in line with Rosenkranz et al. (2013) who showed that MBSR practicing time was inversely related to TNF-α levels in skin blisters in response to psychosocial stress and capsaicin exposure. Although we did not register total practice time, it may be hypothesized that MBSR is most beneficial to those who practice most.

Previous studies have indicated that psychosocial stress impairs wound healing (Bosch et al., 2007; Cole-King & Harding, 2001; Ebrecht et al., 2004; Garg et al., 2001; Kiecolt-Glaser et al., 2005; Maple et al., 2015), and that this effect can be reversed by stress-reducing psychosocial interventions (Broadbent et al., 2012; Law et al., 2020; Robinson et al., 2015; Robinson et al., 2017; Weinman et al., 2008). Given that the stress-reducing effects of mindfulness-based interventions (MBIs) have been consistently demonstrated in previous studies (e.g., Khoury et al., 2015), mindfulness may exert its potential beneficial effect on healing via stress reduction. A first indication for stress reduction as mediator of mindfulness comes from post hoc findings in **chapter 5**. When taking rumination as a proxy for stress vulnerability, MBSR appeared to have profited participants who needed stress reduction the most (men scored highest on rumination before MBSR); in men greater decreases in rumination after MBSR were related to larger decreases in TEWL at day 3 and 4. Additionally, the effect of condition on TEWL was mediated by rumination in the overall sample (**chapter 5**). Thus, investigating whether mindfulness will have positive effects on the process of wound healing through reduced stress levels, is an important direction for future research. Also, given the present findings and the distinct physiological skin properties of men and women (Gilliver et al., 2007), future studies are required examining the moderating role of sex in wound healing processes.

Methodological considerations and recommendations

Some methodological issues that may have had an effect on the findings in this dissertation should be addressed. A first methodological issue relates to the selection of healthy participants only. Because the main objective of this thesis was to examine psychological flexibility (i.e., emotional and cognitive flexibility) and mindfulness as resilience factors for high pain levels and slow recovery, we tested healthy participant samples that did not experience acute or chronic pain at the moment of testing. In pain research, the recruitment of a healthy study population has the advantage that these participants have relatively little experience with persistent pain or pain of high intensity, which permits studying factors contributing to the transition from acute to chronic pain. However, it remains unknown whether we can generalize current findings to the daily experiences of patients with acute or chronic pain. Additionally, given that chronic pain patients exhibit impaired performance on tasks reflecting executive functioning including cognitive flexibility (Attal et al., 2014; Moriarty et al., 2011; Solberg Nes et al., 2009), and given the fact that affective flexibility is a domain-specific instantiation of cognitive flexibility, clinical populations might also demonstrate poorer performance on tests of affective flexibility. Extending current study results to acute and chronic pain patient samples might lead to more insight into the relationship between psychological flexibility and pain experience and recovery, as well as into psychological flexibility as potential underlying mechanism of the benefits of mindfulness. Moreover, generalizability of findings in this dissertation to the general population is limited, as the majority of participants were highly educated female students, of relatively young age, with supposedly above average intelligence levels. It is therefore advisable that future research also examines the role of resilience factors in pain experience and recovery in participant samples that better represent the general population.

Second, a limitation of the current dissertation concerns shortcomings in the measures that are available for the assessment of pain recovery and emotional flexibility. The ischemic pain procedure as a lab analogue for pain recovery differs from the experience of acute and chronic pain patients. However, this may be true for all the available procedures for measuring pain recovery in the lab. In addition, an affective switching paradigm and flexible emotional responsiveness task were used to measure emotional flexibility. In these tasks, participants view static pictures of positively (e.g., a child playing with a puppy) and negatively valenced (e.g., a car accident) emotional scenes, which may not equal the complexity of emotion-inducing experiences in real-life settings. This issue might be tackled by the use of a new technology that allows naturalistic experiments while maintaining experimental control, namely immersive virtual reality (VR). A recent study has demonstrated the utility of VR as a tool for studying human emotions in situations that closely mimic everyday life (Hofmann et al., 2021). Considering context sensitivity as characteristic of emotional flexibility and the dynamic nature of the construct (Coifman & Summers, 2019), VR may be particularly useful for studying emotional flexibility. Therefore, VR would be an interesting new technology to employ in future research to study the role of emotional flexibility in pain experience and recovery.

A third methodological issue concerns potential power issues, as relatively small samples were included in relation to the number of independent variables examined in each study in this dissertation. As we consider it necessary that future research continues studying multiple factors with the goal to increase our knowledge about their relative importance in explaining pain and recovery, the inclusion of participant samples sufficiently large to determine the relative contribution of these variables is recommended. Also, the relatively small participant sample in **chapter 2** did not allow studying how the affective switching task and the emotional responsiveness tasks relate to one another. Additionally, despite a priori power calculations the final sample size in the study described in **chapter 4** was small. This was the result of the exclusion of participants tested by one of the student experimenters who insufficiently adhered to the protocol. Consequently, these sample sizes may have seriously hindered the scope of data interpretation and in-depth data analyses. Future research will therefore have to repeat these studies including larger participant samples. Furthermore, because we did not expect differential effects of MBSR on wound healing across sex, we did not ensure an equal distribution of men and women across experimental conditions in the wound healing study (**chapter 5**). Only a few men participated, and due to missing data the numbers were even smaller for cytokine and growth factor data. Also, the participant sample was not selected for elevated stress levels for whom mindfulness might have most pronounced benefits. Future research should replicate this study, thereby including an equal distribution of men and women across conditions and further examine whether MBSR has an effect on wound healing via reduced stress levels.

Lastly, the studies in this dissertation relied on cross-sectional designs for investigating the contribution of resilience factors to pain experience and recovery. A path for studying the protective role of flexibility and mindfulness may lie in the use of prospective designs in which longitudinal data is collected on pain experience and (non-)recovery. However, implementation of such study designs would be problematic given that participants need to be recruited prior to the experience of pain. Individuals scheduled for surgery may offer a solution, as they are expected to experience future pain. Data on hypothesized resilience factors can then be collected prior to surgery as well as at follow-up moments. In addition, half of the studies in this dissertation are limited by the employment of correlational designs. Experimental studies are necessary to determine causality.

CONCLUDING REMARKS

In the current dissertation, we examined the relationship between the relatively new concepts of psychological flexibility (i.e., emotional and cognitive flexibility) and mindfulness, and pain experience and recovery. Present findings do not uniformly point to such a relationship, however, first indications of associations between emotional flexibility and recovery from pain as well as of beneficial effects of mindfulness for wound healing have been put forward. Continuation and replication of the work presented in this thesis is deemed necessary in order to gain a deeper understanding of the protective value of psychological flexibility and mindfulness against increased pain experience and slow recovery.

Hopefully, current work will stimulate future research to further elucidate the role of psychological flexibility (i.e., emotional and cognitive flexibility) and mindfulness in pain experience and recovery. A better understanding of psychological flexibility and mindfulness as potential resilience factors for pain and recovery may clarify the working mechanisms of existing treatments (i.e., MBIs and Acceptance and Commitment Therapy), and may ultimately provide novel pathways for the development of prevention programs as well as new intervention strategies. This developing body of research indicates an interesting avenue for future studies to contribute to an improved framework for the understanding of pain experience and chronicity, as well as improved models of prevention and intervention.

REFERENCES

Abbate-Daga, G., Buzzichelli, S., Amianto, F., Rocca, G., Marzola, E., McClintock, S. M., & Fassino, S. (2011). Cognitive flexibility in verbal and nonverbal domains and decision making in anorexia nervosa patients: a pilot study. *BMC Psychiatry, 11*(1), 162. https://doi.org/10.1186/1471-244x-11-162

Al-Jabari, R. M. (2012). *Relationships among self-esteem, psychological and cognitive flexibility, and psychological symptomatology.* [Master of Science thesis]. University of North Texas, Denton, TX.

Aldao, A., Sheppes, G., & Gross, J. J. (2015). Emotion regulation flexibility. *Cognitive Therapy and Research, 39*(3), 263-278. https://doi.org/10.1007/s10608-014-9662-4

Attal, N., Masselin-Dubois, A., Martinez, V., Jayr, C., Albi, A., Fermanian, J., Bouhassira, D., & Baudic, S. (2014). Does cognitive functioning predict chronic pain? Results from a prospective surgical cohort. *Brain, 137*(Pt 3), 904-917. https://doi.org/10.1093/brain/awt354

Beshai, S., Prentice, J. L., & Huang, V. (2018). Building Blocks of Emotional Flexibility: Trait Mindfulness and Self-Compassion Are Associated with Positive and Negative Mood Shifts. *Mindfulness, 9*(3), 939-948. https://doi.org/10.1007/s12671-017-0833-8

Biro, B., Kokonyei, G., De Oliveira Negrao, R., Dancsik, A., Karsai, S., Logemann, H. N. A., & Cserjes, R. (2021). Interaction between emotional context-guided shifting and cognitive shifting: Introduction of a novel task. *Neuropsychopharmacol Hung, 23*(3), 319-330.

Block, J., & Kremen, A. M. (1996). IQ and ego-resiliency: conceptual and empirical connections and separateness. *J Pers Soc Psychol, 70*(2), 349-361.

Block, J. H., & Block, J. (1980). *The role of ego-control and ego-resiliency in the origination of behavior.* (W. A. Collings, Ed. Vol. 13). Erlbaum.

Borkovec, T., Alcaine, O., & Behar, E. (2004). Avoidance theory of worry and generalized anxiety disorder. In C. L. T. D. S. Mennin (Ed.), *Generalized anxiety disorder: Advances in research and practice* (pp. 77-108). Guilford Press.

Bosch, J. A., Engeland, C. G., Cacioppo, J. T., & Marucha, P. T. (2007). Depressive Symptoms Predict Mucosal Wound Healing. *Psychosomatic Medicine, 69*(7). https://doi.org/10.1097/PSY.0b013e318148c682

Broadbent, E., Kahokehr, A., Booth, R. J., Thomas, J., Windsor, J. A., Buchanan, C. M., Wheeler, B. R. L., Sammour, T., & Hill, A. G. (2012). A brief relaxation intervention reduces stress and improves surgical wound healing response: A randomised trial. *Brain, Behavior, and Immunity, 26*(2), 212-217. https://doi.org/10.1016/j.bbi.2011.06.014

Broadbent, E., Petrie, K. J., Alley, P. G., & Booth, R. J. (2003). Psychological Stress Impairs Early Wound Repair Following Surgery. *Psychosomatic Medicine, 65*(5), 865-869. https://doi.org/10.1097/01.Psy.0000088589.92699.30

Chavez, J. L., Porucznik, C. A., Gren, L. H., Guan, J., Joyce, E., Brodke, D. S., Dailey, A. T., Mahan, M. A., Hood, R. S., Lawrence, B. D., Spiker, W. R., Spina, N. T., & Bisson, E. F. (2020). The Impact of Preoperative Mindfulness-Based Stress Reduction on Postoperative Outcomes in Lumbar Spine Degenerative Disease: 3-Month and 12-Month Results of a Pilot Study. *World Neurosurg, 139*, e230-e236. https://doi.org/10.1016/j.wneu.2020.03.186

Chiesa, A., & Serretti, A. (2011). Mindfulness-based interventions for chronic pain: a systematic review of the evidence. *J Altern Complement Med, 17*(1), 83-93. https://doi.org/10.1089/acm.2009.0546

Cisler, J. M., & Koster, E. H. W. (2010). Mechanisms of attentional biases towards threat in anxiety disorders: An integrative review. *Clinical Psychology Review, 30*(2), 203-216. https://doi.org/10.1016/j.cpr.2009.11.003

Coifman, K. G., Bonanno, G. A., & Rafaeli, E. (2007). Affect dynamics, bereavement and resilience to loss. *Journal of Happiness Studies, 8*(3), 371-392. https://doi.org/10.1007/s10902-006-9014-5

Coifman, K. G., & Summers, C. B. (2019). Understanding Emotion Inflexibility in Risk for Affective Disease: Integrating Current Research and Finding a Path Forward. *Front Psychol, 10*, 392. https://doi.org/10.3389/fpsyg.2019.00392

Cole-King, A., & Harding, K. G. (2001). Psychological Factors and Delayed Healing in Chronic Wounds. *Psychosomatic Medicine, 63*(2), 216-220. https://doi.org/10.1097/00006842-200103000-00004

Craig, A. D. (2003). A new view of pain as a homeostatic emotion. *Trends Neurosci, 26*(6), 303-307.

Davis, M. C., Zautra, A. J., & Smith, B. W. (2004). Chronic pain, stress, and the dynamics of affective differentiation. *J Pers, 72*(6), 1133-1159. https://doi.org/10.1111/j.1467-6494.2004.00293.x

Dowsey, M., Castle, D., Knowles, S., Monshat, K., Salzberg, M., Nelson, E., Dunin, A., Dunin, J., Spelman, T., & Choong, P. (2019). The effect of mindfulness training prior to total joint arthroplasty on post-operative pain and physical function: A randomised controlled trial. *Complementary Therapies in Medicine, 46*, 195-201. https://doi.org/10.1016/j.ctim.2019.08.010

Duarte, J., & Pinto-Gouveia, J. (2017). Mindfulness, self-compassion and psychological inflexibility mediate the effects of a mindfulness-based intervention in a sample of oncology nurses. *Journal of Contextual Behavioral Science, 6*(2), 125-133. https://doi.org/10.1016/j.jcbs.2017.03.002

Ebrecht, M., Hextall, J., Kirtley, L.-G., Taylor, A., Dyson, M., & Weinman, J. (2004). Perceived stress and cortisol levels predict speed of wound healing in healthy male adults. *Psychoneuroendocrinology, 29*(6), 798-809. https://doi.org/10.1016/S0306-4530(03)00144-6

Eckart, C., Kraft, D., & Fiebach, C. J. (2021). Internal consistency and test-retest reliability of an affective task-switching paradigm. *Emotion, 21*(5), 921-931. https://doi.org/10.1037/emo0000972

Feinstein, A. B., Forman, E. M., Masuda, A., Cohen, L. L., Herbert, J. D., Moorthy, L. N., & Goldsmith, D. P. (2011). Pain intensity, psychological inflexibility, and acceptance of pain as predictors of functioning in adolescents with juvenile idiopathic arthritis: a preliminary investigation. *J Clin Psychol Med Settings, 18*(3), 291-298. https://doi.org/10.1007/s10880-011-9243-6

Feldman Barrett, L., & Barrett, D. J. (2001). An Introduction to Computerized Experience Sampling in Psychology. *Social Science Computer Review, 19*(2), 175-185. https://doi.org/10.1177/089443930101900204

Feldner, M. T., Hekmat, H., Zvolensky, M. J., Vowles, K. E., Secrist, Z., & Leen-Feldner, E. W. (2006). The role of experiential avoidance in acute pain tolerance: A laboratory test. *Journal of Behavior Therapy and Experimental Psychiatry, 37*(2), 146-158. https://doi.org/10.1016/j.jbtep.2005.03.002

Folkman, S., & Moskowitz, J. T. (2000). Positive affect and the other side of coping. *American Psychologist, 55*(6), 647-654. https://doi.org/10.1037/0003-066X.55.6.647

Fredrickson, B. L., Tugade, M. M., Waugh, C. E., & Larkin, G. R. (2003). What good are positive emotions in crises? A prospective study of resilience and emotions following the terrorist attacks on the United States on September 11th, 2001. *Journal of personality and social psychology, 84*(2), 365-376.

Fu, F., Chow, A., Li, J., & Cong, Z. (2018). Emotional flexibility: Development and application of a scale in adolescent earthquake survivors. *Psychological Trauma: Theory, Research, Practice, and Policy, 10*(2), 246-252. https://doi.org/10.1037/tra0000278

Garg, A., Chren, M.-M., Sands, L. P., Matsui, M. S., Marenus, K. D., Feingold, K. R., & Elias, P. M. (2001). Psychological Stress Perturbs Epidermal Permeability Barrier Homeostasis: Implications for the Pathogenesis of Stress-Associated Skin Disorders. *Archives of Dermatology, 137*(1), 53-59. https://doi.org/10.1001/archderm.137.1.53

Garland, E. L., Brintz, C. E., Hanley, A. W., Roseen, E. J., Atchley, R. M., Gaylord, S. A., Faurot, K. R., Yaffe, J., Fiander, M., & Keefe, F. J. (2019). Mind-Body Therapies for Opioid-Treated Pain: A Systematic Review and Meta-analysis. *JAMA internal medicine, 180*(1), 91-105. https://doi.org/10.1001/jamainternmed.2019.4917

Genet, J. J., Malooly, A. M., & Siemer, M. (2013). Flexibility is not always adaptive: affective flexibility and inflexibility predict rumination use in everyday life. *Cogn Emot, 27*(4), 685-695. https://doi.org/10.1080/02699931.2012.733351

Genet, J. J., & Siemer, M. (2011). Flexible control in processing affective and non-affective material predicts individual differences in trait resilience. *Cogn Emot, 25*(2), 380-388. https://doi.org/10.1080/02699931.2010.491647

Gilliver, S. C., Ashworth, J. J., & Ashcroft, G. S. (2007). The hormonal regulation of cutaneous wound healing. *Clinics in Dermatology, 25*(1), 56-62. https://doi.org/10.1016/j.clindermatol.2006.09.012

Glaser, R., Kiecolt-Glaser, J. K., Marucha, P. T., MacCallum, R. C., Laskowski, B. F., & Malarkey, W. B. (1999). Stress-Related Changes in Proinflammatory Cytokine Production in Wounds. *Archives of General Psychiatry, 56*(5), 450-456. https://doi.org/10.1001/archpsyc.56.5.450

Grol, M., & De Raedt, R. (2020). The link between resting heart rate variability and affective flexibility. *Cogn Affect Behav Neurosci, 20*(4), 746-756. https://doi.org/10.3758/s13415-020-00800-w

Grol, M., & De Raedt, R. (2021). The relationship between affective flexibility, spontaneous emotion regulation and the response to induced stress. *Behav Res Ther, 143*, 103891. https://doi.org/10.1016/j.brat.2021.103891

Gu, J., Strauss, C., Bond, R., & Cavanagh, K. (2015). How do mindfulness-based cognitive therapy and mindfulness-based stress reduction improve mental health and wellbeing? A systematic review and meta-analysis of mediation studies. *Clin Psychol Rev, 37*, 1-12. https://doi.org/10.1016/j.cpr.2015.01.006

Hofmann, S. M., Klotzsche, F., Mariola, A., Nikulin, V., Villringer, A., & Gaebler, M. (2021). Decoding subjective emotional arousal from EEG during an immersive virtual reality experience. *eLife, 10*, e64812. https://doi.org/10.7554/eLife.64812

Kashdan, T. B., & Rottenberg, J. (2010). Psychological flexibility as a fundamental aspect of health. *Clinical Psychology Review, 30*(7), 865-878. https://doi.org/10.1016/j.cpr.2010.03.001

Khoury, B., Sharma, M., Rush, S. E., & Fournier, C. (2015). Mindfulness-based stress reduction for healthy individuals: A meta-analysis. *Journal of Psychosomatic Research, 78*(6), 519-528. https://doi.org/10.1016/j.jpsychores.2015.03.009

Kiecolt-Glaser, J. K., Loving, T. J., Stowell, J. R., Malarkey, W. B., Lemeshow, S., Dickinson, S. L., & Glaser, R. (2005). Hostile Marital Interactions, Proinflammatory Cytokine Production, and Wound Healing. *Archives of General Psychiatry, 62*(12), 1377-1384. https://doi.org/10.1001/archpsyc.62.12.1377

Labelle, L. E., Campbell, T. S., Faris, P., & Carlson, L. E. (2015). Mediators of Mindfulness-Based Stress Reduction (MBSR): Assessing the Timing and Sequence of Change in Cancer Patients. *Journal of Clinical Psychology, 71*(1), 21-40. https://doi.org/10.1002/jclp.22117

Law, M., Jarrett, P., Nater, U. M., Skoluda, N., & Broadbent, E. (2020). The Effects of Sensory Enrichment After a Laboratory Stressor on Human Skin Barrier Recovery in a Randomized Trial. *Psychosomatic Medicine, 82*(9), 877-886. https://doi.org/10.1097/psy.0000000000000858

Malooly, A. M., Genet, J. J., & Siemer, M. (2013). Individual differences in reappraisal effectiveness: the role of affective flexibility. *Emotion, 13*(2), 302-313. https://doi.org/10.1037/a0029980

Maple, H., Chilcot, J., Lee, V., Simmonds, S., Weinman, J., & Mamode, N. (2015). Stress predicts the trajectory of wound healing in living kidney donors as measured by high-resolution ultrasound. *Brain, Behavior, and Immunity, 43*, 19-26. https://doi.org/10.1016/j.bbi.2014.06.012

Marais, G., Lantheaume, S., Fiault, R., & Shankland, R. (2020). *Mindfulness-based programs improve psychological flexibility, mental health, well-being and time management in academics*. https://doi.org/10.31234/osf.io/9w4zp

McCracken, L. M. (1998). Learning to live with the pain: acceptance of pain predicts adjustment in persons with chronic pain. *PAIN, 74*(1), 21-27. https://doi.org/10.1016/s0304-3959(97)00146-2

McCracken, L. M., & Velleman, S. C. (2010). Psychological flexibility in adults with chronic pain: a study of acceptance, mindfulness, and values-based action in primary care. *PAIN, 148*(1), 141-147. https://doi.org/10.1016/j.pain.2009.10.034

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The unity and diversity of executive functions and their contributions to complex "Frontal Lobe" tasks: a latent variable analysis. *Cogn Psychol, 41*(1), 49-100. https://doi.org/10.1006/cogp.1999.0734

Moore, P. A., Duncan, G. H., Scott, D. S., Gregg, J. M., & Ghia, J. N. (1979). The submaximal effort tourniquet test: its use in evaluating experimental and chronic pain. *PAIN, 6*(3), 375-382.

Moriarty, O., McGuire, B. E., & Finn, D. P. (2011). The effect of pain on cognitive function: a review of clinical and preclinical research. *Prog Neurobiol, 93*(3), 385-404. https://doi.org/10.1016/j.pneurobio.2011.01.002

Papousek, I., Reiser, E. M., Weber, B., Freudenthaler, H. H., & Schulter, G. (2012). Frontal brain asymmetry and affective flexibility in an emotional contagion paradigm. *Psychophysiology, 49*(4), 489-498. https://doi.org/10.1111/j.1469-8986.2011.01324.x

Pyszkowska, A., & Rönnlund, M. (2021). Psychological Flexibility and Self-Compassion as Predictors of Well-Being: Mediating Role of a Balanced Time Perspective. *Frontiers in Psychology, 12*(2110). https://doi.org/10.3389/fpsyg.2021.671746

Ramaci, T., Bellini, D., Presti, G., & Santisi, G. (2019). Psychological Flexibility and Mindfulness as Predictors of Individual Outcomes in Hospital Health Workers. *Frontiers in Psychology, 10*(1302). https://doi.org/10.3389/fpsyg.2019.01302

Ratcliff, C. G. (2015). *Brief Guided Mindfulness Meditation for Women Undergoing Stereotactic Breast Biopsy: Effects on Patient Self-Report, EEG Activity, and Physiological Measures.* (Unpublished doctoral dissertation). University of Houston, Houston, Texas.

Reddy, K. S. K., Naidu, M. U. R., Rani, P. U., & Rao, T. R. K. (2012). Human experimental pain models: A review of standardized methods in drug development. *Journal of research in medical sciences : the official journal of Isfahan University of Medical Sciences, 17*(6), 587-595.

Robinson, H., Jarrett, P., & Broadbent, E. (2015). The Effects of Relaxation Before or After Skin Damage on Skin Barrier Recovery: A Preliminary Study. *Psychosomatic Medicine, 77*(8), 844-852. https://doi.org/10.1097/psy.0000000000000222

Robinson, H., Jarrett, P., Vedhara, K., & Broadbent, E. (2017). The effects of expressive writing before or after punch biopsy on wound healing. *Brain, Behavior, and Immunity, 61*, 217-227. https://doi.org/10.1016/j.bbi.2016.11.025

Rosenkranz, M. A., Davidson, R. J., MacCoon, D. G., Sheridan, J. F., Kalin, N. H., & Lutz, A. (2013). A comparison of mindfulness-based stress reduction and an active control in modulation of neurogenic inflammation. *Brain, Behavior, and Immunity, 27*, 174-184. https://doi.org/10.1016/j.bbi.2012.10.013

Shiffman, S., Stone, A. A., & Hufford, M. R. (2008). Ecological momentary assessment. *Annu Rev Clin Psychol, 4*, 1-32. https://doi.org/10.1146/annurev.clinpsy.3.022806.091415

Sinke, C., Schmidt, K., Forkmann, K., & Bingel, U. (2015). Phasic and tonic pain differentially impact the interruptive function of pain. *PloS one, 10*(2), e0118363-e0118363. https://doi.org/10.1371/journal.pone.0118363

Smith, G. M., Egbert, L. D., Markowitz, R. A., Mosteller, F., & Beecher, H. K. (1966). An experimental pain method sensitive to morphine in man: the submaximum effort tourniquet technique. *J Pharmacol Exp Ther, 154*(2), 324-332.

Solberg Nes, L., Roach, A. R., & Segerstrom, S. C. (2009). Executive functions, self-regulation, and chronic pain: a review. *Ann Behav Med, 37*(2), 173-183. https://doi.org/10.1007/s12160-009-9096-5

Sternheim, L., van der Burgh, M., Berkhout, L. J., Dekker, M. R., & Ruiter, C. (2014). Poor cognitive flexibility, and the experience thereof, in a subclinical sample of female students with obsessive-compulsive symptoms. *Scand J Psychol, 55*(6), 573-577. https://doi.org/10.1111/sjop.12163

Swift, A. (2018). Understanding pain and the human body's response to it. *Nursing Times, 114*(3), 22-26.

Talaei-Khoei, M., Fischerauer, S. F., Lee, S. G., Ring, D., & Vranceanu, A. M. (2017). Pain Catastrophizing Mediates the Effect of Psychological Inflexibility on Pain Intensity and Upper Extremity Physical Function in Patients with Upper Extremity Illness. *Pain Pract, 17*(1), 129-140. https://doi.org/10.1111/papr.12494

Twivy, E., Grol, M., & Fox, E. (2021). Individual differences in affective flexibility predict future anxiety and worry. *Cogn Emot, 35*(2), 425-434. https://doi.org/10.1080/02699931.2020.1843407

Veehof, M. M., Trompetter, H. R., Bohlmeijer, E. T., & Schreurs, K. M. (2016). Acceptance- and mindfulness-based interventions for the treatment of chronic pain: a meta-analytic review. *Cogn Behav Ther, 45*(1), 5-31. https://doi.org/10.1080/16506073.2015.1098724

Waugh, C. E., Fredrickson, B. L., & Taylor, S. F. (2008). Adapting to life's slings and arrows: Individual differences in resilience when recovering from an anticipated threat. *Journal of research in personality, 42*(4), 1031-1046. https://doi.org/10.1016/j.jrp.2008.02.005

Waugh, C. E., Thompson, R. J., & Gotlib, I. H. (2011). Flexible emotional responsiveness in trait resilience. *Emotion, 11*(5), 1059-1067. https://doi.org/10.1037/a0021786

Weinman, J., Ebrecht, M., Scott, S., Walburn, J., & Dyson, M. (2008). Enhanced wound healing after emotional disclosure intervention. *British Journal of Health Psychology, 13*(1), 95-102. https://doi.org/10.1348/135910707X251207

Wen, A., & Yoon, K. L. (2019). Depression and affective flexibility: A valence-specific bias. *Behav Res Ther, 123*, 103502. https://doi.org/10.1016/j.brat.2019.103502

Westphal, M., Seivert, N. H., & Bonanno, G. A. (2010). Expressive flexibility. *Emotion, 10*(1), 92-100. https://doi.org/10.1037/a0018420

Zautra, A. J., Berkhof, J., & Nicolson, N. A. (2002). Changes in affect interrelations as a function of stressful events. *Cognition and Emotion, 16*(2), 309-318. https://doi.org/10.1080/02699930143000257

Zautra, A. J., Reich, J. W., Davis, M. C., Potter, P. T., & Nicolson, N. A. (2000). The Role of Stressful Events in the Relationship Between Positive and Negative Affects: Evidence From Field and Experimental Studies. *Journal of Personality, 68*(5), 927-951. https://doi.org/10.1111/1467-6494.00121

Zeidan, F., Grant, J. A., Brown, C. A., McHaffie, J. G., & Coghill, R. C. (2012). Mindfulness meditation-related pain relief: Evidence for unique brain mechanisms in the regulation of pain. *Neuroscience Letters, 520*(2), 165-173. https://doi.org/10.1016/j.neulet.2012.03.082

Zeidan, F., & Vago, D. R. (2016). Mindfulness meditation-based pain relief: a mechanistic account. *Annals of the New York Academy of Sciences, 1373*(1), 114-127. https://doi.org/10.1111/nyas.13153

ADDENDUM

SUMMARY

Acute pain is an important sensation that serves a protective role, as it informs the body about potential physical harm or illness. However, acute pain loses its adaptive function when it transitions into chronic pain. As described in the general introduction in **chapter 1**, various psychosocial factors influence pain perception and the transition from acute to chronic pain, with psychological flexibility (including its subcomponents emotional and cognitive flexibility) and mindfulness being among those factors. However, the role of psychological flexibility in the development of chronic pain (i.e., non-recovery) remains largely unknown.

This dissertation aimed to gain insight into the link between psychological flexibility and mindfulness, and pain experience and recovery. Specifically, experimental studies investigated the protective role of two components of psychological flexibility (i.e., emotional and cognitive flexibility) and mindfulness against high pain levels and slow recovery from pain and of wounds. The following questions were addressed: 1) What is the relationship between two aspects of emotional flexibility (i.e., flexible emotional responsiveness and affective flexibility) and tolerance for and recovery from experimentally induced pain (**chapter 2**)? 2) Does affective flexibility have additive predictive value in explaining the experience of pain, above and beyond that of cognitive flexibility (**chapter 3**)? 3) Does mindfulness influence pain experience and recovery, and is this effect mediated by affective and/or cognitive flexibility (**chapter 4**)? Does mindfulness affect the recovery of wounds, and is this effect mediated by physiological wound healing processes (**chapter 5**)?

In a first cross-sectional observational study, pain was induced by means of an ischemic pain task (**chapter 2**). We found that two aspects of emotional flexibility (i.e., flexible emotional responsiveness and affective flexibility) were related to recovery from pain. Specifically, individuals who displayed more flexible emotional responding reflected in more distinct facial expressions (i.e., more divergent corrugator responses) to alternating positive and negative stimuli were more likely to recover faster in terms of pain unpleasantness. This study also found support for a relationship between more flexible switching between emotional contexts and faster recovery from pain. Participants who were more capable to switch attention away from neutral toward the affective meaning of positive stimuli were more likely to recover faster from pain with regards to pain intensity ratings. In disagreement with our hypotheses, none of the emotional flexibility measures was related to pain tolerance.

In order to test the additive value of affective flexibility in explaining the experience

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of pain above and beyond that of cognitive flexibility, our second study contained both a measure of affective flexibility and a non-affective measure of general cognitive flexibility (**chapter 3**). Results did not provide evidence for associations between affective and general cognitive flexibility, and experimentally induced heat pain threshold, pain tolerance and retrospective pain experience.

Chapter 4 describes an experimental study that investigated the effects of a mindfulness induction on pain experience and recovery, as well as on cognitive and affective flexibility. An ischemic pain task was used to induce pain. It was hypothesized that participants in the mindfulness group would display a higher pain tolerance and reduced subjective stress ratings compared to participants in the control condition. Also, we expected faster recovery in terms of pain intensity and pain unpleasantness ratings in the mindfulness group. In addition, mindfulness was expected to improve both cognitive and affective flexibility. However, findings did not support any of our hypotheses. Although mindfulness was successfully induced, results showed no effect on pain tolerance, subjective stress ratings, and recovery in terms of pain intensity and pain unpleasantness ratings, nor on cognitive and affective flexibility.

Chapter 5 presents the results of an experimental study examining the effects of an 8-week Mindfulness-Based Stress Reduction (MBSR) program on recovery, measured as the healing speed of skin blisters, and explored local pro-inflammatory cytokine and growth factor levels in wound fluid as potential mediators of recovery. We found no evidence for the hypothesis that MBSR would improve the healing speed of skin wounds. However, post hoc analyses showed that larger improvements in mindfulness were linked to larger reductions in skin permeability at day 3 and 4 after wounding. Furthermore, results showed that MBSR participants exhibited lower levels of pro-inflammatory cytokines and growth factors such as interleukin (IL)-8, and placental growth factor (PlGF) in wound fluid after 22 h as compared to waiting-list control participants. Post hoc findings demonstrated that larger improvements in mindfulness were associated to greater decreases in IL-1β and IL-8 22 h after blistering. In sum, this study provided preliminary evidence for the potential beneficial effects of mindfulness meditation on early stages of wound healing, and of local pro-inflammatory cytokine and growth factor levels in wound fluid as mediators of recovery.

Lastly, **chapter 6** provides a summary of the main findings of this dissertation, followed by a discussion of these findings in relation to previous literature, future research, and research implications. Altogether, the findings of the current dissertation did not uniformly point to associations among psychological flexibility (i.e., emotional and cognitive flexibility), mindfulness, pain experience, and recovery (i.e., pain recovery and recovery of wounds). However, present work does provide first indications of relations between emotional flexibility and recovery from pain and of beneficial effects of mindfulness for wound healing. Future studies are therefore necessary to disentangle when and how constructs like psychological flexibility (i.e., emotional and cognitive flexibility) and mindfulness exert their influence on pain experience and recovery from pain and of wounds. The current dissertation may inspire future studies to continue this line of research. A deeper understanding of psychological flexibility and mindfulness as potential resilience factors for pain and recovery may ultimately lead to novel avenues for the development of prevention programs as well as new intervention strategies.

IMPACT PARAGRAPH

Relevance

Everyone experiences acute pain at some point in their lifetime. Pain is a vital experience that warns us about potential physical harm or illness. However, acute pain develops into chronic pain when it persists beyond three months. Under those circumstances, pain loses its protective function and becomes detrimental. Chronic pain comprises a serious health burden with approximately 20% of U.S. and European adults suffering from it (Breivik et al., 2006; Dahlhamer et al., 2018). Chronic pain negatively influences physical, social and cognitive functioning. About 50% of chronic pain sufferers receive inadequate pain management, and as a result, work productivity is decreased and health care costs are enormous (Breivik et al., 2006; Medicine, 2011). Indeed, pain is the health condition with the highest annual health care spending, thereby exceeding the costs for diabetes, cancer, and heart disease (Dieleman et al., 2020; Gaskin & Richard, 2012).

Various psychosocial factors influence pain perception. Psychological flexibility (including its subcomponents emotional and cognitive flexibility) and mindfulness may be among those factors. However, the role of psychological flexibility in the transition of acute pain into chronic pain (i.e., non-recovery) remains largely unknown. The general aim of this thesis was to study the protective role of psychological flexibility and mindfulness against high pain levels and slow recovery. Specifically, we aimed to examine associations among psychological flexibility (i.e., emotional and cognitive flexibility), mindfulness, pain experience, and recovery (i.e., pain recovery and recovery of wounds).

Given the significant health burden and accompanying costs of chronic pain and its related disability, more insight into factors contributing to non-recovery of acute pain is of vital importance. The studies in this dissertation were fundamental in nature. Admitting that the implications of fundamental research are generally limited, the findings in this dissertation may have scientific and societal impact in several ways, both in the short term and in the long run.

Scientific impact

Ultimately, the obtained knowledge in this thesis might contribute to the reduction of individual, economic, and societal costs of chronic pain. The scientific impact of this thesis lies in its contribution to the field of pain and recovery (from pain and of wounds). The findings in **chapter 2** showed that two aspects of emotional flexibility (i.e., affective flexibility and flexible emotional responsiveness) were related to recovery from pain. Specifically, more flexibility in emotional responsiveness was associated with faster recovery with regard to self-reported pain unpleasantness. Additionally, more flexibility in switching toward the positive meaning of positive pictures was related to faster recovery in terms of pain intensity ratings. However, findings in **chapter 3** and **4** did not point to associations between affective and general cognitive flexibility, and pain experience and recovery. In **chapter 4**, we did not find an effect of mindfulness on pain experience and recovery, nor on affective and cognitive flexibility. However, tentative results in **chapter 5** suggested the potential beneficial effects of mindfulness meditation on the recovery speed of skin wounds. Taken together, current findings were not always univocal. It is therefore necessary that future studies unravel when and how these constructs exert their influence on pain experience and recovery from pain and of wounds.

The innovative value of this thesis lies in the focus on recovery with the rationale to prevent pain chronicity (as an instance of non-recovery) in the long run. In respect to earlier pain research, the focus on recovery can be described as distinctive and scientifically innovative. With this PhD project, we hope to stimulate future research to continue the study of recovery, and more specifically, to further elucidate psychosocial factors on which to intervene in the prevention of slow and non-recovery.

In addition to its contribution to the field of pain, this dissertation also contributed to the conceptualisation of psychological flexibility (i.e., emotional and cognitive flexibility). Current findings and methodology regarding the study of emotional flexibility have furthered our understanding of this relatively new construct and how it can be measured, as well as how it relates to general cognitive flexibility. The finding that emotional flexibility is related to recovery from pain will inspire more experimental studies on the topic in the short term. More research attention for emotional flexibility is highly warranted in order to maximize the usefulness of this concept in explaining pain and vulnerability. Hopefully, future research efforts will continue studying different aspects of emotional flexibility, given their unique predictive value for recovery from pain. We consider the study of emotional flexibility in relation to pain and mindfulness in relation to wound healing as pioneering work, and have thereby contributed to the development of a relatively new body of research.

For a long time, psychological research has been problem-oriented with a focus on “fixing what is wrong” (weaknesses / risk factors), instead of “building what is strong” (strengths / protective factors). This latter point of view is central to a relatively new movement called positive psychology (Seligman, 2002). This science discipline concentrates on positive subjective experience (e.g., happiness, love, and joy) and positive states and traits (e.g., resilience and compassion). By focusing on psychological flexibility (i.e., emotional and cognitive flexibility) and mindfulness as protective factors against high pain levels and slow recovery, this dissertation contributes to our knowledge about resilience, and as such, fits well within the field of positive psychology. Only when protective factors are identified alongside vulnerability factors, the field of pain will be able to move forward towards a comprehensive understanding of pain perception and (non-)recovery. In the long run, the results of this dissertation may contribute to interventions aiming at strengthening psychosocial factors such as emotional flexibility and mindfulness that protect against high pain levels and slow recovery.

Knowledge transfer

The knowledge that was obtained in this dissertation is relevant for scientist and therapists working in the field of pain and wound healing. Present findings have been reported in scientific articles that are published by international open access peer-reviewed journals (Journal of Behavioral Medicine, impact factor = 2.960; Motivation and Emotion, impact factor = 2.340; Journal of Experimental Psychopathology, impact factor = 1.964). In addition, current findings have been presented at various national and international scientific conferences across the fields of emotion (e.g., Emotions Congress), pain (e.g., Pain Research Meeting, IASP World Congress on Pain, Congress of the European Pain Federation), and behavioral medicine (e.g., International Congress of Behavioral Medicine). We have shared our research findings on popular social media platforms such as ResearchGate, Web of Science, and Twitter. Findings have also been referred to in blog posts (e.g., "Everyday Health", "Information for Practice") and on a Facebook group page ("Meditation Research"). Moreover, our research endeavors have also been shared via teaching activities at Maastricht University, which included the supervision of master students who joined research projects that form a part of this dissertation, and/or have written their master theses on related topics. We plan to keep sharing our research among the scientific community (e.g., scientists and students) and the general public through various online and offline channels.

Potential clinical impact

Given the fundamental approach of the studies in this dissertation, the direct clinical implications of its results are limited and must be carefully interpreted. However, current findings have generated first indications of links between emotional flexibility and recovery from pain, and of potential beneficial effects of mindfulness meditation on the process of wound healing. As such, they do contribute to our understanding of psychosocial protective factors related to pain and recovery, and thereby to our knowledge about factors involved in the transition from acute to chronic pain and the recovery of wounds.

The study presented in **chapter 2** has contributed to the increasingly dominant view that emotional flexibility is generally adaptive and healthy, and that emotional inflexibility or rigidity is broadly maladaptive. Advancing current theoretical models of pain and recovery with the addition of emotional flexibility may increase our knowledge about why some people are more protected against developing chronic pain than others. In the long term, this knowledge may provide clinicians with new insights on how to tailor prevention and treatment programs for patients with acute and chronic pain. For example, training of emotional flexibility before surgery might be of value to the prevention of slow post-operative recovery. Future research is required aiming to explore this potential by testing the trainability of emotional flexibility and its different components. In this context, promising results have already shown that cognitive flexibility can be improved with practice (Grönholm-Nyman et al., 2017; Zhao et al., 2018). Acceptance and Commitment Therapy may offer a way to increase emotional flexibility, as it is directed at improving psychological flexibility, the overarching construct of emotional flexibility (Hayes et al., 2012).

Mindfulness-based interventions (MBIs) are frequently used as treatments for chronic pain (e.g., Garland et al., 2019). Given the link between pain and tissue damage, MBIs may also be promising treatments for recovery from pain and of wounds. In order to prevent further suffering, MBI's may be offered as preventative treatments prior to the onset of acute pain, for instance before surgery. Along this line of reasoning, MBIs such as Mindfulness-Based Stress Reduction (MBSR) might be of use to the process of wound healing. Findings presented in **chapter 5** provide preliminary evidence for the potential of MBSR (delivered prior to wounding) to positively influence early stages of wound healing. Although these results should be confirmed in future research, they may be relevant for clinicians (e.g., surgeons) and people who will undergo surgery in the future and/or are at risk of slow wound healing.

REFERENCES

Breivik, H., Collett, B., Ventafridda, V., Cohen, R., & Gallacher, D. (2006). Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. *Eur J Pain, 10*(4), 287-333. https://doi.org/10.1016/j.ejpain.2005.06.009

Dahlhamer, J., Lucas, J., Zelaya, C., Nahin, R., Mackey, S., DeBar, L., Kerns, R., Von Korff, M., Porter, L., & Helmick, C. (2018). Prevalence of Chronic Pain and High-Impact Chronic Pain Among Adults — United States, 2016. *Morbidity and Mortality Weekly Report, 67*(36), 1001–1006. http://dx.doi.org/10.15585/mmwr.mm6736a2external

Dieleman, J. L., Cao, J., Chapin, A., Chen, C., Li, Z., Liu, A., Horst, C., Kaldjian, A., Matyasz, T., Scott, K. W., Bui, A. L., Campbell, M., Duber, H. C., Dunn, A. C., Flaxman, A. D., Fitzmaurice, C., Naghavi, M., Sadat, N., Shieh, P., Squires, E., Yeung, K., & Murray, C. J. L. (2020). US Health Care Spending by Payer and Health Condition, 1996-2016. *JAMA, 323*(9), 863-884. https://doi.org/10.1001/jama.2020.0734

Garland, E. L., Brintz, C. E., Hanley, A. W., Roseen, E. J., Atchley, R. M., Gaylord, S. A., Faurot, K. R., Yaffe, J., Fiander, M., & Keefe, F. J. (2019). Mind-Body Therapies for Opioid-Treated Pain: A Systematic Review and Meta-analysis. *JAMA internal medicine, 180*(1), 91-105. https://doi.org/10.1001/jamainternmed.2019.4917

Gaskin, D. J., & Richard, P. (2012). The Economic Costs of Pain in the United States. *The Journal of Pain, 13*(8), 715-724. https://doi.org/10.1016/j.jpain.2012.03.009

Grönholm-Nyman, P., Soveri, A., Rinne, J. O., Ek, E., Nyholm, A., Stigsdotter Neely, A., & Laine, M. (2017). Limited Effects of Set Shifting Training in Healthy Older Adults. *Frontiers in Aging Neuroscience, 9*(69). https://doi.org/10.3389/fnagi.2017.00069

Hayes, S. C., Pistorello, J., & Levin, M. E. (2012). Acceptance and Commitment Therapy as a Unified Model of Behavior Change. *The Counseling Psychologist, 40*(7), 976-1002. https://doi.org/10.1177/0011000012460836

Medicine, I. o. (2011). *Relieving pain in America: a blueprint for transforming prevention, care, education, and research.* National Academies Press.

Seligman, M. E. P. (2002). Positive psychology, positive prevention, and positive therapy. In *Handbook of positive psychology.* (pp. 3-9). Oxford University Press.

Zhao, X., Wang, H., & Maes, J. H. R. (2018). Training and transfer effects of extensive task-switching training in students. *Psychol Res*. https://doi.org/10.1007/s00426-018-1059-7

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ABOUT THE AUTHOR

Astrid Gerarda Henrica Meesters was born on October 1st, 1989, in Maastricht, The Netherlands. She graduated cum laude from secondary school (Gymnasium, Trevianum Scholengroep, Sittard) in 2008. After studying medicine at Maastricht University for half a year, she made the switch to psychology and completed a bachelor of science in biological psychology in 2012. During her research master in Cognitive and Clinical Neuroscience (track Fundamental Neuroscience) at Maastricht University, she completed an 8-month research internship at the Swammerdam Institute for Life Sciences, University of Amsterdam, the Netherlands. During this internship, Astrid examined the direct and lasting effects of chronic early-life stress (ES) on hippocampal neurogenesis and dentate gyrus structure in mice. Furthermore, she studied whether methyl donor supplementation of the maternal diet reverses the ES-induced changes in global hippocampal DNA methylation levels. Astrid obtained her master's degree in 2014. After working as a graduate research assistant at the Experimental Health Psychology section at the Clinical Psychological Science department at Maastricht University, she started a PhD position in the same lab in 2015. Under the supervision of Prof. Dr. Madelon Peters and Dr. Linda Vancleef, Astrid investigated flexibility and mindfulness as resilience factors for pain and recovery. After her PhD contract ended in the beginning of 2019, Astrid first worked as a researcher at Research Agency Flycatcher, and next as a lecturer at the Clinical Psychological Science department of Maastricht University. As of January 2022, Astrid has continued her academic career as a lecturer in the General Psychology section at the Open University, Heerlen.

OUTPUT

List of publications

Meesters, A., Hülstrung, S., & Omar, M. (*in preparation*). Psychological flexibility and mental health during the COVID-19 pandemic.

Meesters, A., Vancleef, L. M. G., & Peters, M. L. (*in preparation*). Stress-dependent dynamics of affect and pain: a diary study.

Meesters, A., Vancleef, L. M. G., & Peters, M. L. (2021). The role of cognitive and affective flexibility in individual differences in the experience of experimentally induced heat pain. *Journal of Experimental Psychopathology*. https://doi.org/10.1177/20438087211018447

Vancleef, L. M. G., **Meesters, A.**, & Schepers, J. (2019). The injury illness sensitivity index – Revised: Further validation in a Dutch community sample. *Cogent Psychology, 6*(1). https://doi.org/10.1080/23311908.2019.1629079.

Meesters, A., Vancleef, L. M. G., & Peters, M. L. (2018). Emotional flexibility and recovery from pain. *Motivation and Emotion, 43*, 493-504. https://doi.org/10.1007/s11031-018-9748-5.

Meesters, A., In den Bosch-Meevissen, Y., & Peters, M. (2018). The relationship between pro-inflammatory cytokines, growth factors and wound healing after mindfulness meditation. *International Journal of Behavioral Medicine, 25*(S1), S93-S93. https://doi.org/10.1007/s12529-018-9740-1

Meesters, A., In den Bosch-Meevissen, Y. M. C., Weijzen, C. A. H., Buurman, W. A., Losen, M., Schepers, J., Thissen, M. R. T. M., Alberts, H. J. E. M., Schalkwijk, C. G., & Peters, M. L. (2018). The effects of Mindfulness-Based Stress Reduction on wound healing: a preliminary study. *Journal of Behavioral Medicine, 41*(3), 385-397. https://doi.org/10.1007/s10865-017-9901-8.

Naninck, E. F. G., Hoeijmakers, L., Kakava-Georgiadou, N., **Meesters, A.**, Lucassen, P. J. & Korosi, A. (2015). Chronic early life stress alters developmental and adult neurogenesis and impairs cognitive function in mice. *Hippocampus, 25*(3), 309-328. https://doi.org/10.1002/hipo.22374.

Conference proceedings – Oral presentations

International Congress of Behavioral Medicine (ICBM), Santiago, Chile (2018). A randomized wait-list controlled trial of the effect of mindfulness meditation for wound healing.

Pain Research Meeting, Lanaken, Belgium (2018). The role of mindfulness meditation in pain experience and recovery from pain: affective and/or cognitive flexibility as possible underlying mechanisms?

EPP PhD day, Utrecht, The Netherlands (2018). The predictive value of emotional and cognitive flexibility for pain and recovery from pain.

EPP day, Battle of the Brains, Utrecht, The Netherlands (2017). Emotional flexibility as a predictor of pain tolerance and recovery from pain.

Pain Research Meeting, Gent, Belgium (2015). Psychological predictors and mechanisms underlying pain and recovery from pain: a role for emotional flexibility?

Conference proceedings – Poster presentations

IASP World Congress on Pain, Boston, United States (2018). The predictive value of affective and cognitive flexibility for pain responses.

FPN Research Day, Maastricht, The Netherlands (2018). Psychological predictors and mechanisms underlying recovery from pain: a role for affective flexibility?

10th Congress of the European Pain Federation (EFIC), Copenhagen, Denmark (2017). Emotional flexibility as a predictor of pain tolerance and recovery from pain.

International Congress of Behavioral Medicine (ICBM), Melbourne, Australia (2016). The effect of mindfulness-based stress reduction on wound healing.

Pain Research Meeting, Rauischholzhausen, Germany (2016). Psychological predictors and mechanisms underlying recovery from pain: a role for affective flexibility?

FPN Research day, Maastricht, The Netherlands (2016). Psychological predictors and mechanisms underlying recovery from pain: a role for emotional flexibility?

Emotions Congress, Tilburg, The Netherlands (2015). Mindfulness as an intervention for wound healing.

Research master graduation symposium, Maastricht, The Netherlands (2015). The role of nutritional epigenetic programming in the effects of chronic early-life stress on hippocampal neurogenesis and dentate gyrus structure.

12th Dutch Endo-Neuro-Psycho meeting, Lunteren, The Netherlands (2014). Nutrition and stress during early life induce epigenetic changes in the adult hippocampus.

Psychology Student Conference, Maastricht, The Netherlands (2013). The relationship between impulsivity, weigh concern and the yoyo-effect in healthy women.

APPENDIX A: SUPPLEMENTARY MATERIALS TO CHAPTER 4

Retrospective pain experience, cognitions and coping strategies questions

For each question, please choose the answer that applies to you. Choose the number that best represents your answer.

The following questions refer to the **procedure** during which an inflated cuff was attached to your upper arm and was left there for some time. We are mainly interested in the sensations that were induced by this procedure in your **entire** arm. Thus, when referring to this procedure, we are not only interested in the induced sensations in the area of the cuff, but also in your fingers, hand, entire fore and upper arm.

Among other things, we will ask you to evaluate the procedure in terms of **intensity** (**painfulness**) and **unpleasantness**. To illustrate the difference between intensity and unpleasantness, you can think of listening to a sound, like from a radio. When the volume of this sound goes up, we can ask you how loud this sound is to you or how uncomfortable it is to you. The intensity of a painful sensation is like the volume of a sound; the unpleasantness of a painful sensation depends on the intensity but also on other things that can influence the unpleasantness of the experience.

1. How painful was the procedure with the inflated cuff around your arm on average?
   [0 = *not painful at all* 10 = *extremely painful*]

2. How unpleasant was the procedure with the inflated cuff around your arm on average?
   [0 = *not unpleasant at all* 10 = *extremely unpleasant*]

3. How threatening was the procedure with the inflated cuff around your arm to you?
   [0 = *not threatening at all* 10 = *extremely threatening*]

4. How harmful did you think was the procedure with the inflated cuff around your arm?
   [0 = *not harmful at all* 10 = *extremely harmful*]

5. How fearful were you of the procedure with the inflated cuff around your arm?
   [0 = *not fearful at all* 10 = *extremely fearful*]

6. How much stress did you experience on average during the procedure with the inflated cuff around your arm?
   [0 = *no stress at all* 10 = *an extreme amount of stress*]

7. **During the procedure** with the inflated cuff around your arm, how often did you <u>think</u> or <u>feel</u> the following?

	Almost never so-me-times (1)	Some-times (2)	About half the time (3)	Most of the time (4)	Almost all the time (5)
1. Could this be harmful for my arm?	O	O	O	O	O
2. Is what I am currently feeling, normal?	O	O	O	O	O
3. It's becoming too much for me.	O	O	O	O	O
4. I cannot think of anything else but the pain.	O	O	O	O	O
5. I'm afraid that the pain will get worse.	O	O	O	O	O

8. **During the recovery** period of this procedure (that is, after the cuff was deflated and removed), how often did you think or feel the following?

	Almost never so-me-times (1)	Some-times (2)	About half the time (3)	Most of the time (4)	Almost all the time (5)
1. Could this be harmful for my arm?	O	O	O	O	O
2. Is what I am currently feeling, normal?	O	O	O	O	O
3. It's becoming too much for me.	O	O	O	O	O
4. I cannot think of anything else but the pain.	O	O	O	O	O
5. I'm afraid that the pain will get worse.	O	O	O	O	O

9. How did you try to cope with the procedure with the inflated cuff around your arm? (open question)

10. How did you try to cope with the procedure with the inflated cuff around your arm? Please rank the following coping strategies in the order of most frequently used strategy where 1 is the most frequently used and 7 least frequently used strategy.

    To rank the listed items, drag and drop each item.

    - I distracted myself
    - I consciously choose to experience the pain
    - I constantly concentrated on the pain
    - I tried to relax
    - I focused on my breath
    - I told myself that the procedure was safe
    - I ignored the pain
    - I accepted the situation
    - Other, namely: ...

APPENDIX B: SUPPLEMENTARY MATERIALS TO CHAPTER 5

Table S1. Absolute cytokine and growth factor concentrations (pg/mL) as measured with the multi-array platform of MesoScaleDiscovery

	WLC Women			**WLC Men**		
	T1 (n = 21)	**T2 (n = 21)**	**T3 (n = 18)**	**T1 (n = 5)**	**T2 (n = 5)**	**T3 (n = 2)**
IL-1β	1.44 (1.38)	1.80 (1.58)	1510 (2638)	0.88 (0.90)	2.04 (2.43)	5593 (1842)
IL-6	118 (104)	604 (376)	4843 (4195)	193 (153)	725 (547)	8759 (326)
IL-8	44.3 (37.1)	77.4 (52.7)	5341 (2170)	99.7 (59.8)	144 (94.1)	8255 (268)
TNF-α	4.51 (4.46)	6.23 (5.53)	1201 (2402)	5.08 (3.34)	6.77 (2.71)	5112 (218)
PlGF	-	-	20.0 (11.1)	-	-	26.8 (7.33)
VEGF	-	-	580 (555)	-	-	3351 (1615)
sFlt-1	-	-	482 (717)	-	-	4869 (3776)
	MBSR Women			**MBSR Men**		
	T1 (n = 19)	**T2 (n = 19)**	**T3 (n = 18)**	**T1 (n = 3)**	**T2 (n = 3)**	**T3 (n = 2)**
IL-1β	0.51 (0.39)	1.29 (1.16)	692 (994)	0.30 (0.34)	0.78 (0.80)	3784 (828)
IL-6	118 (101)	565 (482)	4686 (5064)	144 (140)	384 (114)	6582 (3363)
IL-8	45.8 (40.4)	76.4 (51.4)	3970 (2167)	31.7 (13.5)	64.8 (27.4)	7405 (1848)
TNF-α	3.03 (2.24)	5.14 (3.55)	894 (1360)	5.72 (5.23)	7.51 (7.82)	3815 (2042)
PlGF	-	-	11.6 (5.30)	-	-	31.9 (15.4)
VEGF	-	-	412 (381)	-	-	761 (132)
sFlt-1	-	-	477 (692)	-	-	815 (890)

Data are presented as mean (SD). WLC = waiting-list control group; MBSR = Mindfulness-Based Stress Reduction group; T1 = 3 h post wound induction; T2 = 6 h post wound induction; T3 = 22 h post wound induction; IL = interleukin; TNF-α = tumor necrosis factor α; PlGF = placental growth factor; VEGF = vascular endothelial growth factor; sFlt-1 = soluble Fms-like tyrosine kinase-1.