



Are the antidepressive effects of massage therapy mediated by restoration of impaired interoceptive functioning? A novel hypothetical mechanism

Michael Eggart^{a,b}, Silvia Queri^b, Bruno Müller-Oerlinghausen^{c,d,*}

^a Department of Psychiatry and Psychotherapy I, Ulm University, Ravensburg (Center for Psychiatry Südwürttemberg), Germany

^b Faculty Social Work, Health and Nursing, University of Applied Sciences Ravensburg-Weingarten, Weingarten, Germany

^c Charité Universitätsmedizin Berlin, Germany

^d Medical School Brandenburg Theodor Fontane, Neuruppin, Germany

ARTICLE INFO

Keywords:

Major depressive disorder
Depression
Interoception
Mechanism of action
Touch
Massage

ABSTRACT

Interoception is an individual person's sense of the physiological condition of his/her entire body. Recent research has shown that depression is associated with impaired interoceptive accuracy. Treatments that can improve disturbed interoception are scarce in clinical practice and could complement established therapies. Accumulating evidence suggests that massage therapy significantly alleviates symptoms of depression. However, the mechanisms underlying these effects have remained unclear. We are going to propose a novel mechanism linking these antidepressive effects to a massage-induced modulation of interoceptive states. Particularly affective massage therapy applies slow, rhythmic, and caress-like touch that stimulates C tactile (CT) afferents in the non-glabrous skin. CT mediated touch elicits responses in interoceptive brain areas (e.g. the insular cortex) that have been associated with abnormal interoceptive representations in depressed subjects. Thus, we hypothesize that antidepressive effects of massage therapy are mediated by restoration of the impaired interoceptive functioning through stimulation of CT afferents or related interoceptive structures. If our proposed mechanism is valid, massage is probably one of the most ancient interoceptive treatments.

Introduction

Major depressive disorder (MDD) is one of the most common mental disorders with an estimated age-standardized point prevalence of 4.1–4.7% [1] and a cumulative lifetime risk of 14.6% for high-income [2]. Females are more prone to develop MDD, with women having a roughly twofold higher risk compared to men [2]. Depression is a highly recurrent mood disorder [3] that gives rise to chronicity in 15% of all affected subjects [4]. According to data of the Global Burden of Disease Study, depression is the leading cause of disability attributable to mental disorders [5] and ranks third among all leading causes of disability worldwide [6]. Symptoms of depression also occur as a comorbidity in diseases other than MDD, e.g. cancer, Parkinson's disease, inflammatory bowel disease or pain conditions [7–10]. Thus, depression is of significant public health relevance and challenges the medical care system [11].

Pharmacotherapy and psychotherapy are currently the state-of-the-art treatments for the management of depression. Nevertheless, use of complementary and alternative medicine (CAM) for depression is widespread especially in the U.S. [12,13]. Main reasons for using CAM

were negative experiences with conventional medical treatments like adverse effects or non-response to various treatments [14]. Survey data suggest that manual therapies like massage or acupuncture are preferred by depressed subjects using CAM treatments [14]. While most CAM procedures lack any scientific proof of their efficacy accumulating evidence exists that massage therapy alleviates symptoms of depression as well as anxiety, pain, and perceived stress [15–19]. Whereas one review which focuses exclusively on four RCTs having applied classical Swedish massage claimed insufficient evidence for antidepressive or anxiolytic effects of massage [20], an older meta-analysis concluded that the effect size of massage therapy in depression is moderate to large and comparable to those of psychotherapy [17]. In hospitalized MDD patients using a randomized cross-over-design, it could be clearly shown that massage therapy is superior to a relaxing non-touch control situation [21]. Positive effects of a combination of mindfulness practice and touch therapy have also been shown in moderately depressed patients [22]. Massage therapy also alleviates comorbid depression in different medical conditions, such as acquired immune deficiency syndrome [23], breast cancer [24], chronic fatigue syndrome [25] or dementia [26]. Antidepressive and anxiolytic effects of massage

* Corresponding author at: Bartningallee 11-13, 10557 Berlin, Germany.

E-mail address: bruno.mueller-oerlinghausen@web.de (B. Müller-Oerlinghausen).

therapy have also been shown in the perinatal period [27,28]. Meta-analytic evidence suggests that multiple sessions of massage therapy have the largest effects on depression. Some reviewers concluded that two treatments per week over a span of five weeks and a single treatment duration of at least 30 min appear to have the most positive effects [15,17]. Although the antidepressive effects of massage therapy seem to be relatively well established, the basic mechanism of action remains unclear. However, evidence exists for various associated changes on either a biological or psychological explanatory level (see below). Depression is characterized by various symptoms. Thus, the question arises which single symptoms are alleviated by massage therapy? According to some papers [21,29,30] massage therapy is able to reduce depressed mood, state anxiety, perceived stress, somatic and mental fatigue, restlessness and muscular tension. The antidepressive effect seems to be more marked than the anxiolytic effect [15,17].

In the following, we are going to propose a hypothetical mechanism of touch-related antidepressive treatment based on modern interoception research. First, interoceptive disturbances in depression will be presented. Second, we will refer to human skin as a target organ for interoceptive treatments. Third, we will classify massage therapy as possibly one of the most ancient interoceptive treatments and will highlight its transdiagnostic treatment characteristics.

Interoception and depression

Interoception is defined as the sense of the physiological condition of the entire body [31,32]. It comprises the sensation, interpretation, and integration of signals arising from within the body [33]. Different facets of interoception have been proposed [34]: interoceptive accuracy (“objective accuracy in detecting internal bodily sensations”), interoceptive sensibility (“self-perceived dispositional tendency to be internally self-focused and interoceptively cognisant”) and interoceptive awareness (“metacognitive awareness of interoceptive accuracy”). In psychiatric research, most of published work has focused on the study of interoceptive accuracy [35] by using the Schandry task. This heartbeat mental tracking task assesses the ability of a subject to accurately count the number of one’s heartbeats in a series of trials without taking the pulse [36]. The task is widespread since it is an easy to be used and non-invasive accuracy measure. To the best of our knowledge, other interoceptive modalities like gastric or rectum perception accuracy as well as assessment of interoceptive dimensions other than interoceptive accuracy (e.g. interoceptive sensibility) have rarely been assessed so far in depression research, possibly due to their invasiveness and due to incongruencies in construct validity among available interoceptive self-report scales [35,37].

Interoception is increasingly considered as substantial for the understanding of psychopathological and psychosomatic processes. Several mental disorders have been associated with impaired interoceptive functioning [38–40]. It has been shown that severity of MDD is associated with disturbances in interoceptive accuracy (for a comprehensive review, see [41,42]). Thus, moderately depressed subjects exhibit the largest deficits in accurately perceiving their heartbeats [43–48]. These patients may be classified as poor heartbeat perceivers since they underestimate the number of their heartbeats in the heartbeat mental tracking task. However, cardiac interoceptive accuracy scores have been reported to normalize with increasing depression severity. It has been speculated that these “normalizing effects” may be confounded by intake of selective serotonin reuptake inhibitors or by comorbid anxiety disorder [43]. In summary, impairments in interoceptive functioning depend on depression severity with moderately depressed subjects exhibiting the largest deficits to perceive their heartbeats.

It has also been investigated whether single symptoms of depression are associated with interoceptive impairments. In a study with clinically depressed subjects, those with decision-making difficulties exhibited significantly worse heartbeat perception abilities than subjects

without decision-making difficulties [45]. Furthermore, it has been shown that the intensity of positive affect positively correlates with cardiac interoceptive accuracy in MDD. Thus, poor heartbeat perceivers are experiencing reduced intensities of positive emotions [45]. These findings may imply that anhedonia is intimately linked to blunted heartbeat perception in depressed subjects. Finally, suicidality including suicidal ideation as well as planning and attempting suicide has been linked to a distorted interoceptive awareness [49,50].

It is currently unclear if interoceptive impairments are a cause or consequence of depressive disorders [33]. Besides, it is unclear why the perception of heartbeat activity is blunted in depression [45]. Despite increasing interest in depression-related interoceptive deficits [43–48], treatment approaches that explicitly target the interoceptive system of depressed subjects are scarce in clinical practice but currently under investigation, e.g. in the form of whole-body hyperthermia [51], Floatation-REST (Reduced Environmental Stimulation Therapy) sessions [52], or functional magnetic resonance imaging neurofeedback training [53,54].

A plea for interoceptive treatments

There is a need for the development of new treatment strategies that both target the interoceptive system and alleviate interoceptive impairments in a variety of psychiatric or psychosomatic patients [33]. Challenges in developing interoceptive treatments generally raise two substantial issues: a) Is there any way to counteract interoceptive deficits (e.g. impaired interoceptive accuracy)? b) Do interventions that influence interoception (e.g. by increasing interoceptive accuracy) result in changes of mental states? If there is scientific evidence to answer in the affirmative these two basic questions, the essential condition underlying interoceptive treatments may be met. Hence, we will first briefly discuss these topics in the following section. Then, we shall develop a novel hypothesis on the mechanisms of affective massage therapy in depression.

Various studies suggest that interoceptive accuracy can be modulated by therapeutic interventions and is thus not immutable. Both cardiac biofeedback training and exercise in body awareness (“body scan” meditation) have been shown to improve interoceptive accuracy in healthy adults [55–57]. However, interoceptive treatments will only be of clinical significance if changes in interoceptive performance imply significant clinical effects. Thus, Bornemann et al. [56] demonstrated that improvement of interoceptive accuracy through a body scan intervention over nine months is associated with an increase in emotional awareness by reducing alexithymia – an observation which appears significant since alexithymia and depression are closely linked [58]. Alexithymia predicts poor performance in heartbeat perception task [59] comparable to the influence of depression. According to Schaefer et al. [60] a heartbeat perception training significantly reduced symptom distress in participants with somatoform disorder. Against the background that higher somatic symptom severity is correlated with decreased cardiac interoceptive accuracy in somatoform disorder [61], the findings of Schaefer et al. seem to be of special importance. Somatic disturbances are also highly prevalent in depression [62]. Interoceptive impairments may be linked with affective and somatic symptoms of depression for several reasons [42]: First, evidence suggests morphological and functional abnormalities in interoceptive brain areas (e.g. insula, anterior cingulate cortex, orbitofrontal cortex) which have been associated with both depression severity and somatic symptom severity [42,63,64]. Second, vagal nerve stimulation has shown promising results in treatment-resistant depression [65] suggesting an interoceptive involvement [66]. The vagus nerve converges with interoceptive afferents that form interoceptive brain centers. Transcutaneous vagus nerve stimulation is capable to modulate interoceptive brain networks [33,66,67]. Thus, the antidepressant effects might be mediated by increasing interoceptive accuracy since vagal nerve stimulation has shown to increase spontaneous cardiac baroreflex sensitivity [67,68].

Arterial baroreceptors are “cardiac interoceptors” [68,69] and baroreceptor sensitivity has positively been correlated with cardiac interoceptive accuracy in a single report [68]. Hence, vagal stimulation probably impinges on the body-brain-axis by reducing signal-to-noise ratio in interoceptive processing [42]. In conclusion, preliminary evidence suggests that therapeutic modulation of interoceptive accuracy may result in alleviation of affective and somatic symptoms of depression.

Affective massage therapy and its hypothetical antidepressive mechanism

In the following, we are going to delineate the characteristics of those massage techniques which have been shown to elicit mental effects. There exist many different types of massage (e.g. deep tissue massage, hot stone massage, sports massage, shiatsu massage etc.) that focus on various parts of the body resulting into individual massage therapy outcomes (e.g. muscle relaxation in Swedish massage). Following Moyer [70], we prefer the term *affective massage therapy* which includes all types of massage therapies aiming to influence affective states rather than primarily loosening muscles or manipulating fascial tissues. It is important to note that affective massage therapy is not another new therapy type. Instead, the term affective massage therapy comprises various massage styles that induce psychophysical effects and share common characteristics: First, such massages operate within a context emphasizing the intention of the massage therapist to alleviate psychopathological symptoms or to enhance psychophysical well-being. Second, affective massage therapy predominantly makes use of massage techniques such as effleurage (i.e. soft stroking) having been shown to affect positively e.g. mood, anxiety or perceived stress. A major limitation of a wide range of publications on affective massage therapy is the lack of a concise description of the applied massage techniques. However, as we have shown in a clinically depressed population as well as in a mildly depressed community sample, long strokes and caress-like touch yielded clinically significant effect sizes regarding reductions in depression severity [21,71]. Effleurage is also used in the well-known Swedish massage tradition. These techniques closely resemble *affective touch* – a term coined by neurophysiologists defining gentle stroking conditions (e.g. with a brush) within an optimal velocity range between 1 and 10 cm/s that is associated with a response of specialized C fibers in the human skin (see below). Affective touch elicits a subjective sense of psychophysical well-being that has been correlated with activations in limbic cortical areas [72–74]. Recent evidence suggests that manual foot massage for 10 min not only resembles affective touch but elicits stronger activations than machine administered touch in cortical areas that have been linked with affective touch [74]. Therefore, following Occam's razor principle, we shall operationalize affective touch by hand as a core element of affective massage therapy since affective touch is an established and widely accepted concept having gained remarkable scientific interest during the last decade.

The essential mechanisms behind antidepressive effects of affective massage therapy so far have remained unclear [17,18]. For example, it has been reasoned that massage elicits a decrease in stress response [75]. However, effects of massage on cortisol plasma/saliva levels are very small or even not significantly different from zero. Thus, it seems unlikely that decreases in cortisol levels could be seen as the basic mechanism of widely documented antidepressant, anxiolytic and analgesic effects of affective massage therapy [76]. Other mechanisms have been proposed to explain affective outcomes of massage therapy [17]: whereas the Touch Research Institute has always stressed the shift to parasympathetic activity [77], others have underlined influences on body chemistry (serotonin and endorphins), promotion of restorative sleep, interpersonal attention, or simple relaxation effects [12]. The release of oxytocin might play an important role [78]. Effects on the immune system have also been documented [79]. Recent research

suggested that massage therapy may train interoceptive skills that elicit adaptive emotion regulation strategies [80] by improving somatic awareness in posttraumatic stress disorder [81].

Affective massage therapy directly stimulates the interoceptive nervous system by application of affective touch which arouses particular afferents in the non-glabrous skin that respond to social touch interactions and elicit a state of well-being [73]. Accumulating neuroanatomical evidence suggests that the non-glabrous mammalian skin contains numerous mechanosensitive receptors which give rise to subjectively perceived pleasantness in response to slow, rhythmic, and caress-like touch [73]. These unmyelinated C tactile (CT) afferents encode affective rather than discriminative features of touch [72]. CT afferents project to the insular cortex via the lamina I spinothalamocortical pathway that relays homeostatic information to the insula and other interoception-related brain regions [31,32]. It has been speculated that this homeostatic pathway forms the basis for the construction of affective states and self-awareness [31]. An abundance of research has shown that CT afferents are involved in the maintenance of psychophysical and social well-being [73,82–84]. Furthermore, optimal stimulation of CT afferents (stroking touch velocity ~3 cm/s) elicits positive affective states with activation of the zygomaticus major muscle [85]. Accordingly, the antidepressant effects of affective massage therapy might be in part mediated by optimally activating the CT network through application of affective touch [71]. Following this concept, psychosomatic effects of affective touch possibly result in an enhancement of bodily self-awareness [86] and an activation of interoceptive regulation mechanisms [87,88] that presumably mitigate abnormal interoceptive representations in depression. In fact, a recent study has demonstrated that gentle touch increases interoceptive accuracy in healthy adults highlighting the skin as a gateway to modulate interoceptive accuracy [89]. At the neurophysiological level, the insula (or primary interoceptive cortex) might be a key structure to study the proposed interoceptive mechanism. Insula activity is significantly decreased in depressed subjects during a heartbeat perception task compared to healthy controls. Besides, depression severity is negatively correlated with insula activity [63]. Furthermore, it has been shown that CT fiber mediated touch elicits increased activity in the insula in healthy adults [90]. Despite lack of published work, it can be assumed that affective touch also elicits responses in the insular cortex of depressed subjects. Hence, affective massage therapy could mitigate the above mentioned abnormal interoceptive representations in the insula.

Considering impaired interoception in depression, CT afferents and their relation to the interoceptive nervous system could be the missing link for explaining mental effects of affective massage therapy. To our best knowledge, such an association has never been tested before in depressed subjects. Additionally, it has been suggested that effects of massage therapy are mediated by pressure receptors lying in and beneath the skin that, in turn, stimulate vagal activity [91]. The parasympathetic activation possibly complements massage therapy's effects on interoception since the vagus nerve is part of the interoceptive nervous system [for review Ref. [42]]. As outlined above, transcutaneous vagal stimulation improves spontaneous cardiac baroreflex sensitivity [67] that has been associated with higher interoceptive accuracy [68]. In summary, affective touch is not only promoting positive affective responses, but also eliciting psychophysiological changes that are intimately associated with the interoceptive nervous system [92]. Thus, it appears plausible to assume that the human skin could be a particularly safe gateway to modulate interoceptive states.

Future research may examine the hypothetical mechanisms that have been proposed regarding mental effects of affective massage therapy. We recommend the use of manual massage rather than using machine touch since machine administered massage elicits weaker

* The following search terms yielded no document match in PubMed: interocept* AND (massage OR touch) AND depress* (date: November 2018).

cortical and oxytocin responses [74]. First, pilot studies may investigate the impact of affective massage therapy on interoceptive accuracy in healthy adults using the heartbeat tracking task [36]. In addition, randomized controlled trials including clinically depressed subjects would be worthwhile.

Affective massage therapy as a transdiagnostic intervention?

Interoceptive disturbances do not exist exclusively in depression. Instead, impaired interoception is a transdiagnostic characteristic of several mental disorders such as panic and generalized anxiety disorder [93], eating disorder [94,95], substance use disorder [96], somatic symptom disorder [35], or autism spectrum disorder [97]. Furthermore, interoceptive disturbances have been associated with an abundance of painful and nonpainful clinical conditions, e.g. increased/decreased appetite, itch, fatigue, myalgia, or headaches [33]. Accordingly, affective massage therapy has shown to be effective in the complementary management of disorders other than depression, e.g. generalized anxiety disorder [98], chronic pain conditions [99–101], or cancer-related fatigue [102]. Therefore, affective massage therapy may be classified as a transdiagnostic intervention that merits more high-quality research in psychiatry and psychosomatic medicine. Against the background of current neuroscientific knowledge and considering the interoceptive nervous system as well as CT afferents in the human skin [31,32,66,73], studies investigating effects of affective massage therapy may be built upon a scientifically well-established theoretical framework that incorporates interoception research.

Acknowledgement

The authors acknowledge the reviewers for their critical reading of the manuscript and for suggesting significant improvements.

Declarations of interest

BMOe is a member and former chairman of the Drug Commission of the German Medical Association. He belongs to an expert panel for the designing and monitoring of a pharmacogenetic study sponsored by STADA, Germany. SQ and ME declare no conflict of interest.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or non-profit sectors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.mehy.2019.05.004>.

References

- [1] Baxter AJ, Scott KM, Ferrari AJ, Norman RE, Vos T, Whiteford HA. Challenging the myth of an “epidemic” of common mental disorders: trends in the global prevalence of anxiety and depression between 1990 and 2010. *Depress Anxiety* 2014;31(6):506–16.
- [2] Bromet E, Andrade LH, Hwang I, Sampson NA, Alonso J, de Girolamo G, et al. Cross-national epidemiology of DSM-IV major depressive episode. *BMC Med* 2011;9:90.
- [3] Burcusa SL, Iacono WG. Risk for recurrence in depression. *Clin Psychol Rev* 2007;27(8):959–85.
- [4] Eaton WW, Shao H, Nestadt G, Lee HB, Bienvenu OJ, Zandi P. Population-based study of first onset and chronicity in major depressive disorder. *Arch Gen Psychiatry* 2008;65(5):513–20.
- [5] Whiteford HA, Degenhardt L, Rehm J, Baxter AJ, Ferrari AJ, Erskine HE, et al. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. *Lancet* 2013;382(9904):1575–86.
- [6] Vos T, Allen C, Arora M, Barber RM, Bhutta ZA, Brown A, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease

- Study 2015. *Lancet* 2016;388(10053):1545–602.
- [7] Bair MJ, Robinson RL, Katon W, Kroenke K. Depression and pain comorbidity: a literature review. *Arch Intern Med* 2003;163(20):2433–45.
- [8] Marsh L. Depression and Parkinson's disease: current knowledge. *Curr Neurol Neurosci Rep* 2013;13(12):409.
- [9] Martin-Subero M, Anderson G, Kanchanatawan B, Berk M, Maes M. Comorbidity between depression and inflammatory bowel disease explained by immune-inflammatory, oxidative, and nitrosative stress; tryptophan catabolite; and gut-brain pathways. *CNS Spectr* 2016;21(2):184–98.
- [10] Bortolato B, Hyphantis TN, Valpione S, Perini G, Maes M, Morris G, et al. Depression in cancer: the many biobehavioral pathways driving tumor progression. *Cancer Treat Rev* 2017;52:58–70.
- [11] Cassano P, Fava M. Depression and public health: an overview. *J Psychosom Res* 2002;53(4):849–57.
- [12] Ernst E, Rand JI, Stevinson C. Complementary therapies for depression: an overview. *Arch Gen Psychiatry* 1998;55(11):1026–32.
- [13] Kessler RC, Soukup J, Davis RB, Foster DF, Wilkey SA, van Rompay MI, et al. The use of complementary and alternative therapies to treat anxiety and depression in the United States. *Am J Psychiatry* 2001;158(2):289–94.
- [14] Wu P, Fuller C, Liu X, Lee H-C, Fan B, Hoven CW, et al. Use of complementary and alternative medicine among women with depression: results of a national survey. *Psychiatric Serv* 2007;58(3):349–56.
- [15] Baumgart S, Müller-Oerlinghausen B, Schendera CFG. Efficacy of massage therapy on depression and anxious disorders as well as on depressiveness and anxiety as comorbidity—a systematic overview of controlled studies. *Physikalische Medizin, Rehabilitationsmedizin, Kurortmedizin* 2011;21(4):167–82.
- [16] Hou W-H, Chiang P-T, Hsu T-Y, Chiu S-Y, Yen Y-C. Treatment effects of massage therapy in depressed people: a meta-analysis. *J Clin Psychiatry* 2010;71(7):894–901.
- [17] Moyer CA, Rounds J, Hannum JW. A meta-analysis of massage therapy research. *Psychol Bull* 2004;130(1):3–18.
- [18] Rapaport MH, Schettler PJ, Larson ER, Carroll D, Sharenko M, Nettles J, et al. Massage therapy for psychiatric disorders. *Focus* 2018;16(1):24–31.
- [19] Association of Massage Therapists (AMT). Classified Massage Therapy Research. [April 03, 2019]; Available from: <http://www.amt.org.au/downloads/practice-resources/AMT-Classified-Research-January-2018.pdf>.
- [20] Coelho HF, Boddy K, Ernst E. Massage therapy for the treatment of depression: a systematic review. *Int J Clin Pract* 2008;62(2):325–33.
- [21] Müller-Oerlinghausen B, Berg C, Scherer P, Mackert A, Moestl H-P, Wolf J. Effects of slow-stroke massage as complementary treatment of depressed hospitalized patients. *Dtsch Med Wochenschr* 2004;129(24):1363–8.
- [22] Stötter A, Mitsche M, Eandler PC, Oleksy P, Kamenschek D, Mosgoeller W, et al. Mindfulness-based touch therapy and mindfulness practice in persons with moderate depression. *Body Movement Dance Psychotherapy* 2013;8(3):183–98.
- [23] Poland RE, Gertsik L, Favreau JT, Smith SI, Mirocha JM, Rao U, et al. Open-label, randomized, parallel-group controlled clinical trial of massage for treatment of depression in HIV-infected subjects. *J Altern Complement Med* 2013;19(4):334–40.
- [24] Krohn M, Listing M, Tjahjono G, Reissauer A, Peters E, Klapp BF, et al. Depression, mood, stress, and Th1/Th2 immune balance in primary breast cancer patients undergoing classical massage therapy. *Support Care Cancer* 2011;19(9):1303–11.
- [25] Field TM, Sunshine W, Hernandezreif M, Quintino O, Schanberg S, Kuhn C, et al. Massage therapy effects on depression and somatic symptoms in chronic fatigue syndrome. *J Chron Fatigue Syndr* 2011;3(3):43–51.
- [26] Yang Y-P, Lee F-P, Chao H-C, Hsu F-Y, Wang J-J. Comparing the effects of cognitive stimulation, reminiscence, and aroma-massage on agitation and depressive mood in people with dementia. *J Am Med Direct Assoc* 2016;17(8):719–24.
- [27] Deligiannidis KM, Freeman MP. Complementary and alternative medicine therapies for perinatal depression. *Best Pract Res Clin Obstet Gynaecol* 2014;28(1):85–95.
- [28] Field T, Diego M, Hernandez-Reif M. Prenatal depression effects and interventions: a review. *Infant Behav Develop* 2010;33(4):409–18.
- [29] Field T, Diego MA, Hernandez-Reif M, Schanberg S, Kuhn C. Massage therapy effects on depressed pregnant women. *J Psychosom Obstet Gynaecol* 2004;25(2):115–22.
- [30] Shulman KR, Jones GE. The effectiveness of massage therapy intervention on reducing anxiety in the workplace. *J Appl Behav Sci* 1996;32(2):160–73.
- [31] Craig AD. How do you feel? Interoception: the sense of the physiological condition of the body. *Nat Rev Neurosci* 2002;3(8):655–66.
- [32] Craig AD. How do you feel – now? The anterior insula and human awareness. *Nat Rev Neurosci* 2009;10(1):59–70.
- [33] Khalsa SS, Adolphs R, Cameron OG, Critchley HD, Davenport PW, Feinstein JS, et al. Interception and mental health: a roadmap. *Biol Psychiatry: Cogn Neurosci Neuroimaging* 2018;3(6):501–13.
- [34] Garfinkel SN, Seth AK, Barrett AB, Suzuki K, Critchley HD. Knowing your own heart: distinguishing interoceptive accuracy from interoceptive awareness. *Biol Psychol* 2015;104:65–74.
- [35] Khalsa SS, Lapidus RC. Can Interoception Improve the Pragmatic Search for Biomarkers in Psychiatry? *Front Psychiatry* 2016;7:121.
- [36] Schandry R. Heart beat perception and emotional experience. *Psychophysiology* 1981;18(4):483–8.
- [37] Mehling W. Differentiating attention styles and regulatory aspects of self-reported interoceptive sensibility. *Philos Trans R Soc Lond B Biol Sci* 2016;371(1708).
- [38] Cameron OG. Interoception: the inside story – a model for psychosomatic processes. *Psychosom Med* 2001;63(5):697–710.
- [39] Murphy J, Brewer R, Catmur C, Bird G. Interoception and psychopathology: a developmental neuroscience perspective. *Develop Cogn Neurosci* 2017;23:45–56.
- [40] Duquette P. Increasing our insular world view: interoception and psychopathology for psychotherapists. *Front Neurosci* 2017;11:135.

- [41] Eggart M, Lange A, Binsler MJ, Queri S, Müller-Oerlinghausen B. Major depressive disorder is associated with impaired interoceptive accuracy: A systematic review in prep.
- [42] Harshaw C. Interoceptive dysfunction: toward an integrated framework for understanding somatic and affective disturbance in depression. *Psychol Bull* 2015;141(2):311–63.
- [43] Dunn BD, Dalgleish T, Ogilvie AD, Lawrence AD. Heartbeat perception in depression. *Behav Res Ther* 2007;45(8):1921–30.
- [44] Ehlers A, Breuer P. Increased cardiac awareness in panic disorder. *J Abnorm Psychol* 1992;101(3):371–82.
- [45] Furman DJ, Waugh CE, Bhattacharjee K, Thompson RJ, Gotlib IH. Interoceptive awareness, positive affect, and decision making in Major Depressive Disorder. *J Affect Disord* 2013;151(2):780–5.
- [46] Mussgay L, Klinkenberg N, Rüdell H. Heart beat perception in patients with depressive, somatoform, and personality disorders. *J Psychophysiol* 1999;13(1):27–36.
- [47] Terhaar J, Viola FC, Bar K-J, Debener S. Heartbeat evoked potentials mirror altered body perception in depressed patients. *Clin Neurophysiol* 2012;123(10):1950–7.
- [48] van der Does AJW, van Dyck R, Spinhoven P. Accurate heartbeat perception in panic disorder: fact and artefact. *J Affect Disord* 1997;43(2):121–30.
- [49] Forrester LN, Smith AR, White RD, Joiner TE. (Dis)connected: an examination of interoception in individuals with suicidality. *J Abnorm Psychol* 2015;124(3):754–63.
- [50] Rogers ML, Hagan CR, Joiner TE. Examination of interoception along the suicidality continuum. *J Clin Psychol* 2018.
- [51] Janssen CW, Lowry CA, Mehl MR, Allen JJB, Kelly KL, Gartner DE, et al. Whole-body hyperthermia for the treatment of major depressive disorder: a randomized clinical trial. *JAMA Psychiatry* 2016;73(8):789–95.
- [52] Feinstein JS, Khalsa SS, Yeh H-W, Wohlrab C, Simmons WK, Stein MB, et al. Examining the short-term anxiolytic and antidepressant effect of Floation-REST. *PLoS One* 2018;13(2):e0190292.
- [53] Young KD, Siegle GJ, Zotev V, Phillips R, Misaki M, Yuan H, et al. Randomized clinical trial of real-time fMRI amygdala neurofeedback for major depressive disorder: effects on symptoms and autobiographical memory recall. *Am J Psychiatry* 2017;174(8):748–55.
- [54] Mehler DMA, Sokunbi MO, Habes I, Barawi K, Subramanian L, Range M, et al. Targeting the affective brain—a randomized controlled trial of real-time fMRI neurofeedback in patients with depression. *Neuropsychopharmacology* 2018;43(13):2578–85.
- [55] Fischer D, Messner M, Pollatos O. Improvement of interoceptive processes after an 8-week body scan intervention. *Front Hum Neurosci* 2017;11:1231.
- [56] Bornemann B, Singer T. Taking time to feel our body: steady increases in heartbeat perception accuracy and decreases in alexithymia over 9 months of contemplative mental training. *Psychophysiology* 2017;54(3):469–82.
- [57] Meyerholz L, Irzinger J, Witthoft M, Gerlach AL, Pohl A. Contingent biofeedback outperforms other methods to enhance the accuracy of cardiac interoception: a comparison of short interventions. *J Behav Ther Exp Psychiatry* 2018;63:12–20.
- [58] Li S, Zhang B, Guo Y, Zhang J. The association between alexithymia as assessed by the 20-item Toronto Alexithymia Scale and depression: a meta-analysis. *Psychiatry Res* 2015;227(1):1–9.
- [59] Murphy J, Brewer R, Hobson H, Catmur C, Bird G. Is alexithymia characterised by impaired interoception? Further evidence, the importance of control variables, and the problems with the Heartbeat Counting Task. *Biol Psychol* 2018. advance online publication.
- [60] Schaefer M, Egloff B, Gerlach AL, Witthoft M. Improving heartbeat perception in patients with medically unexplained symptoms reduces symptom distress. *Biol Psychol* 2014;101:69–76.
- [61] Schaefer M, Egloff B, Witthoft M. Is interoceptive awareness really altered in somatoform disorders? Testing competing theories with two paradigms of heartbeat perception. *J Abnorm Psychol* 2012;121(3):719–24.
- [62] Grover S, Kumar V, Chakrabarti S, Hollikatti P, Singh P, Tyagi S, et al. Prevalence and type of functional somatic complaints in patients with first-episode depression. *East Asian Arch Psychiatry* 2012;22(4):146–53.
- [63] Avery JA, Drevets WC, Moseman SE, Bodurka J, Barcalow JC, Simmons WK. Major depressive disorder is associated with abnormal interoceptive activity and functional connectivity in the insula. *Biol Psychiatry* 2014;76(3):258–66.
- [64] Lai C-H, Wu Y-T. Frontal-insula gray matter deficits in first-episode medication-naïve patients with major depressive disorder. *J Affect Disord* 2014;160:74–9.
- [65] Berry SM, Broglio K, Bunker M, Jayewardene A, Olin B, Rush AJ. A patient-level meta-analysis of studies evaluating vagus nerve stimulation therapy for treatment-resistant depression. *Med Dev* 2013;6:17–35.
- [66] Critchley HD, Wiens S, Rotshstein P, Ohman A, Dolan RJ. Neural systems supporting interoceptive awareness. *Nat Neurosci* 2004;7(2):189–95.
- [67] Antonino D, Teixeira AL, Maia-Lopes PM, Souza MC, Sabino-Carvalho JL, Murray AR, et al. Non-invasive vagus nerve stimulation acutely improves spontaneous cardiac baroreflex sensitivity in healthy young men: a randomized placebo-controlled trial. *Brain Stimul* 2017;10(5):875–81.
- [68] Gholamrezaei A, van Diest I, Vlaeyen J, Aziz Q, van Oudenhove L. Baroreceptors as interoceptors: association between baroreceptor sensitivity and interoceptive accuracy. *Psychophysiology* 2017;54(S1):S166.
- [69] Schulz A, Vögele C. Interoception and stress. *Front Psychol* 2015;6:993.
- [70] Moyer CA. Affective massage therapy. *Int J Therap Massage Bodywork* 2008;1(2):3–5.
- [71] Kiebgis GM, Eggart M, Thormählen C, Müller-Oerlinghausen B. Psychophysical short-term and long-term effects of massage: results of a naturalistic study. *Physikalische Medizin, Rehabilitationsmedizin, Kurortmedizin* 2018;28(2):120–8.
- [72] McGlone F, Wessberg J, Olausson H. Discriminative and affective touch: sensing and feeling. *Neuron* 2014;82(4):737–55.
- [73] Bjornsdottir M, Morrison I, Olausson H. Feeling good: on the role of C fiber mediated touch in interoception. *Exp Brain Res* 2010;207(3–4):149–55.
- [74] Li Q, Becker B, Wernicke J, Chen Y, Zhang Y, Li R, et al. Foot massage evokes oxytocin release and activation of orbitofrontal cortex and superior temporal sulcus. *Psychoneuroendocrinology* 2019;101:193–203.
- [75] Field T, Hernandez-Reif M, Diego M, Schanberg S, Kuhn C. Cortisol decreases and serotonin and dopamine increase following massage therapy. *Int J Neurosci* 2005;115(10):1397–413.
- [76] Moyer CA, Seefeldt L, Mann ES, Jackley LM. Does massage therapy reduce cortisol? A comprehensive quantitative review. *J Bodywork Movement Therap* 2011;15(1):3–14.
- [77] Field T. Touch therapy. Edinburgh: Churchill Livingstone; 2000.
- [78] Morhenn V, Beavin LE, Zak PJ. Massage increases oxytocin and reduces adrenocorticotropic hormone in humans. *Altern Ther Health Med* 2012;18(6):11–8.
- [79] Rapaport MH, Schettler P, Bresce C. A preliminary study of the effects of repeated massage on hypothalamic-pituitary-adrenal and immune function in healthy individuals: a study of mechanisms of action and dosage. *J Altern Complement Med* 2012;18(8):789–97.
- [80] Price CJ, Hooven C. Interoceptive awareness skills for emotion regulation: theory and approach of mindful awareness in body-oriented therapy (MABT). *Front Psychol* 2018;9:798.
- [81] Price C. Body-oriented therapy in recovery from child sexual abuse: an efficacy study. *Altern Ther Health Med* 2005;11(5):46–57.
- [82] Vallbo AB, Olausson H, Wessberg J. Unmyelinated afferents constitute a second system coding tactile stimuli of the human hairy skin. *J Neurophysiol* 1999;81(6):2753–63.
- [83] Vallbo A, Olausson H, Wessberg J, Norrsell U. A system of unmyelinated afferents for innocuous mechanoreception in the human skin. *Brain Res* 1993;628(1–2):301–4.
- [84] Olausson H, Wessberg J, Morrison I, McGlone F, Vallbo A. The neurophysiology of unmyelinated tactile afferents. *Neurosci Biobehav Rev* 2010;34(2):185–91.
- [85] Pawling R, Cannon PR, McGlone FP, Walker SC. C-tactile afferent stimulating touch carries a positive affective value. *PLoS One* 2017;12(3):e0173457.
- [86] Calsius J, de Bie J, Hertogen R, Meesen R. Touching the lived body in patients with medically unexplained symptoms. how an integration of hands-on bodywork and body awareness in psychotherapy may help people with alexithymia. *Front Psychol* 2016;7:253.
- [87] Farb N, Daubenmier J, Price CJ, Gard T, Kerr C, Dunn BD, et al. Interoception, contemplative practice, and health. *Front Psychol* 2015;6:763.
- [88] Füstös J, Gramann K, Herbert BM, Pollatos O. On the embodiment of emotion regulation: interoceptive awareness facilitates reappraisal. *Social Cogn Affect Neurosci* 2013;8(8):911–7.
- [89] Edwards DJ, Young H, Johnston R. The immediate effect of therapeutic touch and deep touch pressure on range of motion, interoceptive accuracy and heart rate variability: a randomized controlled trial with moderation analysis. *Front Integr Neurosci* 2018;12:41.
- [90] Morrison I. ALE meta-analysis reveals dissociable networks for affective and discriminative aspects of touch. *Hum Brain Mapp* 2016;37(4):1308–20.
- [91] Field T, Diego M, Hernandez-Reif M. Moderate pressure is essential for massage therapy effects. *Int J Neurosci* 2010;120(5):381–5.
- [92] McGlone F, Cerritelli F, Walker S, Esteves J. The role of gentle touch in perinatal osteopathic manual therapy. *Neurosci Biobehav Rev* 2017;72:1–9.
- [93] Paulus MP, Stein MB. Interoception in anxiety and depression. *Brain Struct Funct* 2010;214(5–6):451–63.
- [94] Jenkinson PM, Taylor L, Laws KR. Self-reported interoceptive deficits in eating disorders: a meta-analysis of studies using the eating disorder inventory. *J Psychosom Res* 2018;110:38–45.
- [95] Klabunde M, Acheson DT, Boutelle KN, Matthews SC, Kaye WH. Interoceptive sensitivity deficits in women recovered from bulimia nervosa. *Eat Behav* 2013;14(4):488–92.
- [96] Paulus MP, Stewart JL. Interoception and drug addiction. *Neuropharmacology* 2014;76(Part B):342–50.
- [97] Hatfield TR, Brown RF, Giummarra MJ, Lenggenhager B. Autism spectrum disorder and interoception: abnormalities in global integration? *Autism* 2017. advance online publication.
- [98] Rapaport MH, Schettler P, Larson ER, Edwards SA, Dunlop BW, Rakofsky JJ, et al. Acute swedish massage monotherapy successfully remediates symptoms of generalized anxiety disorder: a proof-of-concept, randomized controlled study. *J Clin Psychiatry* 2016;77(7):e883–91.
- [99] Lee S-H, Kim J-Y, Yeo S, Kim S-H, Lim S. Meta-analysis of massage therapy on cancer pain. *Integr Cancer Ther* 2015;14(4):297–304.
- [100] Furlan AD, Giraldo M, Baskwill A, Irvin E, Imamura M. Massage for low-back pain. *Coch Database SystRev* 2015;9:CD001929.
- [101] Baumgart S. Wirkung psychoregulatorischer Massagetherapie auf Schmerz und Depressivität bei Frauen mit chronischem und/oder somatoformem Rückenschmerz. Eine randomisierte kontrollierte Studie im ambulanten Bereich (Dissertation). Medizinische Fakultät der Martin-Luther-Universität. Halle-Wittenberg 2018.
- [102] Kinkead B, Schettler PJ, Larson ER, Carroll D, Sharenko M, Nettles J, et al. Massage therapy decreases cancer-related fatigue: results from a randomized early phase trial. *Cancer* 2018;124(3):546–54.