

Running head: MASSAGE THERAPY

/A Survey of the Brain Regions Affected by Acute Massage Therapy: a Functional  
Magnetic Resonance Imaging (fMRI) Pilot Study/

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Diane Sliz

Department of Psychology  
Carleton University

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## **Abstract**

Massage therapy has been reported to reduce state anxiety, stress hormonal levels and depressive symptoms in diverse populations. However, the neural mechanisms by which massage might impart therapeutic-like effects have yet to be determined. In the present neuroimaging study, we investigated the impact of different forms of tactile stimulation on neural activity in healthy participants. In this regard, Swedish massage and reflexology were associated with substantially less neuronal activation during the course of the scanner session. These data suggest that tactile stimulation, as provided by different types of massage, may dampen the normal levels of activation in several brain regions important for mood and arousal (e.g. cingulate gyrus, parahippocampal gyrus). Further investigation is ultimately required to understand the long-term mechanisms by which touch operates at a neural level and how massage therapy might have a beneficial role as an adjunct treatment for mood disorders in clinical populations.

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## A Survey of the Brain Regions Affected by Acute Massage Therapy: a Functional Magnetic Resonance Imaging (fMRI) Pilot Study

Recently, the National Health Interview Survey documented that one third of adults use some form of complementary and alternative medicine (CAM) (Barnes, Bloom & Nahin, 2008). CAM use is more common among women (48.9%) than men (37.8%), with many people using this approach to complement conventional care rather than as an alternative to Western medicine (Eisenberg et al., 1998). People aged 35-49 years are reportedly the greatest users (50.1%) of CAM therapies, with massage therapy being the preferred alternative remedy to treat back problems, neck pain, anxiety and depression (Barnes et al., 2008; Eisenberg et al., 1998).

Although psychiatric patients are often interested in complementary and alternative treatments, most psychiatrists do not discuss CAM therapies with their patients. In fact, in one study only 21% of 82 psychiatric inpatients reported discussing their use of CAM therapies with their psychiatrist (Elkins, Rajab & Marcus, 2005). The lack of communication between patient and doctor may hinder treatment outcomes. Since 1997, there has been a 47.3% increase in total visits to practitioners of alternative therapies largely because of increases in visits for relaxation and massage therapy (Eisenberg et al., 1998). Generally, persons who choose CAM approaches are seeking ways to improve their health and well-being. These approaches are also used to relieve symptoms associated with chronic or terminal illnesses as well as the side effects of conventional treatments for these illnesses. It is likely that increased opportunity and greater awareness may explain much of the observed increase in adult use of CAM (Barnes et al., 2008).

The ensuing sections of this thesis will focus on the potential benefits of one specific type of CAM, namely massage, upon symptoms of depression and anxiety. Given the incredibly high prevalence of these two psychiatric conditions, coupled with the obvious “relaxation” effects of massage, this seems a logical approach. The intention is not to suggest that massage could somehow replace standard antidepressant or other conventional treatments, but rather to encourage the possibility that massage might act as an important adjunct treatment strategy, augmenting the impact of conventional treatments. It might be particularly useful to certain depressive sub-populations that have substantial co-morbid anxiety. Surprisingly, however, there is a lack of empirical data on the neuronal pathways that are influenced by massage therapy. Hence, the primary goal of this work was to evaluate (using functional magnetic resonance imaging [fMRI]) the neuronal structures activated, as well as those suppressed by two specific types of massage (Swedish and reflexology) in a healthy population. This study is part of a bigger project which aims to determine whether a massage therapy treatment might have beneficial consequences in a depressed population and if any such effects correlate with neural variations detected by fMRI.

### *Neuroanatomical aspects of emotion*

Neuroanatomically, depressive disorders are likely linked to changes in the emotional neuro-circuitry, encompassing the limbic structures as well as the prefrontal and parietal cortices. The amygdala, in association with other fronto-limbic structures, plays a pivotal role in the processing of emotional stimuli and arbitrates emotional influences in other brain regions related to attention, memory and decision-making

(Wang, LaBar & McCarthy, 2006; Hariri, Bookheimer & Mazziotta, 2000). The amygdala also has a visceral function and its response is dependent on the relevance of the stimulus to the individual's current behavioural state (Wang et al., 2006). Therefore, a depressive state would yield greater activation in the amygdala and associated regions, in response to negative affect. The emotional circuitry in the limbic system outputs from the hippocampal formation to the mamillary body, passing via the anterior thalamus nuclei and extends to the cingulate gyrus, which is the receptive region for the experience of emotion (Morgane, Galler & Mokler, 2005). This pathway is mediated by the hypothalamus, which subserves autonomic functions and the neuroendocrinological and autonomous expression of emotion and motivation (Morgane et al., 2005; Beaugard, Lévesque & Bourgouin, 2001; Iidaka et al., 2001). Nevertheless, the frontal cortical and sub-cortical structures are as important in mediating the emotional response.

Ochsner et al. (2002) illustrated that the neural basis for the cognitive control of emotion extends to the prefrontal cortex, the medial orbitofrontal cortex as well as the amygdala. The latter two structures are involved in emotional processing, with the prefrontal cortex playing a role in awareness, executive functions, behavioural inhibition, attention and working memory (Ochsner, Bunge, Gross & Gabrieli, 2002; Morgane et al., 2005). By examining how individuals reappraise highly negative scenes, Ochsner et al. (2002) were able to illustrate that the cognitive transformation of an emotional experience (i.e. negative photos) decreases negative affect in healthy participants. Consequently, reappraisal may modulate the emotional processes employed in the amygdala and medial orbitofrontal cortex, which are involved in the evaluation of the affective salience and contextual relevance of the stimulus (Ochsner et al., 2002). These findings suggest that

the intricate connections between the amygdala and prefrontal cortex, allow the frontal structures to act as top-down modulators of the emotional response in the amygdala (Beauregard et al., 2001; Bermpohl et al., 2006). In fact, cortical connections from the amygdala and other limbic structures, i.e. parahippocampal formation, are directed to the orbito- and medial prefrontal cortices, which interact with the thalamus and basal ganglia. This pathway forms a circuit involved in the stimulus-reward association, reward guided behaviour and mood determination (Price, 1999).

Using functional magnetic resonance imaging, Rolls et al. (2003) explored brain areas involved in the representation of affectively positive aspects of somatosensory stimulation. It was found that affectively positive touch triggered activation in the orbitofrontal cortex and the anterior cingulate cortex, the latter being involved in representing the affective qualities of the stimulus. It was also posited that the anterior cingulate cortex may be involved in the generation of autonomic and emotional responses. Another type of touch, massage therapy, applied to the backs of adult subjects, was also found to activate the cingulate cortex as examined through positron emission tomography (Ouchi et al., 2006). In addition, increased regional cerebral blood flow was detected in the parietal and occipital lobes, the precuneus and the pons, the amygdala and orbitofrontal cortex, suggesting an increased arousal and greater conscious functioning for stimuli having a positive affect (Ouchi et al., 2006). As such, massage therapy seems to lead to mental relaxation by modulating the activities of the amygdala and the cingulate cortex due to the positive affect in receiving this massage.

Substantial data supports the preeminent influence of early adverse experience in increasing the vulnerability for later development of mood and anxiety disorders. Genetic

predispositions combined with environmental influences likely act upon the neural circuits that mediate stress/fear responsiveness and affect modulation (Meaney & Szyf, 2005; McEwen & Magarinos, 2001). Alterations in limbic corticotrophin releasing factor (CRF) systems and brainstem norepinephrine (NE) and serotonin (5-HT) systems likely contribute to these increased vulnerabilities. When an individual is unable to adequately deal with a stressor, either behaviourally or physiologically, the capacity of brain monoaminergic systems may fail to meet the resulting excessive or prolonged demand, resulting in further loss of coping ability and increased vulnerability to subsequent stress, ultimately leading to depression (Anisman, Merali & Hayley, 2008). Thus, monoaminergic dysregulation could contribute to stress vulnerability as a factor in the development of major depression and anxiety disorders (Ressler & Nemeroff, 2000). Antidepressant therapies remain focused on shifting the NE/5HT balance, yet a further understanding of the interacting systems that likely mediate and maintain the depressed or anxious state will advance approaches to treatment.

### *Standard and alternative treatments for anxiety and depression*

There is extensive comorbidity between depression and anxiety disorders, with as many as 85% of adults with depression having significant symptoms of anxiety (Gorman, 1996/1997). Anxiety, the emotional response to stress, is a key element of depression as well as the defining feature of anxiety disorders, and many antidepressants appear to be effective in the treatment of anxiety disorders as well as depression (Rouillon, 1999). Therefore, the pharmacological actions of these drugs must account for their efficacy in both. Most patients will eventually remit from any given depressive episode; however,

symptoms typically re-occur at a later time to such a degree that depression is now considered to be a largely recurrent disorder. Antidepressant medication has been shown to be superior to placebo controls and tends to suppress symptoms for as long as it is continued or maintained, although, it is not considered a prophylactic treatment (Hollon, Stewart & Strunk, 2006). Rather, the continued presence of the drug, perhaps indefinitely in some patients, is necessary to maintain whatever alterations they induce in neurotransmitter function to produce their beneficial effects (Morilak & Frazer, 2004). Although the exact mechanisms remain to be fully determined, many antidepressant treatments seem to reset the balance of neurotransmitters, most prominently NE and 5-HT, while concomitantly decreasing adrenal steroid release and promoting increased neurotrophic factor activity (Ressler & Nemeroff, 2000).

Although the evidence is mixed as to whether newer antidepressants have better tolerability and safety advantages over older tricyclic antidepressants (TCAs), it is as yet unclear if drug classes or specific drugs may differ from one another in their ability to elicit remission (Smith, Dempster, Glanville, Freemantle & Anderson, 2002). TCAs produce a response (i.e. a reduction of at least 50% in the severity of symptoms) in only about two thirds of patients (Morilak & Frazer, 2004). Newer antidepressant medications, such as selective serotonin reuptake inhibitors (SSRIs) are indicated for a wide range of anxiety disorders and are commonly used in the treatment of depression with associated anxiety (Rouillon, 1999). Antidepressants with dual action of inhibiting the reuptake of both noradrenaline and serotonin may be more effective than drugs acting on a single monoamine (e.g. SSRIs). In a recent study, 45% of patients on the serotonin norepinephrine reuptake inhibitor (SNRI) venlafaxine remitted compared to 35% of SSRI

treated patients (Anderson, 2001). It is increasingly recognized that improvement of depression on antidepressants is often incomplete or partial so that remission rates are relatively low (Smith et al., 2002).

In addition to pharmacological approaches, increasing emphasis is being placed upon the importance of various cognitive based interventions, such as cognitive therapy, in producing enduring beneficial effects in depressed individuals (Hollon et al., 2006). Cognitive approaches assume that depressive pathology stem from and can be modified by changes in one's processing of information. More specifically, the underlying beliefs and information-processing propensities, such as core beliefs about the self or the way an individual explains the causes of negative life events tend to change over the course of the therapy (Hollon et al., 2006). Cognitive therapy and medication both produce a comparable change in depression, with 90% of the symptom changes occurring in the first six weeks of both treatment regimens (Hollon et al., 1992). However, patients treated to remission with cognitive therapy are only half as likely to relapse following treatment termination compared to patients treated to remission with medications alone (Evans et al., 1992). This is important since depressed patients appear to be at particularly elevated risk for symptom return (relapse) for the first six to nine months following initial response to medications (Hollon et al., 1992). Current medical practice is moving in the direction of maintaining patients with a history of recurrence (the vast majority of all depressed patients) on medication indefinitely. There also are indications that cognitive behavioural therapy or related interventions may have enduring effects when provided after medications have been used to reduce acute distress. For instance, adding cognitive therapy to medication treatment for partial responders not only helps resolve residual

symptoms but also reduces the risk for subsequent relapse after the end of the psychosocial treatment (Paykel et al., 1999).

In addition to conventional cognitive and behavioural based therapies, many patients opt for alternative and complementary treatment options. The use of these therapeutic treatment approaches aid with the management of negative side effects of many antidepressant medications. Similarly, many patients seek different treatment options when other traditional approaches result in a lack of response to treatment or when they simply prefer a complementary approach in their treatment of major depressive disorder. One such alternative therapy is yoga which emphasizes controlled breathing to help focus the mind and achieve relaxation (Pilkington, Kirkwood, Rampes & Richardson, 2005) by modulating the stress response (Kamei et al., 2000). Unlike cognitive therapy which treats current symptoms and patterns of thought, yoga addresses new ways of regulating one's mood (Butler et al., 2008). Yoga interventions are deeply intertwined with meditation practices, known as mindfulness-based relaxation therapies. The meditation component allows the practitioner to focus their attention and maintain their awareness of the present moment (Butler et al., 2008). This technique has been known to alleviate depressive symptoms (Finucane & Mercer, 2006) and reduce rates of relapse and recurrent major depressive episodes (Teasdale et al., 2000). In fact, reductions have been observed in depressive and anxiety symptoms following a two week treatment program incorporating yoga and meditation which also increased feelings of well-being and tension release in anxiety-ridden individuals (Kozasa et al., 2008). Butler et al. (2008) recently reported a 77% remission rate in depressed individuals undergoing a meditation treatment. This finding is quite impressive considering that remission rates

with antidepressants and psychotherapy rarely peak above 75% (Kocsis, 2000).

Interestingly, the control condition developed new major depressive episodes whereas the meditation group did not show exacerbation of depressive symptoms, implying that meditation can have prophylactic in addition to beneficial effects on mood disorders (Butler et al., 2008).

Another widely adopted therapeutic alternative in both Western and non-Western countries is acupuncture. Although acupuncture has been widely used for conditions such as fibromyalgia, migraines, post-operative pain, osteoarthritis and low back pain, other than producing an analgesic effect, its efficacy is not clinically significant (British Medical Journal, 2009). Despite its widespread use, a recent meta-analysis reported a lack of evidence to determine whether the practice of acupuncture in a depressed population is more effective than sham acupuncture or a wait list control (Smith & Hay, 2005). In addition, trials using acupuncture as an adjunct treatment to antidepressant medications failed to show any effect (Smith & Hay, 2005; Mukaino, Park, White & Ernst, 2005). This inconsistent evidence may be attributable to the placebo effect; however its use in the treatment of depression is not warranted.

The effects of massage therapy as a complementary treatment have also been evaluated in depressed populations. Due to methodological problems in design of the studies (e.g. massage administered by psychology students in one study; criteria for establishing depression not provided in another), one review was unable to draw conclusions regarding the effectiveness of massage therapy in a depressed population (Coelho, Boddy & Ernst, 2007). Nevertheless, a lack of clinical evidence does not infer lack of efficacy in individuals suffering from mood disorders.

Investigations into the neural correlates of these CAM therapies have led to a surge in imaging studies, particularly with acupuncture and meditation. By examining cerebral activation patterns in vivo, researchers have been capable of capturing the functional hemodynamic response of these adjunct therapies and inferring how they function at a neural level. The following section will examine recent neuroimaging data concerning depressed subjects, as well as imaging studies exploring neural activity in meditation and acupuncture.

### *Neuroimaging data regarding mechanisms of depression*

Since the early 1990s, magnetic resonance imaging (MRI) technology has dominated the neuroimaging field due to its high spatial and temporal resolution and low invasiveness. Functional MRI is based on the physiological principle that whenever neural activity is generated, the vasculature in that localized region vasodilates, causing freshly oxygenated blood to rush into the activated brain structure and thereby reducing the amount of deoxyhemoglobin (i.e. oxygen free blood) (Bammer et al., 2005). The increase in blood flow to the local vasculature that accompanies neural activity in the brain is termed the hemodynamic response (Koretsky, 2004). Since the blood contains iron, which is the oxygen-carrying part of hemoglobin within red blood cells, these iron atoms cause small distortions in the magnetic field around them (Bammer et al., 2005). As such a small change in the magnetic field is generated, leading to the observed MRI signal in the activated region. The resting condition image (the baseline) is subtracted from the image corresponding to the average of the stimulation condition. This contrast is referred to as the blood oxygenation level-dependent (BOLD) contrast (Howseman & Bowtell, 1999).

Block designs are the most commonly used experimental paradigm in functional MRI studies. The block design uses alternating periods of rest and task during each of which, a discrete cognitive state is maintained. This ensures that variations arising from fluctuations in scanner

sensitivity, participant movement or attention shifts have a similar impact on the signal responses associated with each of the different states. With block designs, the underlying hemodynamic responses acquired during one block condition are compared to the signals acquired from baseline, or from other blocks involving different task conditions (e.g., "cognitive task" blocks versus "resting" blocks). As such, regions of signal activity that change between one condition and another can be identified with considerable statistical power. Therefore, in order to generate a change in the BOLD signal, one must induce a change in neural activity by creating a block which serves as a baseline comparison for all subjects.

Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies have provided new insights into the neural circuits involved in the pathophysiology of depression. Numerous studies have found changes in frontal cortical activity in depressed states. Dorsal prefrontal cortical (PFC) activity is generally suppressed, in contrast to ventral PFC and orbital cortex that have been found to be overly activated in depressed patients when compared to controls (Drevets, 2000). Antidepressant treatments were reported to normalize both of these abnormalities, increasing dorsal PFC activity, and decreasing ventral PFC and orbital activity. The amygdala has also been consistently demonstrated to be abnormally activated in depressed individuals. As with the cortical abnormalities, the amygdala activity decreases towards that of controls with antidepressant treatment response and remission (Ressler & Nemeroff, 2000).

Multiple studies have demonstrated that hippocampal volume is decreased in patients with major depression (Videbech & Ravnkilde, 2004). Interestingly, volumetric changes reflect the actual number of days that individuals have been depressed with prolonged symptomatic periods corresponding to smaller hippocampal volumes

(Videbech & Ravnkilde, 2004). The elevated glucocorticoid levels often seen in severely depressed patients along with the decreased hippocampal volume suggest a mechanism for putative neuronal loss seen within depressive patients either by apoptosis (programmed cell death) or inhibition of neurogenesis (Eriksson et al., 1998; Lee, Ogle & Sapolsky, 2002). Indeed, stressor induced prolonged glucocorticoid elevations are known to inhibit hippocampal neurogenesis and promote atrophy of hippocampal dendrites (Caetano et al., 2004; McEwen & Magarinos, 2001). Other non-corticoid mechanisms are, however, also possible, such as reduction of the volume of individual neurons or reduction of glial tissue. One study quantified the reductions in hippocampal volume and found that on average, depressed patients had degenerations of 8% in the left hemisphere and 10% in the right hemisphere relative to comparison subjects (Videbech et al., 2001). Often this atrophy is found to correlate with poor treatment response and shorter time to recurrence of the disease (Videbech & Ravnkilde, 2004).

The hippocampus has been firmly established as playing a critical role in episodic, declarative, contextual, and spatial learning and memory (Burgess, Maguire & O'Keefe, 2002); of which deficits in each of these often accompany depression (Ravnkilde et al., 2002). A few recent MRI studies have supported a connection between hippocampal abnormalities in depressed patients and cognitive deficits. In one such study, depressed subjects displayed a reduced volume of the left temporal cortex, including the hippocampus, as well as a tendency toward reduction of the right hippocampus (Caetano et al, 2004). As well, euthymic women with recurrent depression showed smaller bilateral hippocampal volumes and lower scores in verbal memory, which is a neuropsychological measure of hippocampal function, compared to controls

(MacQueen et al., 2003). Others reported impairments on hippocampus-dependent verbal memory tests in both patients with first-episode depression and those with multiple episodes. However, only the latter group had hippocampal volume reductions, which suggests that dysfunctions of the hippocampus may predate detectable structural changes (MacQueen et al., 2003).

Recently, imaging studies have surfaced exploring the neural correlates of complementary and alternative treatments, such as meditation and acupuncture, in healthy individuals. Since many depressed individuals use CAM therapies in addition to their current treatment (or while being wait-listed to receive treatment), these therapeutic treatments might be beneficial in preventing relapse, dropping out, preventing lack of effect and even helping with side effects of antidepressant medication. The practice of meditation is characterized by a willingness to let go of personal concerns and experience an enhancement of the sensory world (Kjaer et al., 2002). The detached observation of one's bodily sensations, emotions and thoughts interrupts automatic responding and increases behavioural flexibility, thus facilitating emotional regulation and enhancing well-being (Bishop et al., 2004). Regular meditative practice is thought to promote structural changes in cortical areas related to interoception, attention and somatosensory processing (Holzel et al., 2008; Lazar et al., 2005).

Imaging studies have shown greater grey matter concentration in the right hippocampus and insula in meditators, suggesting a role for the insula in the experience of a mindful state (Holzel et al., 2008). Moreover, the hippocampus is thought to play a role in cortical arousal and responsiveness and modulate amygdala activity in attentional and emotional processing, with the parahippocampal region playing a role in emotional

memory and sensory function (Holzel et al., 2008). The volume of grey matter within the medial orbitofrontal cortex was shown to be positively correlated with the total hours of meditative practice (Holzel et al., 2008). Importantly, this brain region plays a role in emotional regulation by down-regulating amygdala activity. Kjaer et al. (2002) further found increased dopamine release in the ventral striatum during relaxation meditation, the first study to examine this conscious state at a synaptic level. It is believed that dysfunctions in the frontal-subcortical circuits (including the ventral striatum) regulating behaviour may result in a lack of interest and initiative, apathy, poverty of speech and movement (Kjaer et al., 2002), all of which are noted symptoms in depressed individuals. As well, changes in the basal ganglia striatal-thalamic pathway that have been observed in meditators may explain how these individuals are capable of focusing on an internal state of consciousness, void of external interference (Alexander, Crutcher & Delong, 1990). Indeed, the basal ganglia is critical for selecting, focusing and filtering context-dependent information.

Lazar et al. (2005) also found increased cortical thickness in individuals practicing meditation in regions related to somatosensory, auditory, visual and interoceptive processing. Interestingly, older meditation participants (aged 40-50 years) had the same average cortical thickness in region BA9/10 as younger meditators (aged 20-30 years) and control subjects. This suggests that long-term meditation may slow the rate of neural degeneration in this particular brain region (Lazar et al., 2005). Hence, the relaxation properties brought on by meditation through the learnt processes of breathing and focusing awareness on thoughts and emotions may underlie this experience-dependent cortical plasticity. The right BA9/10 (dorsolateral prefrontal cortex and

anterior frontal cortex, respectively) have been reported to be involved in the integration of emotion and cognition and may thus play an important role in the processing of emotionally salient stimuli and adaptive decision making (Lazar et al., 2005). Having a better established sense of self-awareness may help one better deal with daily stresses.

Imaging studies using acupuncture as the alternative treatment have suggested that its effects are of a neuromodulatory nature on the central nervous system that activates analgesia systems and stimulates pain modulation pathways to release endogenous opioids (Fang, Krings, Weidemann, Meister & Thron, 2004). However, acupuncture has also been found to be mediated by the activation of deep proprioceptive neurons in area BA3a (encoding deep tissue sensation), as well as area BA1 and BA2 which are associated with tactile stimulation and pain, and orienting the direction of tactile stimulation, respectively (Yoo et al., 2007). This area may relate to other CAM therapies like Swedish massage, which manipulates deep tissue. It seems likely that any complementary therapy which aims to let go of thoughts that maintain depressive affect will also alter seemingly inflexible cognitions. Massage may be one such adjunct technique used to give a feeling of pleasant physical relaxation which could help restructure environmental situations that typically exacerbate depressive affect.

Interestingly, a neuroimaging study was conducted using vibrotactile stimulation on the plantar surface of the foot. This form of stimulation activated the secondary somatosensory cortex, the inferior and posterior cingulate gyrus, left posterior insula, thalamus, caudate nucleus and cerebellum. In addition, the inferior and superior parietal lobules also showed activation, indicating that this brain region integrates tactile sensory information from mechanoreceptors in the integumentary system with proprioceptive

input from underlying muscles and joints (Golaszewski et al., 2006). As such, the parietal lobule and cingulate gyrus are involved in the attentional processes of incoming somatosensory information. Since somatic sensory inputs to the orbitofrontal cortex originate in sensory-association cortical areas, such as the secondary somatosensory cortex and the parietal area, its function would be to integrate different sensory modalities with limbic inputs from the amygdala, hippocampus and parahippocampal gyrus (Price, 1999).

### *Massage therapy: potential mechanisms*

Massage therapy has been shown to facilitate the normal developmental increase in epinephrine and norepinephrine levels in preterm infants during their newborn period. At one year of age, the preterm babies also showed better mental and motor functioning, suggesting long-term benefits of this tactile manipulation at such a critical stage in life (Kuhn et al., 1991). More elaborate dendritic arborization noted in MRIs of the hippocampal region in massaged preterm neonates by Modi and Glover (2001) may be related to the superior memory performance noted in the massaged newborns and their performance again at one year of age (Field, 1998). In an animal model, Meaney et al. (1991) tracked a relationship between increased glucocorticoids, decreased dendritic arborization in the hippocampal region, and inferior maze performance, suggesting impaired memory function in the aging rats that had been deprived of tactile stimulation as rat pups. As well, Wang et al. (1996) discovered that the gene, ornithine decarboxylase, responds selectively to tactile stimulation (Wang, Bartolome &

Schanberg, 1996). These studies suggest the importance of touch in mammals especially in the early stages of life which are vulnerable and critical developmental periods.

Hospitalized depressed children and adolescents who received back massages for a week were less depressed and anxious and had lower stress hormone levels (lower saliva cortisol levels as well as lower urinary cortisol and norepinephrine levels), more organized sleep patterns compared to the control group that viewed relaxing videotapes (Field et al., 1992). In a similar pilot study on adult patients with anxiety, massaged patients showed a decrease in stress response patterns including decreased heart rate, electromyography (EMG) and skin resistance (Field, 1998).

One potential mechanism underlying the beneficial impact of touch is suggested by a recent study measuring frontal EEG activation following massage in depressed adolescents. Shifts to a more positive mood were notably accompanied by shifts from right frontal EEG activation (normally associated with “sad affect”) to left frontal EEG activation (normally associated with “happy affect”) or at least to symmetry (midway between sad and happy affect) in both depressed adolescent mothers and their infants (Jones & Field, 1999). Besides changes in electrical potential, increased activity of the vagus nerve following massage therapy might also be of importance. The increased vagal activity, which is associated with reduced sympathetic activity, may relate to the improvements in mood via the nucleus-ambiguous branch of this nerve which stimulates facial expression and vocalizations. This in turn can contribute to less depressed affect, which could feedback to less depressed feelings (Field, 1998). Indeed, there is substantial recent evidence indicating that stimulation of the vagus nerve can impart antidepressant effects. For instance, vagal nerve stimulation therapy was associated with ventromedial

prefrontal cortex deactivation (Pardo et al., 2008), similar to antidepressant treatment, although the clinical effects with vagal nerve stimulation occur later (after several months as opposed to several weeks as is seen with antidepressants) (Nahas et al., 2007).

Moreover, acute vagal nerve stimulation diminished activation of the right insula, a brain region activated in the depressive state playing a role in visceral autonomic and limbic functions, in mild to moderate depression (Nahas et al., 2007). Vagal nerve stimulation also decreased depressive symptoms in the short and long term of treatment resistant depression patients, although its efficacy in major depressive disorder needs to be confirmed (Daban, Martinez-Aran, Cruz & Vieta, 2008).

Massage therapy also has been noted to beneficially impact upon peripheral immunity. Indeed, HIV+ adolescents who received massage therapy treatments reported feeling less anxious and depressed, and showed improved immune function, as indicated by T helper cell responding (Diego et al., 2001). Another study reported that 20 days of massage therapy diminished stressor associated signs of anxiety and elevations of urinary cortisol, while increasing natural killer cell activity (Field, 1998). The positive massage therapy effects on natural killer cell number and cytotoxicity might be explained by the massage treatment's ability to reduce signs of anxiety, which in turn might impose a reduction in HPA activity, thereby lowering cortisol levels and resulting in improved immune function. Alternatively, massage induced suppression of sympathetic activation might also boost immunity. Indeed, suppression of immune functioning observed in depressed individuals has been linked to excessive epinephrine and norepinephrine activity, resulting in decreased CD4+ T lymphocytes (Field, 1998). In effect, massage therapy might bolster T-lymphocyte activity, including CD4/CD8 ratio and CD4 number,

in HIV infected adolescents (Diego et al., 2001). Because natural killer (NK) cells are the front line of defense in the immune system, combating the growth and proliferation of viral cells, the HIV+ patients who receive massage therapy might experience fewer opportunistic infections such as pneumonia, rare cancers and other viruses that often have fatal consequences in such patients.

Additional support for massage benefits include a study reporting that HIV+ infected children (aged two to eight years) from the Dominican Republic who received twice weekly massage demonstrated enhanced self-help and communication skills. The findings revealed that massage therapy was effective in reducing maladaptive internalizing behaviours (anxiety, depressed mood, negative thoughts) in children aged 6 and older, infected with HIV who had no access to anti-retroviral medication (Hernandez-Reif et al., 2008). Another study examining the effects of massage therapy on immune system functioning involved evaluation of the effects of a single massage session in women suffering from breast cancer. In this study, lymphocyte markers (CD56+ cells, CD3+ cells, CD11a+ cells) and NK cell numbers were significantly increased for the women in the massage group and these women reported less anxiety, anger, pain and improved mood (Field, 1998). Follow up studies subsequently revealed long term changes in breast cancer survivors following massage, including improved body image awareness, physical well-being as well as decreased signs of negative mood (Hernandez-Reif et al., 2004).

In general, across all studies that evaluated the psychological and physiological effects of massage therapy, significant decreases are noted in anxiety, depression, cortisol and catecholamine levels, with benefits comparable to those from standard

psychotherapy. The benefits of massage may accrue from biochemical changes induced directly from the tactile aspect of touch involved in the massage. Indeed, the pressure stimulation as well as the relaxing and calming feature associated with touch may increase vagal activity, which in turn lowers physiological arousal and stress hormone levels. Parasympathetic activity promoted by massage is also associated with increased alertness and better performance on cognitive tasks. The pressure is critical because light stroking is generally aversive (much like a tickle stimulus), and the above effects have not been noted for light stroking (Field, 1998). In addition to the basic element of touch alone, the emotional outlet provided by a massage therapy session itself may have tremendous clinical benefit. Indeed, the supportive environment and high degree of attention given by a well trained massage therapist can be expected to provide some comfort and encourage the therapeutic expression of emotions hence, deriving potentially anti-depressive consequences. In this regard, numerous studies have demonstrated that social support of virtually any type can have marked positive effects in depressed individuals who experience long standing feelings of loneliness and isolation (Giese-Davis et al., 2002).

Current pharmacologic treatments for major depression modulate brain monoamines, whereas psychotherapeutic and psychosocial interventions focus on stress reduction, coping techniques, and changing perceptions and attitudes toward events perceived as stressful (Ressler & Nemeroff, 2000). However, more patients are seeking alternatives to conventional treatments of mood disorders. The increases in use of complementary and alternative forms of therapy have been primarily utilized to alleviate the physiological symptoms of the anxiety and depressive affect. For instance, meditation

has been shown to reduce risk for relapse and recurrence following treatment termination in patients first treated to remission with antidepressant medications (Teasdale et al., 2000). Less attention has been formally devoted to exploring the benefits of a massage therapy treatment in attenuating the bodily response to anxiety and stress.

### *Study objectives & hypotheses*

Massage is often used as a therapeutic means to relax the body by increasing the parasympathetic response via the hypothalamus-amygdala system, which reduces sympathetic bodily responses to stress and anxiety (Critchley, Melmed, Featherstone, Mathias & Dolan, 2001; Moyer, Rounds & Hannum, 2004). Massage therapy can also aid with emotional self-regulation, which moderates how one interprets their external environment. Since massage is deemed to be a rewarding experience, it can be hypothesized that the neural circuitry involved in massage therapy can result from neuronal activation playing on the mesocorticolimbic dopaminergic pathway. Additionally, this therapeutic treatment would be considered a pleasurable stimulus and would be expected to trigger greater activation of brain areas involved in motivation, memory and emotions, specifically, the prefrontal cortex and the anterior cingulate cortex. Essentially, we posit that massage therapy may be used as an adjunct therapy that may be useful in maintaining positive well-being and preventing a progression to serious distress among individuals with mild to moderate anxiety, depression and stress perception (Sharpe, Williams, Granner & Hussey, 2007). The present study involving assessment of the impact of massage in a healthy population was meant to act as an initial step to first verify the feasibility of the fMRI approach to assessment of massage.

Thereafter, we plan to assess whether massage might differentially affect neural activity in clinical populations with mood or anxiety problems. Indeed, this study will thus provide a template against which we can further examine the effects of a massage treatment in clinical populations suffering with stressor-related pathology.

Specifically, the objective of the present study was to examine by means of fMRI whether massage therapy influences the activity of several key limbic and cortical regions important in the pathophysiology of mood disorders and arousal. It was hypothesized that, in a healthy population, massage will elicit greater neural activation of structures involved in positive salience of the treatment, namely, the striatum, prefrontal cortex and anterior cingulate cortex. Moreover, by delineating the neural circuitry of a massage therapy treatment in healthy individuals, we will have a template against which to evaluate these effects in a depressed population.

In this study, fMRI was used to assess the neural underpinnings of massage therapy. It was proposed that different neural circuits would be activated when a massage treatment was performed versus no massage (i.e. a resting condition void of tactile stimulation). The resting condition served as the control condition and was also used for comparative purposes in terms of neural activation in each of the tactile stimulation conditions. These conditions included a massage of the plantar surface of a foot with an inanimate object, a Swedish foot massage and a reflexology massage. In the latter two conditions, the participants experienced human touch in addition to a massage. As such, it was posited that the Swedish massage and reflexology conditions would elicit greater neural activation in the fronto-limbic structures than any other condition (i.e. massage with an object and resting condition).

In the massage condition with an inanimate object (a wooden object commonly used by massage therapists) for the right foot, the limbic system was expected to be activated in response to the emotional processing of afferent somatosensory signals. In this circuit, due to the lateralization of the brain, the left cingulate gyrus and parahippocampal gyrus, which play a role in representing the positive affective quality of a stimulus, would convey their information to the left amygdala, which attends to the stimulus and activates the prefrontal cortex leading to the perception of feeling the external stimulus (Golaszewski et al., 2006).

In the massage and reflexology conditions, which will manipulate the soft tissues of the plantar surface of the right foot, the mesocorticolimbic pathway, implicated in reward and motivation is expected to be activated in this neuroimaging study. The neurons from the left ventral tegmental area, forming the majority of the mesocorticolimbic projections involved in reward, send their axons to the nucleus accumbens, striatum and frontal cortex, structures involved in motivation. The nucleus accumbens is part of a neural circuit responsible for motivated and goal-directed behavior. In this brain area, dopamine innervation mediates the immediate pleasurable aspects of rewards, leading to further activation in the limbic system, particularly the left amygdala that will attend to and process the stimulus as a reinforcer (Morgane et al., 2005). The limbic system consequently sends projections to the prefrontal cortex, specifically the orbitofrontal cortex, as well as the left anterior cingulate cortex. The anatomical connections of the amygdala with the temporal (cingulate cortex) and the frontal association cortices provide the cognitive interpretation of the emotional state. Since touch activates sensory receptors, the left posterior parietal lobe was also believed

to show neural activation since it has an associative function with the somatosensory cortices. It is therefore expected that this condition will provide greater activation in the limbic system and frontal association cortices more than any of the other conditions in this study.

## Materials and Method

### *Subjects*

Forty two healthy participants were recruited through Carleton University, Ottawa University and the three Ottawa Hospitals (General, Civic, and Riverside) via flyer announcements and word of mouth. An advertisement was also run in the 'Metro', a free daily newspaper servicing the Ottawa region. Informed consent was obtained as approved by the Ottawa Hospital Research Ethics Internal Review Board. Participants provided written informed consent and were screened to ensure that they satisfied MRI safety requirements. One participant was excluded from analyses due to a high score on the Beck Depression Inventory, indicating depressive tendencies. In total, forty one healthy individuals were imaged for this study as they performed a Go/No Go task. The participants were right-handed (13 male, 28 female) ranging in age from 20 to 62 years ( $M=32.29$ ,  $SD=9.66$ ). Each participant, on the day of testing, was randomly assigned to a tactile condition (massage with an object, Swedish foot massage or reflexology massage) or the control condition (naïve to any tactile manipulation). The repartition of subjects across groups is summarized in Table 1.

Table 1

*Descriptive statistics across experimental conditions*

Condition	Number of Participants (females/males)	Mean age (S.D)
Nothing	10 (8/2)	30.1 (8.13)
Object	9 (7/2)	37.5 (14.00)
Massage	11 (6/5)	32.00 (8.84)
Reflexology	11 (7/4)	30.27 (6.65)

### *Questionnaire assessments*

Prior to the scanning session, each participant completed questionnaires assessing overall mood state and depressive tendency. The Positive Affect Negative Affect Scale (PANAS) is a 41-item scale that requires participants to rate a series of single-word adjectives on a 5-point scale to indicate the extent to which that emotion (e.g., distressed, upset, scared, irritable) is present during their daily life. The scale shows good internal consistency reliability (Watson, Clark, & Tellegen, 1988). We also administered the Beck Depression Inventory (BDI) in order to ensure that our sample did not express any depressive tendencies. The BDI is a 21-item self-report inventory designed to measure the severity of depressive symptomatology. The cut-off points for the BDI were as follows: minimal or none (0–9), mild (10–16), moderate (17–29), and severe (30–63). The BDI total score correlates significantly with diagnoses of clinical depression and it has well-established psychometric properties in both psychiatric and non-psychiatric samples (Beck, Steer & Garbin, 1988). In order to assess each participant's subjective experience to their specific condition, we verbally administered a Likert question, whereby each participant was asked to rate their feeling of well-being on a 5-point scale. This was done immediately before the scanning session and following the termination of the study while the subjects lay supine in the scanner.

### *Tactile Paradigm*

In the massage with an object condition, a wooden massage therapy tool was used to roll over the right plantar surface of the right foot. The Swedish massage condition was also performed utilizing maneuvers aimed at muscle relaxation by manipulating the soft

tissues of the plantar surface of the right foot. In the third tactile condition, a reflexology treatment, whereby pressure points are used to restore the flow of energy throughout the body, was applied on the right plantar surface of the foot using the basic techniques employed in this particular therapy. Each tactile treatment was administered for a duration of 8.5 minutes. Because of the pressure generated by these tactile treatments, each subjects' legs were strapped down to the scanner bed in order to minimize movement, and hence, reduce any motion artifacts in the brain images.

### *Go/No Go Task*

Stimuli were presented to the participant by a computer controlled projection system that delivered a visual stimulus to a rear-projection screen located at the entrance to the magnet bore. Stimuli were presented as white letters on a black background. A mirror on the head coil allowed subjects to observe the screen which projected these stimuli. The distance between the subject's eyes and the screen was approximately six feet. The scanning room and magnet bore were darkened to allow easy visualization of the experimental stimuli. Button-press responses were recorded via a MRI compatible fibre optic device (Lightwave Medical, Vancouver, British Columbia, Canada). Subjects were instructed to press as quickly and correctly as possible and if they made a mistake, to continue without thinking about the mistakes. The scanning session began with an initial rest epoch of 15 seconds to allow longitudinal magnetic relaxation (T1 effects) to stabilize. Images collected during this initial rest epoch were not included in the image analysis. The Go/No Go block design procedure involved presentation of letters, one at a time on a screen for a period of 125 ms, with an inter-stimulus interval of 875 ms. Fifty

percent of the stimuli were 'X' and the other 50% were other capital letters randomly selected from the remainder of the alphabet. The 'X' and 'non-X' stimuli were presented in random order. There were two types of Go/No Go condition. In the 'respond to X' condition, the subject was instructed to press a button with the right index finger when an 'X' was presented, and refrain from pressing for all other letters. In the 'respond to non-X' condition, the subject was instructed to refrain from pressing for 'X' and to press for all other letters with the right index finger. Both Go/No Go conditions were presented in epochs of 27 seconds duration. Each Go/No Go epoch was preceded by a 3 second instruction epoch and followed by a 30 second rest epoch. During instruction epochs, the instruction 'Press for X' or 'Press for all letters except X' was presented on the screen. During rest epochs, the word 'REST' was presented and the subject was not required to make any motor response. Within the scanning session there were four 'X' (termed ABCD) and four 'non-X' epochs (termed A<sup>1</sup>B<sup>1</sup>C<sup>1</sup>D<sup>1</sup>), presented in a counterbalanced order, starting with the 'X' condition.

### *Imaging*

Imaging was performed using a 1.5 Tesla Siemens Magnetom Symphony MR scanner with the quantum gradient set (maximum amplitude = 30 mT/m and slew rate = 125 T/m/s). The participants' lay supine and their head was firmly secured using a custom head holder and positioned approximately parallel to the anterior commissure posterior commissure (AC-PC) line using external references. A conventional T1-weighted spin echo localizer was acquired and used to prescribe a subsequent 3D FLASH (TR/TE 11.2/21 ms, flip angle 60°, field of view (FOV) 26x26 cm<sup>2</sup>, 256x256 matrix,

slice thickness 1.5 mm) volume acquisition used for further structural analyses. Whole brain echo planar fMRI based on the BOLD effect was performed using an echo planar pulse sequence (TR/TE 3000/40 ms, flip angle 90°, FOV 24x24 cm<sup>2</sup>, 64x64 matrix, slice thickness 5 mm, 27 axial slices, bandwidth 62.5 kHz). A total of 167 images of the entire brain were collected in a total period of 501 sec. The presentation of stimuli did not commence until after 15 sec, to allow time for T1 effects to stabilize, and the five scans performed during this time were excluded from the analysis. In addition, scanning continued for 18 sec after the final stimulus, to ensure that the hemodynamic response to that stimulus was adequately sampled.

### *Image processing*

The functional images were reconstructed and for each subject, the scans were realigned and corrected for motion using the procedure of Friston et al. (1995) as implemented in Statistical Parametric Mapping (SPM5). The motion correction did not exceed 2mm for any of the participants. A mean functional image volume was constructed for each participant from the realigned image volumes. This mean image volume was then used to match the echo planar imaging (EPI) template provided in SPM5. These parameters were then applied to the corresponding functional image volumes for each participant. The normalized functional images were smoothed with a 10 mm full width at half-maximum Gaussian filter.

*Imaging Whole Brain Analysis*

Voxel-based analyses were performed to assess global brain structure changes without limiting ourselves to *a priori* regions of interest. Separate fixed effects analyses were performed on all 4 conditions for the comparison of the first four rest blocks (Rest1) minus the last four rest blocks (Rest 2) of the Go/No Go task and vice versa (i.e. R2-R1). Fixed effects analyses refer to within group analyses, whereby the only variance is the variance between scans for each individual subject. Specifically, all images collected during Rest1, for each participant, were averaged together and, all images during Rest2, for each participant, were also averaged together prior to subtraction. These were used to determine neural activity in subjects as a function of time.

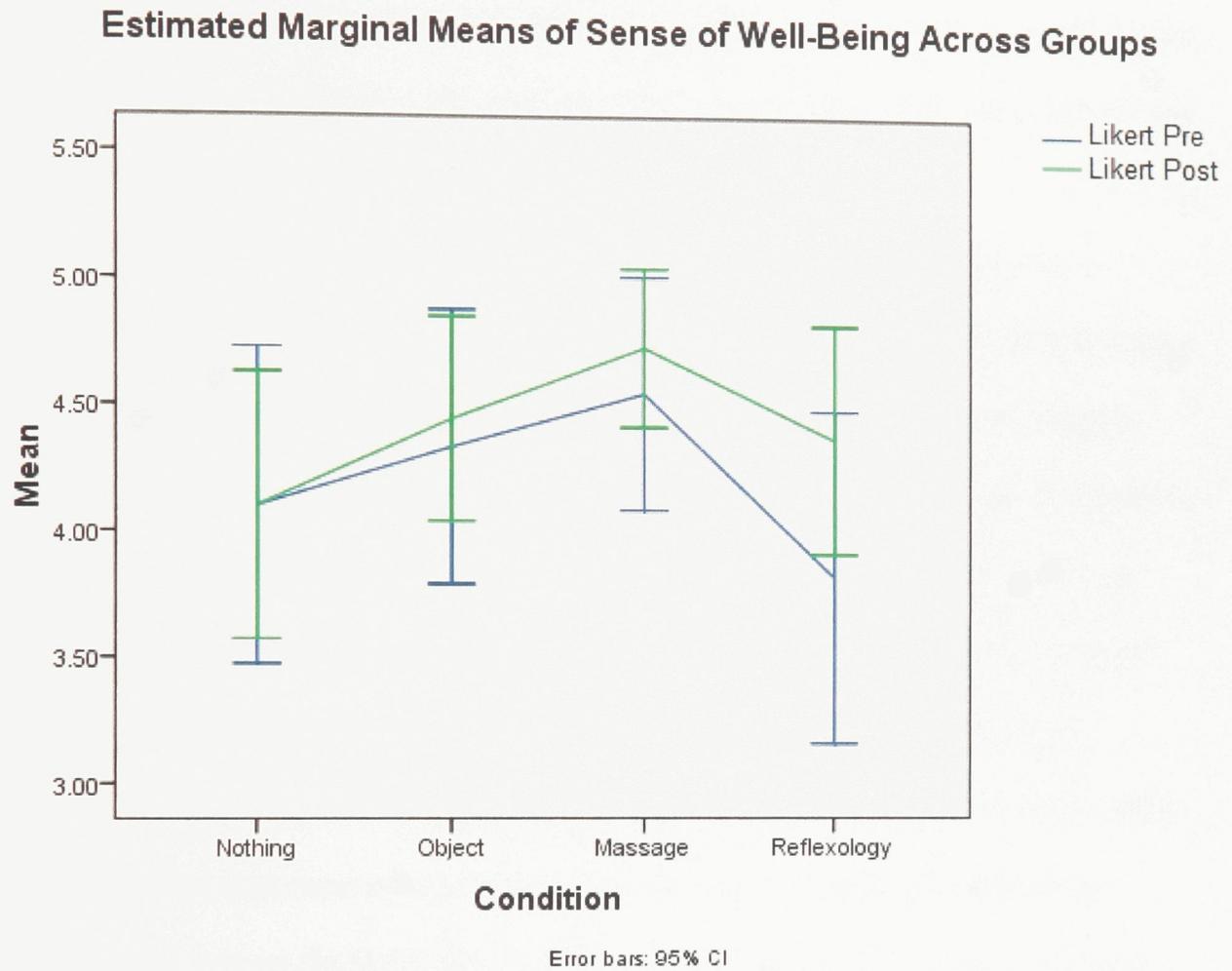
A second-level random effects analysis (i.e. between groups analysis) was subsequently performed; wherein, the contrast images obtained for each participant (Rest2 – Rest1) were used for a full factorial ANOVA design to determine statistical differences across treatment groups. The condition-specific images were contrasted in a general linear model to determine the appropriate t-statistics. Specifically, the t-statistics were normalized to Z scores obtained from the linear model in order to determine significant clusters of activation. Random effects analyses should eliminate highly discrepant variances between and within individuals. Post-hoc contrasts between the massage group and all other groups were performed. For all statistical analyses performed, PANAS (positive) and Reaction time for the ‘non-X’ condition across the first two trials ( $A^1B^1$ ) were used as covariates (due to their significant differences between groups).

## Results

### *Behavioural data*

A 5-point Likert scale question was posed by a member of the research team while the participant was positioned in the scanner awaiting study commencement, and once again immediately following the scanning session, while still lying in the scanner. As such, each participant provided a pre- and post- measure of their current state of well-being. These scores were analyzed using a 2 (time: pre and post)  $\times$  4 (condition: nothing, object, massage, reflexology) repeated measures analysis of variance (ANOVA) examining the main effects of time and condition as well as the interaction between these factors. There was a significant difference across time ( $F(1, 37)=4.99$ ,  $MSE=0.894$ ,  $p=0.032$ ) although no main effect of group was detected ( $F(3, 37)=1.67$ ,  $MSE=1.46$ ,  $p=0.19$ ). Moreover, the interaction did not reach significance ( $F(3, 37)=1.65$ ,  $MSE=0.30$ ,  $p=0.20$ ), indicating that although participants reported increased feelings of well-being following the experiment (Pre:  $M=4.20$ ,  $SEM=0.13$ ; Post:  $M=4.41$ ,  $SEM=0.1$ ), this effect did not differ across groups (Figure 1).

Figure 1. 5-point Likert scale item assessment across groups, pre- and post- experimental treatment.

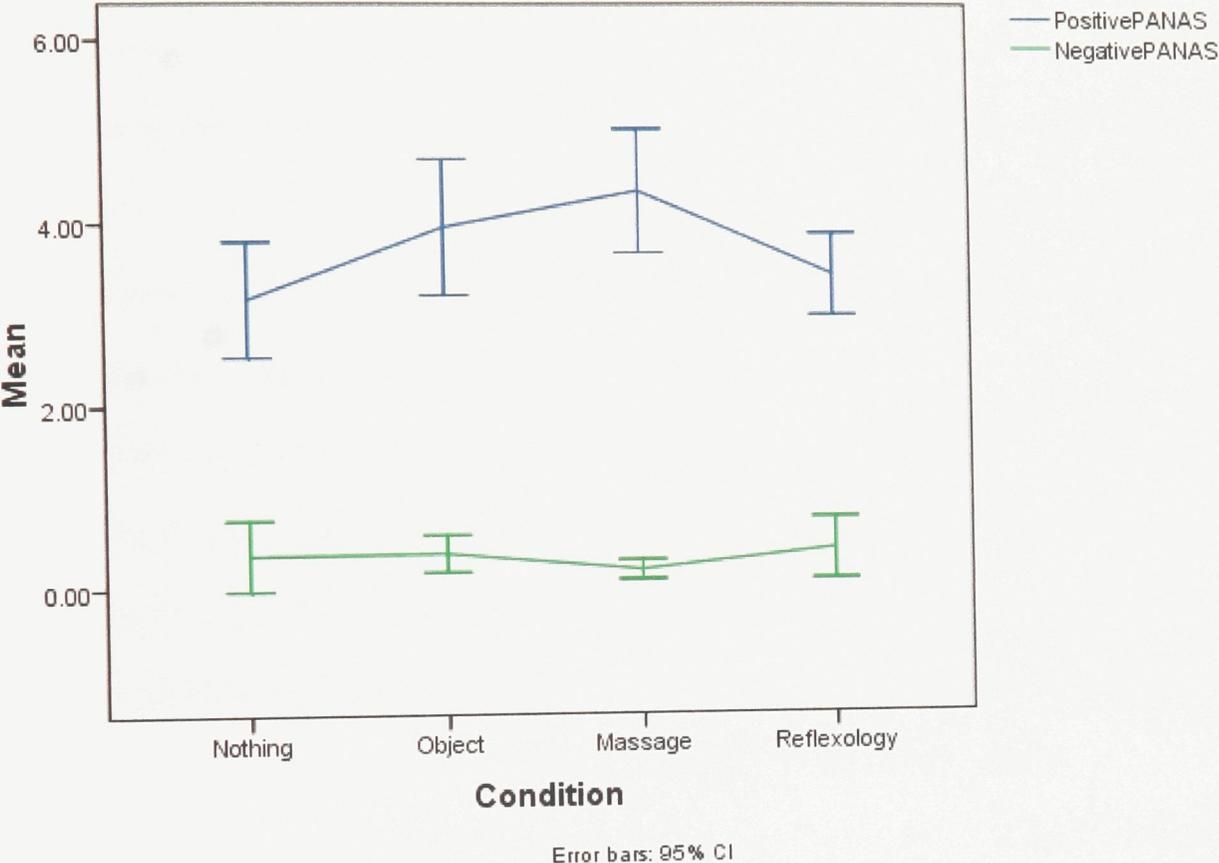


A one-way analysis of variance was conducted to assess whether the BDI scores varied across treatment groups. In this regard, no significant main effect of group was observed ( $F(3, 40)=1.50$ ,  $MSE=8.73$ ,  $p=0.23$ ), implying that groups did not differ from each other in depressive tendencies detected using this scale. In fact, the mean BDI score across groups was 2.88 ( $SD=3.00$ ), indicating that, as expected, there was no substantial indication of depression in this population.

The Positive Affect Negative Affect Scale (PANAS) questionnaire was administered to subjects prior to entering the fMRI scanner in order to determine if there were any pre-existing differences in positive and negative affect. Thus, we sought to ensure that participants that might score overly high or overly low on PANAS would not preferentially accumulate in any particular treatment group. Surprisingly, a one-way analysis of variance revealed a significant main effect of group for the positive mood states ( $F(3, 40)=3.70$ ,  $MSE=0.79$ ,  $p=0.02$ ) but not the negative mood states ( $F(3, 40)=0.67$ ,  $MSE=0.16$ ,  $p=0.57$ ). Specifically, post hoc analyses (Tukey's HSD) revealed that the subjects that were to be assigned to the Massage condition showed greater positive affect scores ( $M=4.34$ ,  $SD=1.00$ ) compared to the Nothing control condition ( $M=3.17$ ,  $SD=0.88$ ) ( $p < 0.05$ ,  $SE=0.39$ ; Fig.2). As such, we used the positive affect as a covariate in our group imaging analyses.

Figure 2. PANAS scale assessment of positive and negative moods states across groups.

**Estimated Marginal Means for Positive and Negative Affect Across Groups**



*Whole brain data*

Fixed effects (within subject) analyses were conducted for each participant to create contrast images which were subsequently used for random effects analysis. For group analysis, a random effects (between subjects) model was used to determine voxel-wise t-statistics (i.e. brain clusters) contrasting specific conditions of interest. As will be recalled from the methods section, differences in brain activity over time (i.e. R2-R1) were used as contrasts to compare between the treatment groups. This model estimates the error variance for each condition of interest across subjects, rather than across scans, providing better generalization to the subject population.

Fixed effects were analyzed as a function of time (i.e. R1-R2 and R2-R1), delineating the regions activated during the rest periods of the first half and the second half, respectively, of the experimental procedure. For the nothing group, receiving no tactile stimulation, significant brain activity was observed in several brain areas during the first half of the experiment (i.e. R1-R2), including: frontal gyrus, primary somatosensory area (S1), occipital lobe, parietal and temporal lobes (see Table 2, Fig. 3). In contrast, during the second half of the experimental procedure (i.e. R2-R1), maximally activated neural activity was apparent in the cingulate gyrus, parahippocampal gyrus and the superior temporal gyrus (see Table 3 for complete list of regions activated, Fig. 4). Interestingly, there appeared to be less overall brain activity, and different regions activated, over time in the nothing control condition.

Table 2

*Activation clusters detected for the image contrasts acquired during the first half of the experimental procedure in the nothing control condition (R1-R2)*

Anatomical location	P value	t value	Cluster size	MNI coordinates of max. t value		
				x	y	z
<b>Superior frontal gyrus</b>	<b>0.000</b>	<b>109.94</b>	<b>9409</b>	<b>-15</b>	<b>0</b>	<b>75</b>
Inferior frontal gyrus (BA 47)						
Inferior temporal gyrus (BA 20)						
Superior temporal gyrus (BA38)						
Precentral gyrus						
Medial frontal gyrus						
Middle temporal gyrus						
Fusiform gyrus						
Postcentral gyrus						
Middle frontal gyrus						
<b>Cuneus</b>	<b>0.000</b>	<b>28.92</b>	<b>272</b>	<b>-12</b>	<b>-93</b>	<b>30</b>
Middle occipital gyrus						
Lingual gyrus						
Declive						
Precuneus						

*Note.* BOLD responses are reported for clusters that surpassed an uncorrected threshold of  $p < 0.001$  and a corrected  $p$ -value of 0.05 on cluster level. BA=Brodman Area; MNI= Montreal Neurological Institute.

*Figure 3.* Surface rendering of the fMRI map for the first 4 rest periods of the experimental procedure (R1-R2): fMRI group data of 10 subjects in the nothing control treatment. Clusters are reported as being significant if they passed an uncorrected threshold of  $p < 0.001$  with a corrected  $p$ -value on cluster level of less than 0.05.

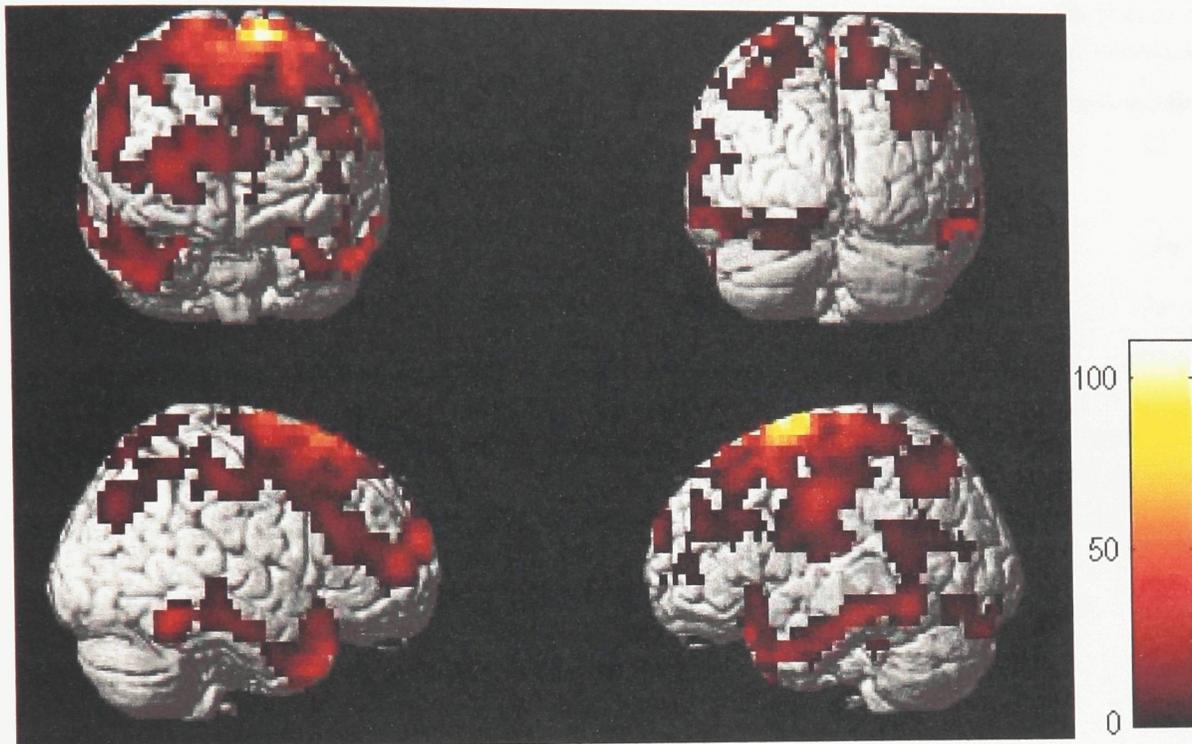


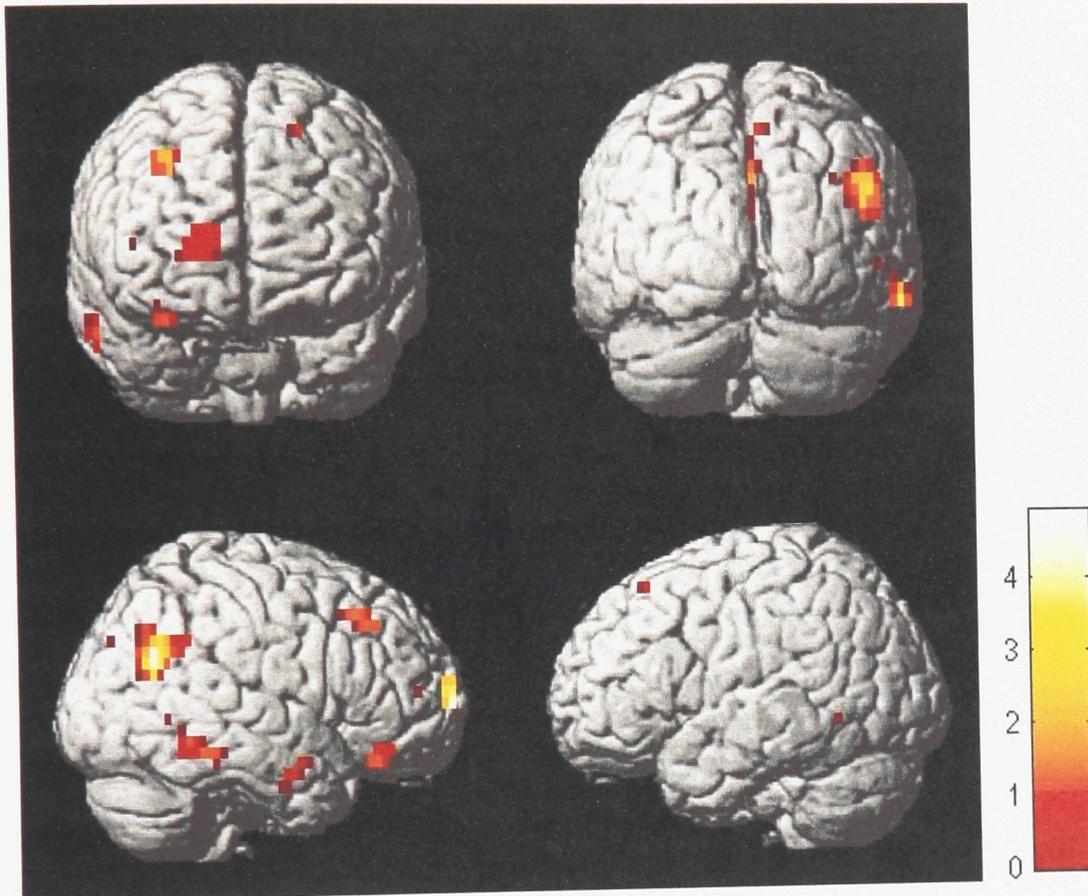
Table 3

*Activation clusters detected for the contrasts of the images acquired during the last half of the experimental procedure in the nothing condition (R2-R1)*

Anatomical location	<i>p</i> value	<i>t</i> value	Cluster size	MNI coordinates of max. <i>t</i> value		
				<i>x</i>	<i>y</i>	<i>z</i>
<b>Cingulate gyrus</b> Precuneus Posterior cingulate	<b>0.000</b>	<b>4.93</b>	<b>181</b>	<b>3</b>	<b>-60</b>	<b>25</b>
<b>Parahippocampal gyrus</b> Fusiform	<b>0.004</b>	<b>4.21</b>	<b>73</b>	<b>-33</b>	<b>-45</b>	<b>-10</b>
<b>Superior temporal gyrus</b> Middle temporal gyrus Supramarginal gyrus Angular gyrus	<b>0.001</b>	<b>4.10</b>	<b>89</b>	<b>48</b>	<b>-63</b>	<b>25</b>

*Note.* BOLD responses are reported for clusters that surpassed an uncorrected threshold of  $p < 0.001$  and a corrected *p*-value of 0.05 on cluster level. BA=Brodman Area; MNI= Montreal Neurological Institute.

*Figure 4.* Surface rendering of the fMRI map for the last 4 rest periods of the experimental procedure (R2-R1): fMRI group data of 10 subjects in the nothing condition. Clusters are reported as being significant if they passed an uncorrected threshold of  $p < 0.001$  with a corrected  $p$ -value on cluster level of less than 0.05.



In marked contrast to the substantial neural activation observed in the nothing control group, the fixed effects for subjects that received tactile manipulation on the plantar surface of the foot with a wooden object, showed no significant brain activity during the first half of the experiment (i.e. R1-R2; see Figure 5). However, in the latter four rest periods (i.e. R2-R1), the parietal lobe (including the precuneus and angular gyrus) and medial frontal gyrus were activated (see Table 4, Fig. 6).

*Figure 5.* Surface rendering of the fMRI map for the first 4 rest periods of the experimental procedure (R1-R2): fMRI group data of 9 subjects in the object condition. Clusters are reported as being significant if they passed an uncorrected threshold of  $p < 0.001$  with a corrected  $p$ -value on cluster level of less than 0.05.

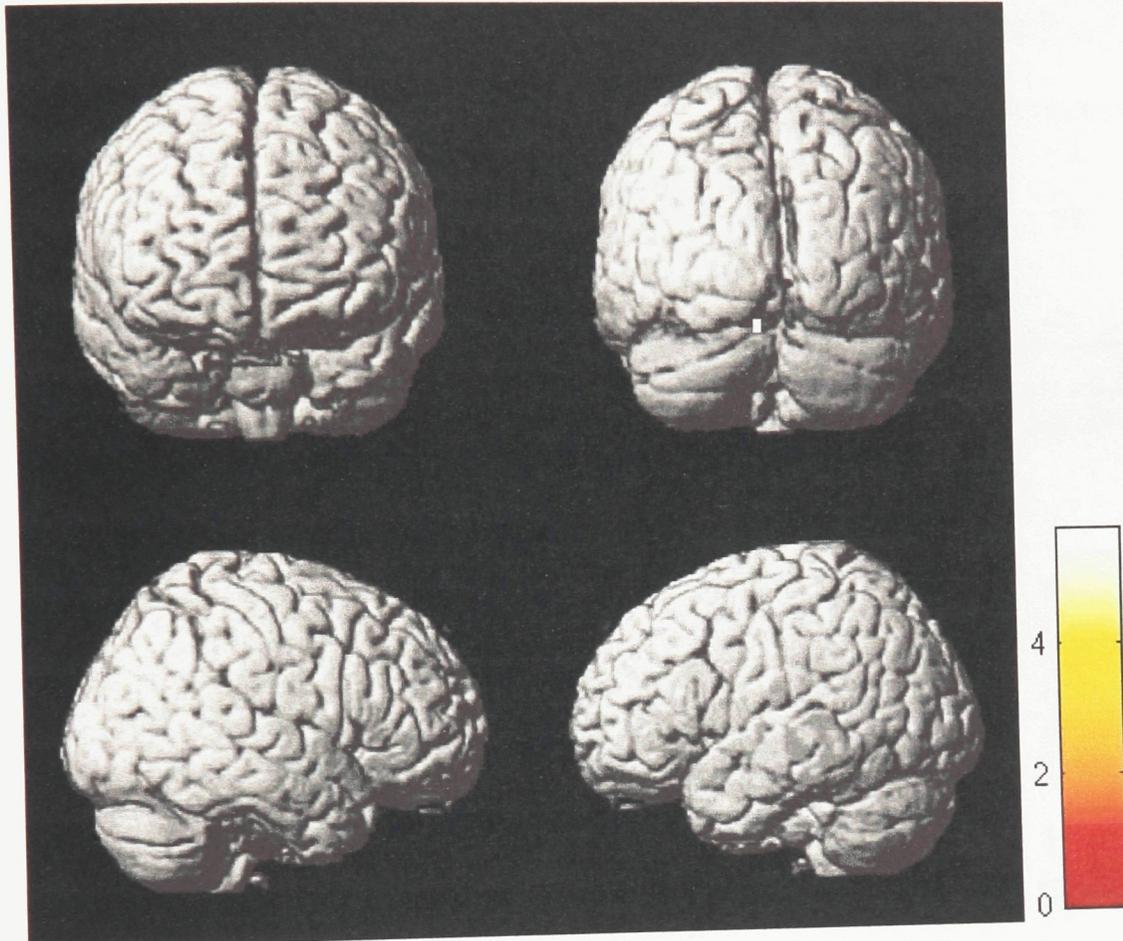


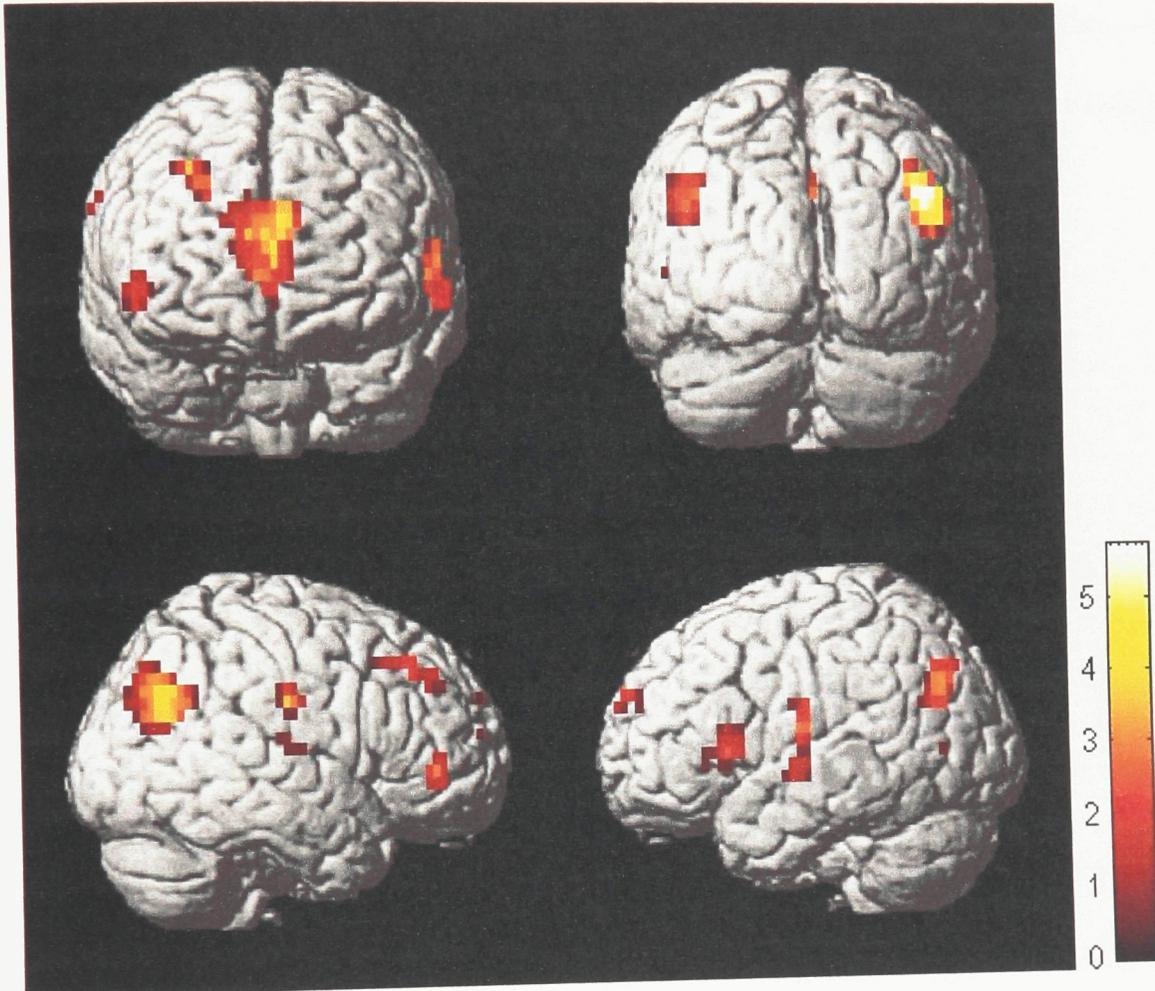
Table 4

*Activation clusters detected for the contrasts of the images acquired during the last half of the experimental procedure (R2-R1) for subjects in the object condition*

Anatomical location	<i>p</i> value	<i>t</i> value	Cluster size	MNI coordinates of max. <i>t</i> value		
				<i>x</i>	<i>y</i>	<i>z</i>
<b>Precuneus</b>	<b>0.000</b>	<b>5.73</b>	<b>245</b>	<b>6</b>	<b>-51</b>	<b>30</b>
<b>Angular gyrus</b>	<b>0.000</b>	<b>4.68</b>	<b>127</b>	<b>45</b>	<b>-66</b>	<b>30</b>
Inferior parietal lobule Precuneus	<b>0.000</b>	<b>4.42</b>	<b>204</b>	<b>3</b>	<b>51</b>	<b>15</b>
<b>Medial frontal gyrus</b>	<b>0.000</b>	<b>4.42</b>	<b>204</b>	<b>3</b>	<b>51</b>	<b>15</b>

*Note.* BOLD responses are reported for clusters that surpassed an uncorrected threshold of  $p < 0.001$  and a corrected *p*-value of 0.05 on cluster level. BA=Brodmann Area; MNI= Montreal Neurological Institute.

*Figure 6.* Surface rendering of the fMRI map for the last 4 rest periods of the experimental procedure (R2-R1): fMRI group data of 9 subjects in the object condition. Clusters are reported as being significant if they passed an uncorrected threshold of  $p < 0.001$  with a corrected  $p$ -value on cluster level of less than 0.05.



In the Swedish massage condition, the fixed effects of the first four rest periods (R1-R2) revealed significant brain activity mainly in the cerebellum, temporal and occipital lobes (see Table 5, Fig. 6). In contrast, during the last four rest periods, brain activity was limited to the cerebellum and parietal lobe (see Table 6 for complete list of regions, Fig. 7), indicating a dampened effect following the massage therapy treatment.

Table 5

*Activation clusters detected for the contrasts of the images acquired during the first half of the experimental procedure (R1-R2) in the massage condition*

Anatomical location	p value	t value	Cluster size	MNI coordinates of max. t value		
				x	y	z
<b>Cuneus</b> (BA18/19) Postcentral gyrus (BA3) Superior occipital gyrus (BA19) Inferior frontal gyrus Superior frontal gyrus Middle occipital gyrus Cingulate gyrus Middle frontal gyrus Middle temporal gyrus	<b>0.000</b>	<b>59.85</b>	<b>16714</b>	<b>-18</b>	<b>-99</b>	<b>5</b>
<b>Culmen</b>	<b>0.000</b>	<b>18.27</b>	<b>157</b>	<b>27</b>	<b>-33</b>	<b>-35</b>
<b>Superior temporal gyrus</b>	<b>0.025</b>	<b>16.13</b>	<b>58</b>	<b>-66</b>	<b>-18</b>	<b>0</b>
Inferior temporal gyrus						

*Note.* BOLD responses are reported for clusters that surpassed an uncorrected threshold of  $p < 0.001$  and a corrected p-value of 0.05 on cluster level. BA=Brodman Area; MNI= Montreal Neurological Institute.

*Figure 7.* Surface rendering of the fMRI map for the first 4 rest periods of the experimental procedure (R1-R2): fMRI group data of 11 subjects in the massage condition. Clusters are reported as being significant if they passed an uncorrected threshold of  $p < 0.001$  with a corrected  $p$ -value on cluster level of less than 0.05.

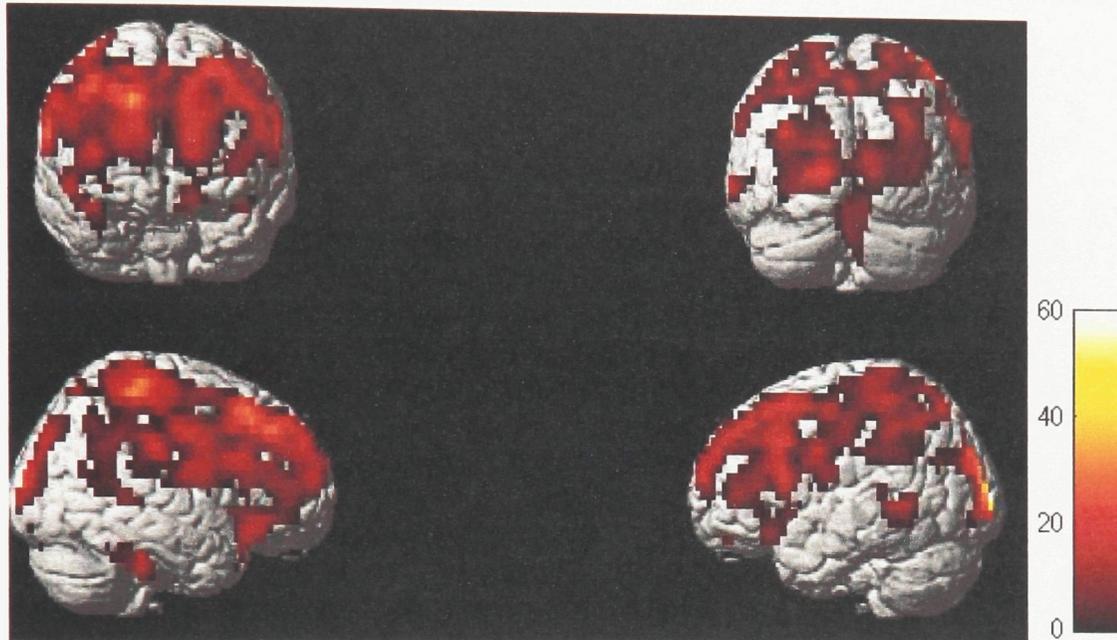


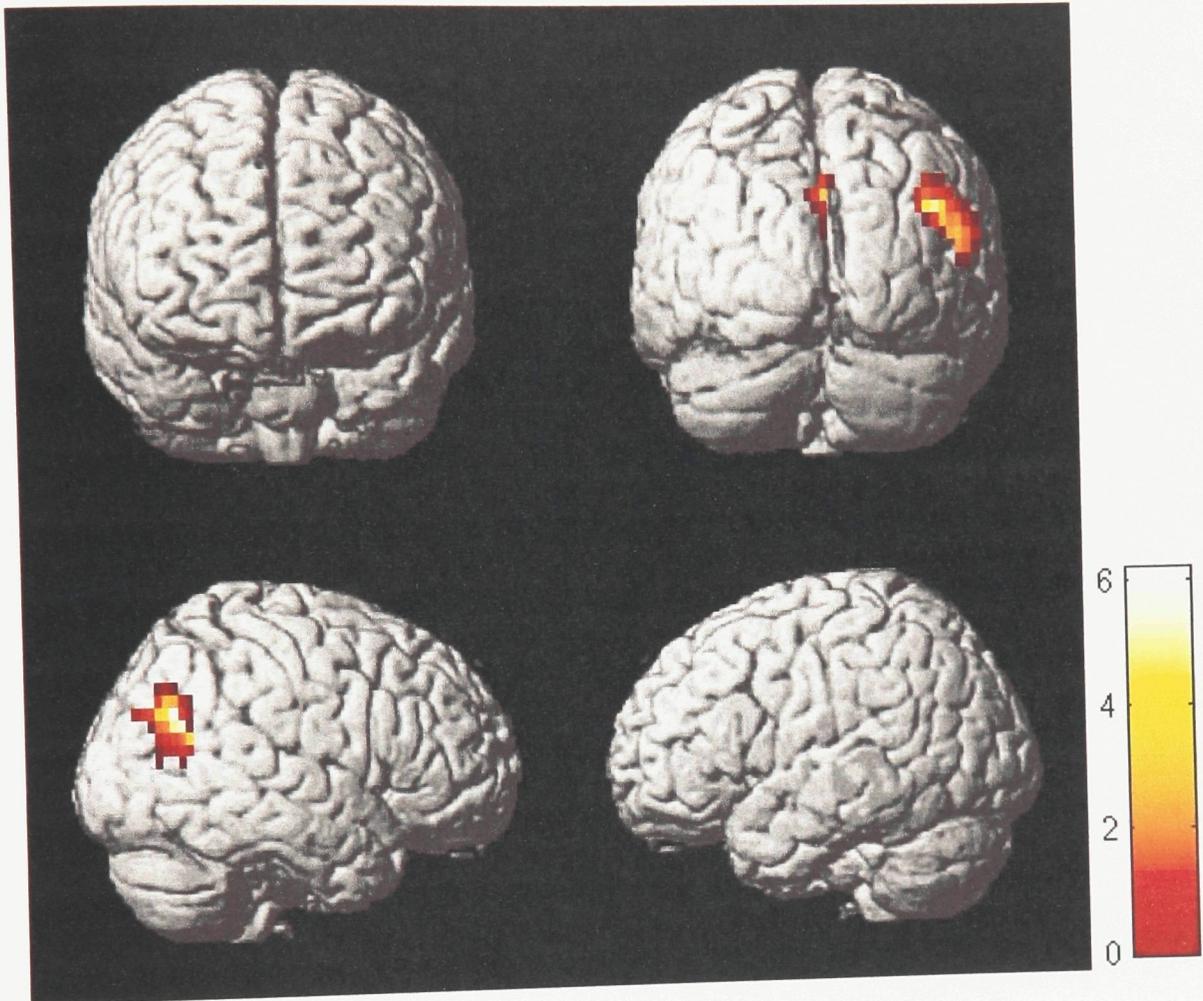
Table 6

*Activation clusters detected for the contrasts of the images acquired during the last half of the experimental procedure (R2-R1) in the massage condition*

Anatomical location	<i>p</i> value	<i>t</i> value	Cluster size	MNI coordinates of max. <i>t</i> value		
				<i>x</i>	<i>y</i>	<i>z</i>
<b>Cuneus</b>	<b>0.000</b>	<b>6.19</b>	<b>403</b>	<b>0</b>	<b>-51</b>	<b>20</b>
<b>Angular gyrus</b>	<b>0.001</b>	<b>4.35</b>	<b>114</b>	<b>45</b>	<b>-69</b>	<b>30</b>
Middle temporal gyrus						

*Note.* BOLD responses are reported for clusters that surpassed an uncorrected threshold of  $p < 0.001$  and a corrected *p*-value of 0.05 on cluster level. MNI= Montreal Neurological Institute.

*Figure 8.* Surface rendering of the fMRI map for the last 4 rest periods of the experimental procedure (R2-R1): fMRI group data of 11 subjects in the massage condition. Clusters are reported as being significant if they passed an uncorrected threshold of  $p < 0.001$  with a corrected  $p$ -value on cluster level of less than 0.05.



Brain activity in the fixed effects of the subjects in the reflexology condition showed abundantly significant activation of several brain regions during the first 4 rest periods of the experiment (R1-R2, including frontal gyrus, temporal gyrus and primary motor cortex (see Table 7, Fig. 8). Curiously, however, significant less brain region specific activation was observed during the latter half of the experiment (R2-R1).

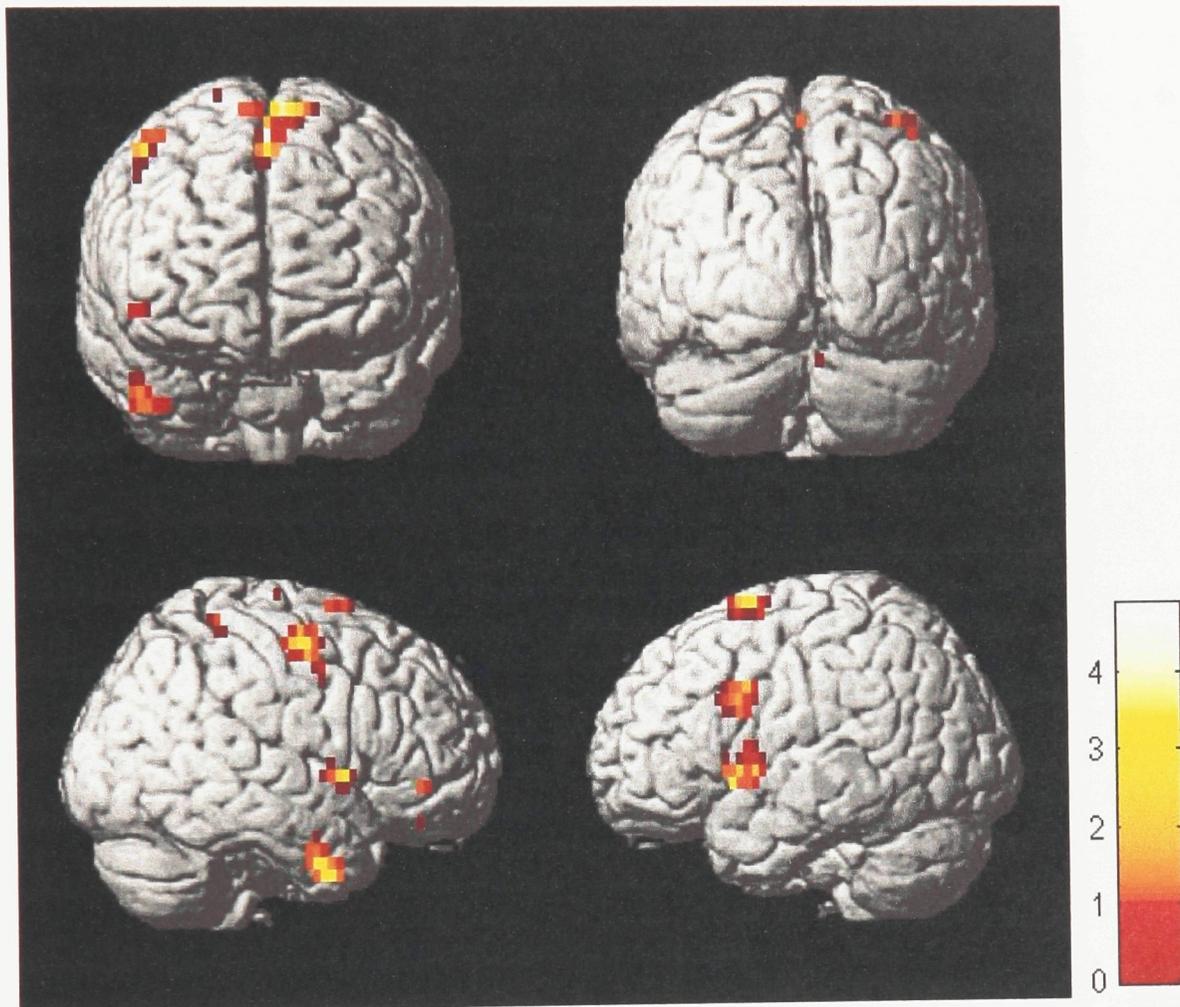
Table 7

Activation clusters detected for the contrasts of the images acquired during the first half of the experimental procedure (R1-R2) in the reflexology condition.

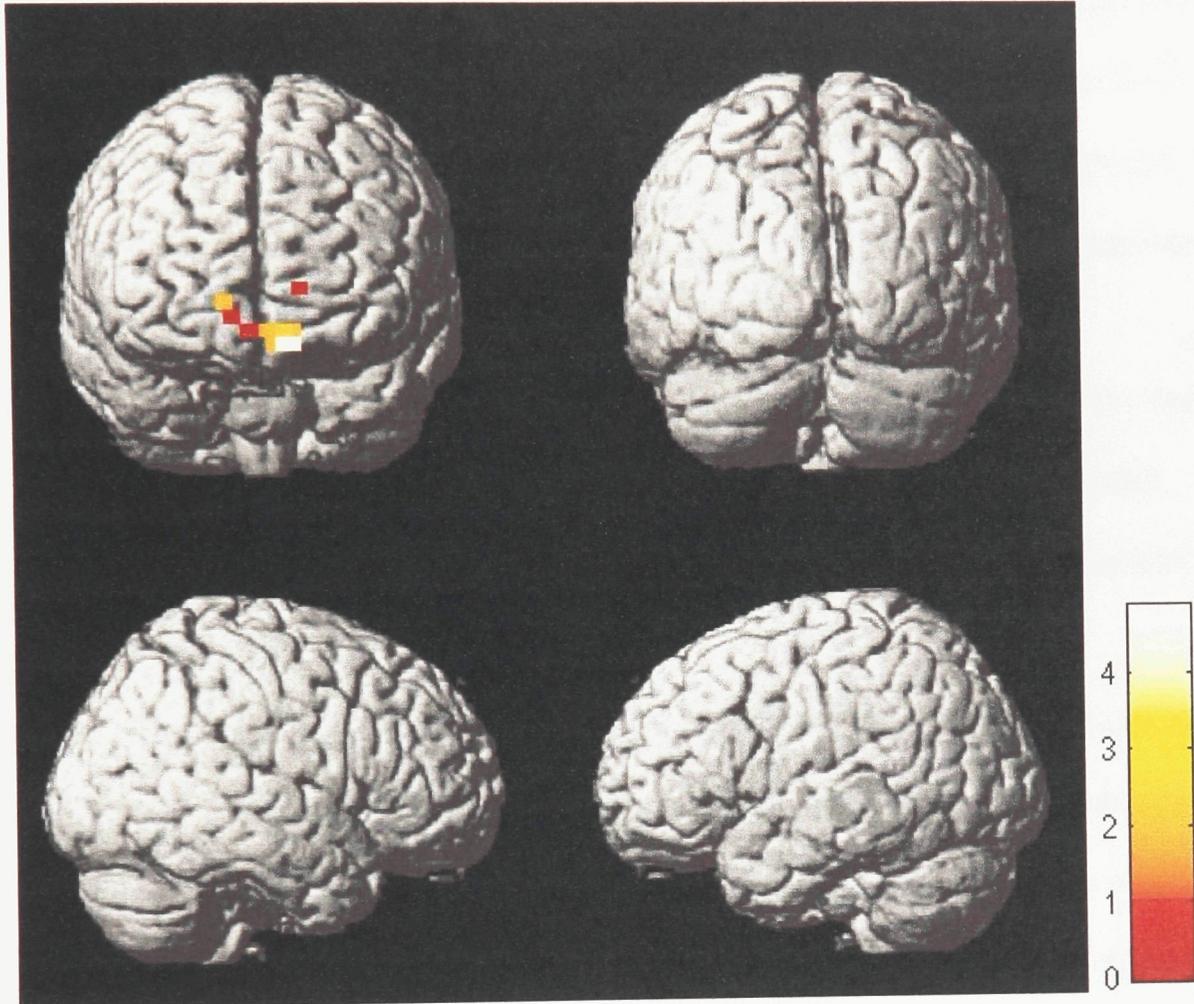
Anatomical location	<i>p</i> value	<i>t</i> value	Cluster size	MNI coordinates of max. <i>t</i> value		
				<i>x</i>	<i>y</i>	<i>z</i>
<b>Superior frontal gyrus (BA6)</b>	<b>0.000</b>	<b>4.89</b>	<b>176</b>	<b>-6</b>	<b>9</b>	<b>60</b>
<b>Frontal lobe</b>	<b>0.000</b>	<b>4.54</b>	<b>179</b>	<b>24</b>	<b>12</b>	<b>-15</b>
Lentiform nucleus						
Putamen						
Lateral globus pallidus						
Superior temporal gyrus						
Insula						
<b>Middle frontal gyrus</b>	<b>0.030</b>	<b>4.48</b>	<b>46</b>	<b>-42</b>	<b>9</b>	<b>30</b>
<b>Middle temporal gyrus</b>	<b>0.038</b>	<b>4.43</b>	<b>43</b>	<b>45</b>	<b>0</b>	<b>-35</b>
<b>Lentiform nucleus</b>	<b>0.000</b>	<b>4.20</b>	<b>182</b>	<b>-15</b>	<b>3</b>	<b>0</b>
Insula (BA13)						
<b>Precentral gyrus (BA6)</b>	<b>0.027</b>	<b>3.98</b>	<b>47</b>	<b>42</b>	<b>-9</b>	<b>55</b>

*Note.* BOLD responses are reported for clusters that surpassed an uncorrected threshold of  $p < 0.001$  and a corrected  $p$ -value of 0.05 on cluster level. BA=Brodman Area; MNI= Montreal Neurological Institute.

*Figure 9.* Surface rendering of the fMRI map for the first 4 rest periods of the experimental procedure (R1-R2): fMRI group data of 11 subjects in the reflexology condition. Clusters are reported as being significant if they passed an uncorrected threshold of  $p < 0.001$  with a corrected  $p$ -value on cluster level of less than 0.05.



*Figure 10.* Surface rendering of the fMRI map for the last 4 rest periods of the experimental procedure (R2-R1): fMRI group data of 11 subjects in the reflexology condition. Clusters are reported as being significant if they passed an uncorrected threshold of  $p < 0.001$  with a corrected  $p$ -value on cluster level of less than 0.05.

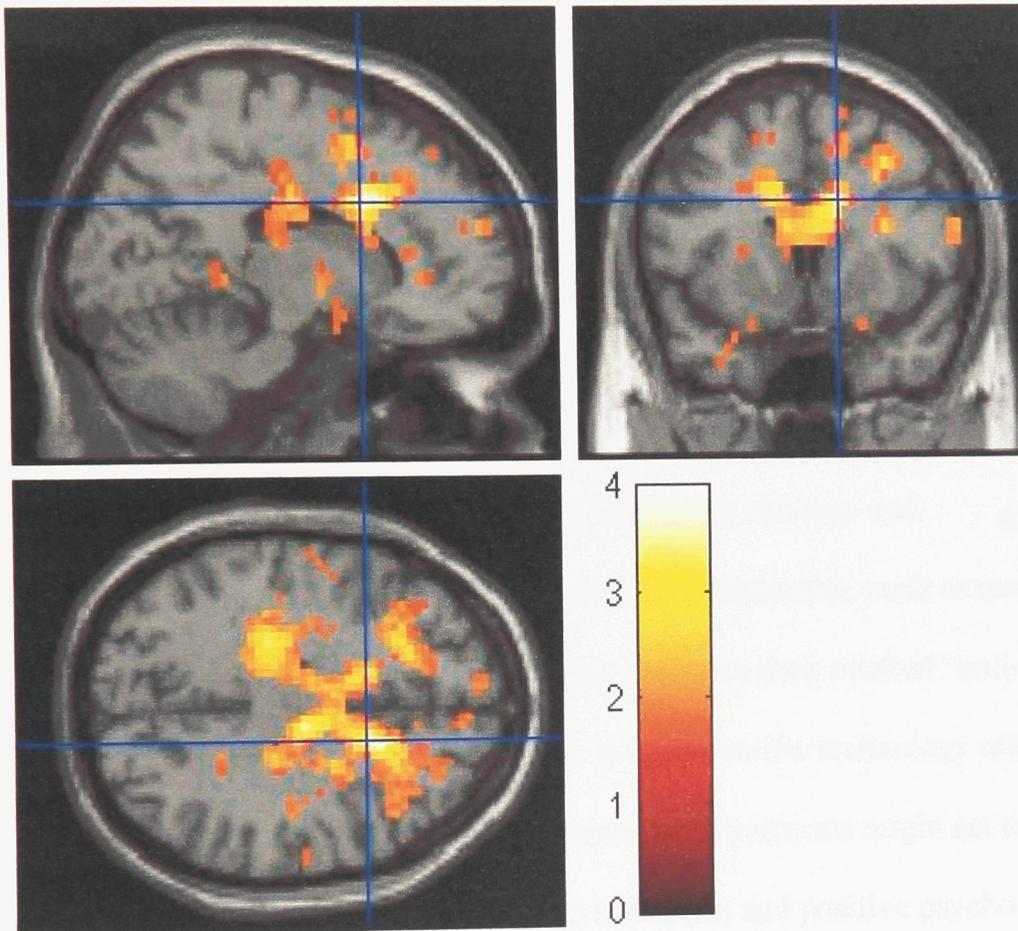


Overall, the fixed effects analyses revealed substantial region-specific brain activity at the beginning of the experimental procedure (R1-R2), which tended to subside in the latter part of the experiment (R2-R1) in most treatment conditions. Since our interests were primarily in the impact of the tactile treatment conditions, particularly, the Swedish massage, further analyses focused primarily on how this treatment differed from the other conditions during the last 4 rest periods of the study (R2-R1). To this end, the random effects ANOVA model at R2-R1 indicated a main effect of treatment group ( $F(3, 111)=8.97, p<0.05$ ) with a maximally activated voxel at  $x, y, z: -30, -39, -5$  corresponding to the temporal lobe (hippocampus) ( $Z=3.61$ , voxel size,  $K=183$ ). Indeed, the limbic lobe ( $x, y, z: 15, 12, 30$ ) overall was found to be significantly activated ( $Z=3.54$ , voxel size,  $K=693$ ) along with somewhat less activation in the frontal lobe and medial globus pallidus in this particular cluster.

Follow up comparisons were performed for the massage condition in contrast to the remaining conditions. In this regard, no significant differences in neural activity were observed when comparing the massage condition to the nothing or the object and reflexology groups (i.e. massage-nothing, massage-object or massage-reflexology at R2-R1). Yet, when the reverse difference was compared, that is comparison of the object condition (having a tactile but no human contact component), to the massage (i.e. object-massage at R2-R1) significantly less neural activity in the cingulate gyrus was observed ( $t=3.98, p=0.001$ , cluster size = 1576 voxels,  $x, y, z: 15, 12, 30$ ; see Figure 9). In this same cluster, we also detected significantly less neural activation in the anterior cingulate ( $Z=3.24, x, y, z: 9, 9, 25$ ) and the caudate ( $Z=3.11, x, y, z: -18, -24, 25$ ). In contrast to the aforementioned treatments, the Swedish massage condition was associated with

significantly greater neural activity (in the post-central gyrus in this case) when contrasted with the reflexology condition (i.e. massage-reflexology at R2-R1) ( $t=3.75$ ,  $p=0.035$ , cluster size=841 voxels, x, y, z: 39, -30, 55). Yet, correction after applying Tukey's HSD adjustment revealed a significance of 0.0125 alpha level was required (hence the comparison just missed the corrected significance level).

*Figure 11.* The cross hairs highlight the brain region of decreased activity in the Massage condition when contrasted with the Object condition during the last 4 rest periods (R2-R1). The most significantly activated voxel in the cingulate gyrus was  $x, y, z = 15, 12, 30$ , cluster size = 1576 voxels,  $p = 0.001$ . The colored bar to the right of the axial slice image indicates the t-scores of the activity shown in this particular cluster.



## Discussion

Complementary and alternative treatment approaches, such as massage, have been part of ancient cultures and were considered to be a medicinal practice as they promoted health and well-being (Fritz, 2000). Although massage continued to be practiced in the context of folk medicine, it would fall out of favor with the advent of Western medicine at the beginning of the nineteenth century (Moyer et al., 2004). However, over the last several decades, increasing attention has again been devoted to these ancient techniques (Barnes et al., 2008; Eisenberg et al., 1998). Indeed, the biopsychosocial model of health has come to have a prominent influence over Western medicine in recent years, clearly favoring a holistic approach to health and treatment of illness. Along these lines, emerging fields of specialization including Health Psychology and Psychoneuroimmunology have embraced alternate treatments, such as meditation, relaxation, massage and acupuncture, largely owing to their marked “anti-stress” consequences (Moyer et al., 2004). Hence, novel scientific technology may eventually uncover the basic mechanisms through which such treatments might act to impart beneficial effects. Indeed, besides obvious relaxation and positive psychological consequences, alternate treatments might also affect underlying biological processes that might be involved in illness states.

The present study attempted to identify the neuronal regions affected by acute massage therapy in a healthy population. Massage is a well-known complementary and alternative treatment approach used by both healthy and non-healthy individuals. It has wide-ranging beneficial effects, which have been measured on physiological and psychological levels; however, its neural substrates remain unknown. Moreover, it has

yet to be determined whether the type of massage used may differentially affect neuronal pathways and other biological processes. Therefore, in addition to comparisons with a control condition that received no tactile stimulation (termed nothing), we compared a Swedish foot massage treatment to reflexology (another less commonly used type of foot massage). We also compared these treatments to a massage using a wooden object (a tool commonly used by massage therapists), which was used to remove the human touch component from the treatment.

By examining each treatment condition separately over time, we found that several brain areas were activated across all groups during the course of the experimental scanning session. The exception being the object massage condition which did not show any significant differential brain activity during the first half of the experimental session (i.e. testing at the first 4 rest periods) and the reflexology condition, which failed to show any significant variations of activity during the last 4 rest periods of the session comparatively to the first four rest periods. In general, the tactile stimulation resulted in appreciably less global neuronal activation during the entire treatment session, relative to subjects that did not receive any tactile stimulation. Moreover, when compared to the control subjects, the Swedish massage appeared to diminish neuronal activation at several brain regions important for both emotional and cognitive processing, including the precuneus, posterior cingulate and fusiform gyrus. Thus, we will discuss the nature of these differential changes in brain activation (as detected using fMRI) with a particular focus on contrasting the early vs. late stages (first and second half of experimental study) of neuronal activation and their potential clinical relevance.

*Tactile-motor elements of massage: Somatosensory and motor pathways*

The primary somatosensory cortex (BA 3a, 3b, 1 and 2) contains a complete somatotopic representation of the body and sends projections (through BA2 and 3b) to the primary motor cortex, secondary somatosensory cortex and thalamus (Schwark, Esteky & Jones, 1992). After receiving primary somatosensory and motor input, the secondary somatosensory cortex further projects to the posterior parietal association areas where tactile information becomes integrated with other sensory information (Gilman, 2002; Haggard, 2006). Finally, tactile information is relayed to diverse cerebral cortical neurons that ultimately provide affective, attentional and motivational properties to the stimulus. In general, we observed a trend towards decreased activation of sensory-motor brain regions over time during the course of the fMRI scanner session. The following sections will discuss the observed alterations of neural activity in the post-central (somatosensory) and pre-central (motor) brain regions.

For many brain regions, the control group displayed appreciably higher basal levels of neural activation during the first half of the session (i.e. first 4 rest periods), relative to the tactile treatment groups. Yet, the type of massage given clearly had differential effects across brain regions. For instance, the reflexology and object massage groups had diminished neural activity in the somatosensory cortex during the first half of the experimental scanning session, relative to those that did not receive any tactile stimulation. However, the Swedish massage group did not differ in this respect. Yet, the Swedish and object massage conditions had appreciably lower activation of the precentral gyrus during the early phase of testing relative to the control group. Importantly, this region includes the primary motor cortex which sends axons to the lower motor neurons

of the neuromuscular junction. As already indicated, the somatosensory cortex is normally substantially activated by tactile stimuli, with BA1-3 receiving input from cutaneous mechanoreceptors and proprioceptors signaling muscle stretch (Golaszewski et al., 2006) and sends projections to primary motor neurons. Thus, short stretches within the musculature of the foot induced by massage would be expected to elicit activation of these regions. It is unclear why some of the massage treatments differentially affected somatosensory-motor activity but others did not. Moreover, the fact that these regions had lower activity in the second half of the session, suggests the possibility that non-tactile elements of the experiment were at play.

In terms of subcortical motor regions affected by the treatments, the reflexology condition was associated with significantly increased neural activity in the basal ganglia (specifically, the lateral globus pallidus, caudate and putamen) and the insula, relative to controls, in the early sampling period. These basal ganglia nuclei collectively play an active role in pre-filtering of external stimuli relevant for the planning and execution of motor functions (Awh & Vogel, 2008). In particular, these nuclei are critical for the initiation and termination of movement, which becomes particularly apparent when one considers cases of basal ganglia degeneration, as occurs in Parkinson's disease (PD), which results in a paucity of movement, coupled with abnormal gait and tremor (Halliday, 2007). Thus, specific alterations of basal ganglia activity that might be imparted by reflexology could conceivably have some beneficial role in clinical aspects of movement disorders, such as PD. Indeed, recent attention has been devoted to using non-traditional interventions, such as Tai Chi and aerobic exercise, to improve PD patient functioning (King & Horak, 2009).

In addition to basal ganglia variations, the cerebellum also appeared to show differential neural activity over the course of treatments. Specifically, during the first four rest periods, all three tactile conditions had diminished activity in the declive region of the cerebellum. Interestingly, however, the Swedish massage condition alone appeared to be initially associated with enhanced activity in the culmen lobule of the cerebellum. Both of these lobules are located in the vermis of the cerebellum, and are critical for fine motor coordination (Jantzen, Oullier, Marshall, Steinberg & Kelso, 2007). Several studies have also shown that cortical motor projections to the cerebellum following tactile stimulation are represented topographically in the vermis and intermediate zones of the cerebellar lobes (Bushara et al., 2001). It stands to reason that the altered cerebellar activity may have somehow been linked to the motor performance of the cognitive task (pressing keypad). It is unclear why the Swedish massage preferentially activated the culmen region of the cerebellum, but suggests the possibility that this region is more attuned to certain aspects of deep muscle manipulation (Bushara et al., 2001).

Our findings suggest that the nature of somatosensory and motor cortical activity patterns is affected in a complex fashion by different types of tactile stimulation. Since we posit the possibility that massage therapy might have a complementary role in conventional treatments of mood disorders, such as anxiety and depression, it is important to note that traditional antidepressant treatments have been shown to affect these brain regions. Indeed, antidepressants were reported to induce dendritic spine remodeling of pyramidal cells in the somatosensory region (Guirado et al., 2009). Thus, the possibility exists that massage therapy may be effective in facilitating such structural plastic events (i.e. spine remodeling, synaptogenesis) in a clinical population.

*Emotional aspects of massage: Cortical-limbic processes*

A recent meta-analysis on massage therapy delineated its efficacy in improving relaxation, overall mood and feelings of well-being as well as reducing feelings of pain, depression and anxiety (Moyer et al., 2004). Putative mechanisms concerning its immediate effects were proposed to involve the gate control theory, wherein the manual pressure from the massage would interfere with the transmission of pain signals to the brain. This would essentially 'close the gate' to the reception of pain before it could be processed (Moyer et al., 2004). This notion therefore suggests that massage therapy may have an analgesic effect. Moreover, it has been suggested that massage therapy may provide its benefits by shifting the autonomic nervous system from a sympathetic to a parasympathetic response state, leading to decreases in cardiovascular activity and stress hormone levels (Field, 1998). This change in arousal would thus create feelings of calmness and well-being. Another potential mechanism might involve a modulation of neurotransmission. In fact, it has been suggested that tactile manipulation may stimulate the release of endorphins and serotonin, which have an important inhibitory role upon the transmission of spinal pain signals (Field, 1998; Moyer et al., 2004; Kuhn & Schanberg, 1998). However, no attempts at delineating the neural circuitry of a massage therapy treatment have yet been reported in the literature.

Although little is known concerning the neural mechanisms of massage, greater attention has been devoted to the neural circuits affected by the closely related therapy, acupuncture. Different types of acupuncture exist and are employed for different purposes, the most common being that used to induce analgesia, such as that used in surgical settings. Imaging studies looking at acupuncture analgesia have demonstrated

that this treatment provokes a desensitization of brain regions involved in pain modulation, particularly the anterior cingulate cortex (Cho et al., 2003). Additionally, such acupuncture treatment is thought to block pain signals by stimulating endogenous opiate release and has even been reported to decrease the release of pro-inflammatory cytokines (Cho et al., 2006). Therapeutic acupuncture is also thought to enhance neuroplasticity, as indicated by a facilitation of long-term synaptic depression of afferent A $\delta$  neuronal fibers (Carlsson, 2002). This long-term depression has been shown to last for days and even weeks, potentially explaining the therapeutic pain relief that usually occurs following acupuncture treatment.

Much of the available evidence regarding tactile stimulation has involved rodent studies that assessed the long term effects produced by neonatal maternal licking and grooming (Caldji et al., 1998; Francis & Meaney, 1999). In general, such studies have shown that early life tactile stimulation had enduring consequences on offspring that shaped their emotional responses and biological responsivity to stressors during adulthood (Francis & Meaney, 1999). Specifically, offspring exposed to substantial neonatal maternal tactile stimulation (which of course is a very biological significant stimulus with evolutionary implications clearly beyond simple tactile stimulation) exhibited reduced behavioral signs of fearfulness to novelty and decreased corticotrophin releasing hormone receptor density in the locus coeruleus, relative to animals deprived of such early stimulation (Caldji et al., 1998). Although the data are admittedly sparse concerning massage, one recent study did assess the impact of body massage in pre-term human infants, as well as rat pups (Guzzetta et al., 2009). Interestingly, these authors found that massage increased serum levels of the neurotrophic factor, insulin growth

factor-1 (IGF-1). Similarly, massage increased cortical IGF-1 levels and this effect was associated with accelerated maturation of the visual system (Guzzetta et al., 2009). Given that an IGF-1 antagonist blocked the impact of massage it was suggested that early life tactile treatment might act to influence brain development by affected neurotrophic factors.

In the present study, the Swedish massage condition was associated with specific activation of the cingulate gyrus and cuneus regions, both of which have important consequences for emotional processing. Indeed, the cingulate gyrus is part of the limbic lobe and is widely believed to be involved in the integration of emotions and in the motivational relevance of novel stimuli (Paus, 2001). Likewise, the cingulate gyrus is also a part of a distributed network of brain regions responsible for allocating attentional resources to novel objects (Feinstein, Goldin, Stein, Brown & Paulus, 2002). The cingulate cortex also functions in the coordination of sensory input with emotions (Thompson & Robertson, 1987). Indeed, connections between the cingulate and the frontal cortex are believed to play an integral role in self-regulation of arousal (Davidson, Jackson & Kalin, 2000) and may monitor the motivational significance of stimuli (Tucker, Luu & Pribram, 1995). Hence, the hedonic value of the massage may influence activity of this emotional circuit.

The fact that the cuneus was activated in the Swedish massage condition over the course of the entire testing session suggests a particular significance of this region in the effects of the treatment. In this regard, the cuneus has a well documented role in processing episodic memories, particularly those that are considered emotionally significant (Hartmann et al., 2008; Addis, McIntosh, Moscovitch, Crawley & McAndrews, 2004). The fact that the Swedish massage but not the object and reflexology massage treatments preferentially affected this brain region could conceivably have

stemmed from the fact that Swedish massage is far more common than the other two tactile conditions. In effect, prior experience with this type of massage might have influenced activity of this brain region. Indeed, one criterion for inclusion in the study was previous experience receiving massage from a professional therapist, thereby ensuring that all participants had some idea of what to expect concerning standard massage procedures. Hence, it may be that subjects in the Swedish massage group recalled previous memories of massage episodes during the testing session, whereas those in the alternate massage groups may have found the present procedure markedly different from what was expected (given that these techniques are far less commonly employed) and hence, differential neuronal elements were activated.

Besides the Swedish massage, the only other tactile stimulation that affected emotionally relevant brain regions was the reflexology condition which was associated with enhanced activation of the insula, a paralimbic structure involved in the perception and modulation of sensory and autonomic sensations (Craig, 2003), at the start of the testing session. This brain region also plays a role in evaluating the emotional intensity of an experience and the subsequent assessment of the subjective value of this stimulus (Lovero, Simmons, Aron & Paulus, 2009). Essentially, the insula functions to link the higher cognitive and affective processes together with the visceral states associated with emotional experience (Craig, 2003). Receiving information from "homeostatic afferent" sensory pathways via the thalamus, it sends output to a number of other limbic-related structures, such as the amygdala, the ventral striatum and the orbitofrontal cortex (Dupont, Bouilleret, Hasboun, Semah & Baulac, 2003). Interestingly, one recent imaging study reported that the right anterior insula and prefrontal cortex were significantly thicker in individuals who regularly meditated, thus providing evidence for experience-dependent cortical plasticity (Lazar et al.,

2005). Whether massage or other alternative forms of therapy might also engender such a degree of neuroplasticity remains to be determined. These results corroborate with the participants' subjective emotional state as evidenced by their ratings on the Likert-scale. All subjects in the tactile conditions rated their feelings of well-being higher at the end of the experimental session, whereas no such difference occurred in the control group.

*Cognitive aspects of massage: attentional-executive functioning*

As was the case with respect to the somatosensory-motor and emotionally relevant brain regions already discussed, the control group that received no tactile stimulation displayed the most profound and varied activation in cognitively relevant brain regions. Hence, the tactile stimulation appeared to generally “dampen” neural activity, as determined in the fMRI sampling over the scanning session. In particular, the fusiform gyrus, lingual gyrus and precuneus all exhibited a substantial degree of activation (particularly during the early portion of testing), in the control condition, whereas the activation state was not appreciably altered in the three tactile conditions. Essentially, activation of these regions in the control group likely reflect the “background” state of neural activation associated with being in the scanner and performing the Go/No Go cognitive task. Indeed, these subjects are simply lying still in the supine position after pressing the keypad in response to the stimulus presentation. However, it is not immediately clear why *these* particular brain regions would be preferentially active or their importance. One possibility is that these brain regions were involved in the processing of the novel aspects of the experiment. Alternatively, these brain regions may have been intimately involved in the performance of the cognitive task and still remained activated at the time of sampling (i.e. 24 sec after each of the four Go/No Go trials). This may certainly be the case, given that the precuneus has been shown to be involved in

error monitoring of cognitive tasks, such as the Go/No Go task (Menon, Adleman, White, Glover & Reiss, 2001).

As mentioned above, the precuneus was activated throughout the experimental session in the control condition but had appreciably less activation in the three tactile groups (with the exception of the second half of the testing session in the object massage treatment). The precuneus is part of the posterior parietal cortex which receives input from the primary somatosensory cortex and projects to motor areas of the frontal lobe (Reed, Klatzky & Halgren, 2005; Culham & Kanwisher, 2001). This brain area and interconnected cortical regions (posterior cingulate and medial prefrontal cortices) are believed to normally play a role in self-referential processing or essentially, the representation of the self in relation to the external environment (Gusnard & Raichle, 2001; Cavanna & Trimble, 2006). Indeed, this brain region is posited to be a part of the default-mode network which contributes to our 'self-conscious' state. Briefly, as already alluded to, the default mode network is an organized group of cortical brain regions that are believed to be continuously active under resting conditions and may give rise to one's concept of self and maintain a normal state of consciousness (Buckner, Andrews-Hanna & Schacter, 2008). Thus, activation of this region early in the course of the experimental session may reflect one's overt awareness or self-consciousness of being in a novel experimental situation or alternatively, of being focused on the fact that one is being evaluated on a specific task. Similarly, the novelty of the object as a massage tool may have led to the greater degree of activation in this group during the second half of the testing session. Alternatively, Ouchi et al. (2006) have shown precuneus and fusiform activation in response to a back massage treatment. These authors concluded that such a therapeutic treatment may operate on parieto-occipital regions and stimulate the sympathetic nervous system.

The other regions that were particularly activated during the early phase of testing in the control condition have also been linked to attentional processing, as well as motor functioning. For instance, the lingual gyrus (also known as the ventral pre-striate cortex in the occipital lobe) has been shown to be activated during the passive recognition of objects (Malach et al., 1995; Kanwisher, Woods, Iacoboni & Mazziotta, 1997). Specifically, Toni et al. (1998) have posited that the lingual gyrus, due to its convenient location between the primary visual and higher-order cortical areas, might be involved in visuo-motor conditioned learning tasks. In the case of the fusiform gyrus, several studies have implicated this region in responding to novel situations (Tulving et al., 1996) and in the performance of lexical based decision tasks (Price et al., 1994). Similarly, Kopelman et al. (1998) found that increased blood flow in the fusiform gyrus was associated with learning trials, whereby subjects recalling 15 different words on a list required a greater degree of lexical processing than those processing single words; reinforcing the role of this region in attentional processes related to learning new tasks.

#### *Between treatment group differences that emerged over time*

So far we have discussed the brain-region specific changes in fMRI signal within each treatment group that occurred in the early or late phase of the experimental testing session. Thus, revealing the neural regions that were preferentially activated rapidly or over time following commencement of either of the three types of massage or nothing condition. In general, to reiterate, we essentially found that multiple brain regions important for somatosensory/motor, cognitive and emotional processing were activated simply in response to the experimental setting, but that the degree of activation subsided over time. Moreover, the tactile stimulation, particularly the Swedish massage, appeared

to be associated with dampened overall neural activation, given that this group generally displayed far less activation than the control condition over time. In the current section, we will specifically discuss the contrasts between Swedish massage and other conditions that were conducted to address whether the massage interacted with the nothing condition (i.e. lying still and performing Go/No Go task) to influence the neural regions activated.

Contrary to our hypothesis, the Swedish massage treatment did not significantly differ from the nothing control or reflexology groups when compared over time. The lack of significance between the nothing and massage groups is puzzling and unclear at present. However, the massage group could have still have had some effects that went undetected owing to its potential to inhibit some brain regions due to the relaxation effects induced. However, the analysis revealed significant difference in brain activity when comparing the Swedish massage to the object condition during the last four rest periods.

The one statistical between groups contrast that did reach significance was that comparing the Swedish massage to the object condition with regard to activation of the cingulate gyrus and caudate. The cingulate gyrus is a known center in the integration of emotions and draws upon the motivational relevance of novel stimuli. Particularly, the anterior cingulate has been shown to be engaged in affective processing by modulating internal and emotional responses (Thompson & Robertson, 1987). As such, it has been deemed an important neural substrate for the integration of affective and sensory aspects of touch (Paus, 2001). Since we have isolated the rest periods in this analysis, it is posited that the greater neural activation in the anterior cingulate stems from the rewarding properties of the sensory stimulation rather than the cognitive task. In addition, we also

detected significant neural activity in the caudate nucleus, a structure within the basal ganglia. As mentioned previously, the basal ganglia is important for planning and inhibition of movement (Awh & Vogel, 2008; Halliday, 2007). In this study, the movement inhibition might occur when subjects refrain from pressing the key pad during the rest periods and pay more attention to the stimulation of the foot. Yet, it is once again, it is unclear as to why the object massage appeared to differ so markedly from the Swedish massage condition. At this point, we can only speculate that some intrinsic differences in the subjects' perception of the treatments or other yet to be identified aspects of the experimental procedure influenced the fMRI outcomes.

### Conclusions, Caveats & Future directions

The current results demonstrate time-dependent changes in neural activity as a function of different types of tactile stimulation. The generally greater neural activation that is observed across all groups in the beginning of the experiment may possibly be due to the reaction to the initial novelty of the testing environment. Although our inclusion criteria required participants who have had previously received massages by professional massage therapists, not everyone might have been exposed to foot reflexology or a massage with an object (which are far less common than Swedish massage). Indeed, it is interesting to note that participants in the Swedish massage condition showed greater positive affect (as determined through the PANAS scale) than any other condition. We would have expected all conditions to score the same on this measure, meaning no differences in baseline positive or negative affect upon starting the experiment. Although this could be attributable to chance alone, we must also take into consideration that we may have inadvertently pre-selected a non-anxious population. In fact, individuals who regularly solicit massage therapy treatments might be supposed to be less anxious than the general population. Future assessments of behavioural states such as anxiety and mood would probably be insightful in developing a better representation of our sample's state prior to the experiment. Because of the difference observed in the Swedish massage group on the positive affect dimension, we used this as a covariate in our analysis, minimizing the within group variance and increasing the power of our design.

Moreover, the duration of the experiment might not have been sufficient to detect long-term effects of the tactile stimulation conditions. However, due to the loud nature of the MRI machine and the enclosed space in which subjects were placed, longer testing

sessions might have caused undue anxiety and distress in these participants, thereby overshadowing any relaxation effects in response to the tactile stimulation conditions. Future studies will need to have a long-term massage component in order to clearly elucidate the mechanisms of this therapy.

The cognitive association task may have also influenced to some extent the neural activity observed across all the conditions. While the task was administered as a means of creating a reliable neural activity baseline across subjects, the task might have led to carryover effects during the rest periods. Consequently, our analyses might have been unduly affected by processes specific to the cognitive task and not the tactile stimulation. Indeed, the reflexology condition had slower cognitive response rates to the Go/No Go task than the control and Swedish massage groups during the first half of the experiment. This raises the possibility that attentional mechanisms in the reflexology group were more exhausted, as their processing was split between the cognitive task and sensory stimulation to a greater degree than in any other group.

Our core hypothesis centered on the possibility that the emotional response and associated neural circuitry would be particularly affected by the Swedish massage treatment. However, once again, the limited time of the treatment (8.5 minutes) might not have allowed sufficient time for the expression of these emotional aspects. Indeed, limbic structures (e.g. amygdala) and the prefrontal cortex, which regulate alertness and arousal functions and are also known to be crucial in fear processing and learning (Gallagher & Chiba, 1996) were not appreciably affected by massage in the current study. We might not have tapped into these networks with our current design, as the increased arousal

level potentially associated with the experimental conditions may have masked the beneficial effects stemming from the tactile stimulation.

One particularly interesting finding was that the activation of the cingulate gyrus appeared to be appreciably greater over time in the control group relative to the other tactile conditions. This has been implicated in the processing of both physical, as well as psychologically painful stimuli (e.g. social exclusion (Eisenberger, Lieberman & Williams, 2003)) and may play an important role in affective disorders. In fact, significantly smaller cingulate cortex volumes have been reported in patients suffering from major depression, compared to healthy controls (Paus, 2001) Given that complementary and alternative treatments such as meditation have been shown to increase the plasticity of other cortical areas important for emotional processing, such as the paralimbic insula (Holzel et al., 2008; Farb, Segal, Mayberg, et al., 2007), it stands to reason that such novel “therapeutic” strategies may have beneficial consequences for clinical conditions with perturbed neuroplasticity. Finally, massage at neonatal or times early in life might have particularly potent effects upon the maturation of limbic and other emotional circuits by affecting neurotrophic or other neural factors, just as has been reported for the visual system (Guzzetta et al., 2009).

Importantly, this is the first neuroimaging study that assessed the neural activity in response to different types of massage in healthy subjects. We have been successful in showing that MRI is an appropriate tool to provide empirical evidence for the effects of massage therapy on brain functioning. As such, future studies will further investigate these effects in clinical populations suffering from mood disorders.

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