THE ROLE OF GENTLE TOUCH IN PERINATAL OSTEOPATHIC MANUAL THERAPY

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Abstract

Osteopathic medicine is a system of manual diagnosis and treatment. While there is growing evidence that osteopathy is effective in a range of clinical conditions, the underlying biological basis of its therapeutic effects remain largely unknown. Given that the sense of touch plays a critical role in osteopathy, in this perspective article, with a particular focus on perinatal care, we explore the potential mechanisms by which stimulation of the skin senses can exert beneficial physiological and psychological effects, aiding growth and development. We propose that a class of low threshold mechanosensitive c-fibre, named c-tactile afferents, which respond optimally to gentle, slow moving touch are likely to play a direct and significant role in the efficacy of manual therapies. A greater understanding of the impact the type and quality of touch plays in therapeutic tactile interventions and in particular the neuroscience underpinning these effects will aid the development of more targeted, population specific interventions.

Keywords (max 6): Touch; Osteopathy; C-Tactile Afferents; Health; Paediatrics; Development

Highlights (3-5 bullet points):

- The sense of touch plays a fundamental role in nurture and attachment during development
- The response properties of C-tactile afferents suggest they might play a critical and significant role in perinatal care
- The efficacy of osteopathic manipulative treatment may be underpinned by activation of C-tactile afferents

1. Introduction

Healthcare services are coming under increasing pressure to demonstrate that all therapeutic procedures and interventions are predicated on evidence-based practice (EBP), with for example the British Medical Association (BMA) stating that some Complementary and Alternative (CAM) treatments should no longer be funded or commissioned by the National Health Service (NHS) in the UK. This may well be the tip of an iceberg when it comes to evaluating less contentious, but non-mainstream, therapies in healthcare and one that, according to Kasiri-Martino & Bright (2016), is 'creating a climate of criticality' amongst many healthcare professionals.

Osteopathic medicine (or osteopathy), which is still regarded by some as CAM, is a system of manual diagnosis and treatment for a range of musculoskeletal and non-musculoskeletal clinical conditions. Osteopaths utilise a wide range of therapeutic techniques to promote adaptation and support homeostasis that has been altered by impaired function of skeletal, arthrodial, and myofascial components of the body framework and their related vascular, lymphatic, and neural elements (WHO, 2010). There is growing evidence that osteopathic manipulative treatment (OMT) is effective in the management of musculoskeletal conditions such as low back pain (e.g., Licciardone et al., 2013a), chronic migraine (Cerritelli et al., 2015a) and in specific clinical populations such as paediatrics (Cerritelli et al., 2015b). Notwithstanding the therapeutic effects of OMT, its underpinning biological mechanisms are largely unknown. It is therefore understandable why a number of science and mainstream medical writers have recently questioned the plausibility and clinical effectiveness of osteopathic care, particularly in the field of paediatrics.

As part of an initiative to address the growing pressure for osteopathy to demonstrate adherence to EBP (Thomson et al., 2011), Kasiri-Martino & Bright (2016) have found that within the profession (albeit from a qualitative study with a small sample size of n= 9) there is a clear polarization regarding adherence to Osteopathic Principles (OP) (Ward, 1997), which have themselves undergone many metamorphoses since being first laid down by the founder, A.T.Still (Stark, 2013). One cohort in this study believed that the 'philosophy' of OP was fundamental in driving patient care and that it was even superior to the science, with another cohort believing that relying on a limited evidence-base was restricting progress in the osteopathic profession and that an EBP approach was required in order to maintain credibility within the healthcare profession. It was further found that a reliance on anecdote was unacceptable for a system of osteopathic principles that should guide best professional practice. Lewis (2012) has recently highlighted the current ambiguity in OP, suggesting that on the one hand A.T.Still expected a rigorous scientific approach from students, while on the other promoting intuition and clairvoyance as key guiding factors. According to Fryer (2008) and Thomson et al. (2014a,b), a better understanding of the translation of OPs to osteopathic practice by applying evidence-based medicine principles would encourage best practice in osteopathy.

It is axiomatic that the sense of touch plays a central role in osteopathic diagnosis, treatment, and in the development of therapeutic relationships with patients. However, little is known regarding the impact that touch is having on the patient's nervous system during osteopathic procedures for example on pain modulation, autonomic nervous system (ANS) function and emotional processing. The sense of touch plays a fundamental role in nurture and attachment during development (Walker & McGlone 2013 for review), and in many social and dyadic interactions in adulthood, with well documented positive impacts on health and well-being (House at al., 1988; Berscheid, 2003).

In this perspective paper we aim to explore and explain, in the light of recent advances in our knowledge of the sensory innervation of the skin, the effects of touch in a broader sense, where 'touch' will be viewed as a sub-modality of the "somatosensory system", a term which covers the wide array of specialized receptors, peripheral nerves, and central processing stages underlying the transduction and processing of somatosensory signals. Collectively, these sub modalities are engaged in sensing, perceiving, and acting upon stimulation of the body surface, or during muscle activity. Cutaneous sensations are essentially multimodal and include the senses of touch, temperature, itch and pain. Here we explore how, and why, stimulation of the skin senses, particularly during perinatal therapeutic procedures common to the field of osteopathy, has quantifiable beneficial effects on both the physiology and psychology of the infant. We hypothesize the clinical impact of OMT is in large part due to a recently identified and characterized system of gentle-touch responsive nerves, found only in the hairy skin of the body.

2. The Importance of Touch to Development

Touch is a critical communication channel during nurturing behaviour, a topic first addressed in the classical work of Harlow (1958) and Harlow & Harlow (1962a) who found that the absence of comforting touch led to long lasting psychological stress in monkeys. The neonatal period is a time of significant neurodevelopment, and hence a period when the degree and type of social interaction is likely to have a disproportionate influence on the development and expression of social behaviour in adulthood (Meredith, 2015; Porges & Furman 2011). The stress-reducing effects of touch have been confirmed in rodent studies where licking and grooming of rat pups by their mothers was found to permanently change how the rat, as an adult, responded to stressful events (Champagne and Meaney, 2007; Menard et al 2004). This demonstration that levels of affiliative and nurturing touch, between the mother and offspring, can affect behaviours in adult life is further supported by Hellstrom et al. (2012) who found that the adult offspring of mothers that displayed high levels of pup licking-grooming, as the result of epigenetic programming, showed increased levels of glucocorticoid receptor expression and lower physiological responses to stress. This type of licking-grooming behaviour targets specific body sites on the pup, in particular, around the dorsal back and head/ears. These studies show clearly that tactile nurturing interactions during the neonatal period impact the subsequent expression of adult behaviour by altering sensitivity to neuropeptides (e.g., oxytocin and arginine vasopressin), thereby influencing the expression of behaviours such as affiliation, aggression, socio-sexual behaviour, parental behaviour, and responses to stress (Cushing and Kramer, 2005). Close physical proximity between newborn infants and caregivers results in improved growth and development as measured by a wide range of physiological, behavioral and neuropsychological indices (Harlow & Harlow, 1962b; Spitz, 1945; Kuhn & Schanberg 1998). Conversely, by assaying a growth enzyme biomarker that is a sensitive index of tissue growth, Schanberg & Field (1987) found that low weight gain correlated with a lack of maternal touch, independent of whether the mother was lactating. This biomarker was reduced in pups that failed to thrive, but at normal levels in those that were in physical contact with their mother. Interestingly, the authors found that levels of the biomarker dropped within just a few hours of separation, returning to normal when the pups and dams were reunited. Several authors (Kuhn et al., 1990; Suchecki et al.,1993; van Oers et al., 1998) have shown that even in the absence of maternal licking and grooming input, these effects are mimicked by stroking with a soft brush – highlighting the critical importance of tactile stimulation (see also Walker & McGlone, 2013 for a review). Further evidence for how early life experiences can impact on brain development can be found in a study from Baldini et al (2013) who demonstrated that insulin like growth factor-1 (IGF-1) is a key mediator of the efficacy of massage type stroking in counteracting the negative effects of maternal separation. Their findings suggest that the mechanism of action is probably the same as that found with licking and grooming i.e., it leads to a significant increase in glucocorticoid receptor expression in the hippocampus. These effects occurred in various body organs where tissue differentiation was taking place, including the brain, suggesting that maternal contact contributes to brain growth as well as weight gain.

Looking at human mother-infant behavior, Stack & Muir (1990) found that touch occurred ~ 65% of the time during face-to-face interactions which, claim the authors, acts to reduce stress and increase positive affect (see also Hertenstein et al, 2006). Interestingly, the specific quality of touch mattered, with stroking, gentle touch rather than passive touch leading to facial signs of reward i.e., the infants smiling (Jean et al., 2009; Stack and Muir, 1990, 1992). In human infants, as in rodents, parental touch is a key regulator of physiological and behavioral arousal (Hofer 1994). For example, touch has been shown to decrease stress activated cortisol production with lower levels of cortisol correlating with increased cell development in the hippocampus, impacting on both short and long-term memory function (Miles et al., 2006). In order to test if postnatal maternal behaviours could modify the negative consequences of prenatal stress in human infants, Sharp et al (2012) examined whether maternal stroking during the first weeks postpartum altered associations between prenatal depression and physiological and behavioral outcomes in infancy. The authors found that high self-reported levels of maternal stroking reduced the negative impact of maternal depression on both physiological and behavioral indices of emotional reactivity in the infant. Furthermore, high levels of maternal stroking were associated with reduced methylation at the glucocorticoid receptor gene (Murgatroyd et al 2014). Taken together these studies provide the first evidence in humans that gentle stroking touch has similar beneficial neurodevelopmental effects to those reported from licking and grooming in rodents, providing a modern epigenetic interpretation of the nurture/nature debate. Clearly, touch matters to growth (Field et al, 1986; Field et al, 2008).

3. Touch in Perinatal Care

Recognition of the benefits gentle touch has on infants can be traced back to the introduction of massage in China in 2nd century BC. Over the past 50 years there has been a growing interest in, and application of, various forms of touch based therapies in the Western world, supported by a large body of research demonstrating the benefits of touch and massage therapy during the peri- and post- natal periods (Guzzetta et al, 2009; Procianoy et al, 2010; Harrison et al, 2000; Im et al, 2009). However, although the putative clinical links between touch and perinatal care have been explored in the last few decades, robust data remain elusive and findings contradictory.

Kangaroo Care (KC), a technique used on preterm infants where the infant is held in skin-to-skin contact with a parent, reliably reduces mortality and morbidity in stabilized low birth weight infants and is therefore recommended as an alternative to conventional neonatal care in resource-limited settings (Conde-Agudelo et al, 2014; Conde-Agudelo & Díaz-Rossello (2016). Furthermore, Moore et al (2012) reported that immediate skin-to-skin contact after birth benefits the health of mothers and newborns by increasing breastfeeding rates, stabilizing the newborn's temperature, and encouraging bonding. Indeed, in a well-designed prospective longitudinal study, Feldman et al (2014) found that a KC intervention for 14 consecutive days compared to standard incubator care produced positive long-term physiological and cognitive changes from 6 months to 10 years. The authors argue that touch-based interventions in the neonatal period have a positive impact on physiological organization and behavioral control across long developmental epochs in humans and have important implications for the care of preterm infants.

From a manual therapy perspective, infant massage procedures have been demonstrated to be useful in reducing transcutaneous bilirubin levels (Dalili et al, 2014), modifying the global EEG spectral power (Guzzetta et al, 2011), and influencing brain development, specifically, visual development (Guzzetta et al, 2009) suggesting that massage can be mediated by specific endogenous factors such as IGF-1. In support of this assertion, Field et al (2008) report that pre-term infants receiving 15 minutes of massage for 5 consecutive days showed increased weight gain, compared to non-treated controls. Complementary to findings in rodents discussed earlier, weight gain was positively correlated with levels of IGF-1. Additionally, using a combination of tactile and kinesthetic stimulation (body massage and passive movements of the limbs) over a 10-day period, Scafidi et al (1990) reported that compared to a no-treatment control group the treated preterm infants (GA = 31 weeks) averaged a 47% greater weight gain per day and spent significantly more time awake and active during sleep/wake behavior observations. Also, on Brazelton scale measures, such as motor, habituation, and range of state behaviors, treated infants showed marked developmental improvements which resulted in them being discharged 6 days earlier, on average, than their non-treated peers (with a reported cost saving of $3K/infant). It is of interest to note in the context of this perspective paper that the authors comment that “Although these data confirm the positive effects of tactile/kinesthetic stimulation, the underlying mechanisms remain unknown.” Recently, Smith et al (2014) conducted a randomized controlled trial to investigate the cumulative effects of a structured manual method of touch on infant neurodevelopment in hospitalized very preterm infants (26-30 weeks gestation). Although based on a small sample, the results provide evidence of positive weight, physiological, and behavioral state adaptations. Despite these positive findings from basic research and clinical trials, in 2004 a Cochrane Systematic Review concluded that the evidence supporting the use of preterm infant massage for developmental outcomes, such as weight gain, was weak and, given the time consuming nature of the intervention, unlikely to be cost-effective (Vickers et al, 2004).

Concerning osteopathy, several recent clinical trials have demonstrated that twice-a-week osteopathic treatments are effective in the context of preterm infants, significantly reducing the length of hospitalization (LOS) (Cerritelli, 2013, 2015b; Pizzolorusso, 2014). Indeed two recent systematic reviews concluded that, despite the small sample sizes of the reviewed studies, OMT is effective in reducing the LOS of the treated infants, suggesting that osteopathy is a safe approach, which could be included in neonatology routine care (Lanaro et al, 2016; Bagagiolo et al, 2016). Conversely, another systematic review of 17 clinical trials concluded that the effectiveness of OMT for pediatric conditions remains unproven, primarily due to the limited number and low methodological quality of studies conducted (Posadzki et al 2013). Indeed, while a recent study further demonstrated the safety of osteopathic approach in extreme preterm infants; no clinically significant findings were found in relation to spontaneous general movements (Raith et al, 2016).

Thus, despite some positive results, further research is clearly needed to determine the clinical efficacy of OMT and other touch based therapies in perinatal care. For example, there is currently a wide variation in the literature regarding intervention frequency, duration, and type of touch administered. In order to define the potential limitations of such interventions in pre-terms, both healthy and with specific pathologies, hypothesis driven protocols are required which will enable a deeper understanding of the neurobiological mechanisms underlying their observed efficacy (Lanaro et al 2016).

4. Hypothesized mechanisms underlying the efficacy of OMT / Touch therapies

Speculating on the possible mechanisms of action of OMT there is evidence that it modulates autonomic nervous system (ANS) functions (Henley, 2008; Giles, 2013; Ruffini et al., 2015) and has also been shown to reduce pro-inflammatory cytokines. OMT has been associated with a reduction of pro-inflammatory substances both *in vitro* (Meltzer, 2007) and *in vivo* (Licciardone, 2012; 2013b), indicating an anti-inflammatory role, partially confirmed by recent clinical-based research (Degenhardt, 2014). We would argue that OMT can putatively reduce the release of cytokines and sympathetic activity, creating a cascade of physiological and neurobiological events that modulate the inflammatory and ANS mechanisms. Preliminary laboratory-based evidence showed the effect of specific osteopathic techniques on the enhancement of the lymphatic and immune system (Schander, 2013; 2012), where it improves leukocyte counts and interleukin-8 (IL-8) levels. These findings were confirmed by more recent human research which demonstrated significant differences in the levels of immune molecules, including IL-8, between OMT and sham light-touch control (Walkowski, 2014), and from more basic animal research where massage-like stroking of mice with a hand (but not a brush) was shown to boost the immune system (Major et al., 2015). It is therefore plausible to speculate that OMT may also have an effect on the immunological profile of specific circulating cytokines and leukocytes.

Although focusing on OMT in this report, of relevance here is a study by Rapaport et al (2012) which compared the effects of repeated (twice/week – same dosage as the one used in osteopathic clinical trials with preterm infants) Swedish massage, and what the authors considered as a control condition – light touch – on a number of biomarkers: oxytocin (OT), arginine-vasopressin (AVP), adrenal corticotrophin hormone (ACTH), cortisol (CORT), circulating phenotypic lymphocyte markers, and mitogen-stimulated cytokine function. They report sustained cumulative effects caused both by the massage and the 'control' light touch conditions. The twice-a-week massage group demonstrated potentiated changes in OT, AVP, ACTH, and cortisol compared to the twice-a week touch group: changes that were sustained over a 3–4-day period between treatments. Interestingly, and surprisingly for the authors of this study, the light touch condition which involved "gentle, systematic, and comprehensive stroking of an individual for 45 minutes" also induced quantifiable positive effects on neuroendocrine and immune parameters (Rapaport et al., 2012; see also Diego et al 2004). The fact twice weekly touch had a greater moderating effect on stress hormone levels than once per week sessions highlights the importance when comparing the results of such studies of considering the effects that "dosage" may have.

It has been shown repeatedly that low intensity stimulation of cutaneous somatosensory nerves, particularly through stroking touch, warmth and light pressure, induces the release of endogenous peptides such as OT and opioids which promote relaxation and well-being (Uvnas-Moberg, 1998; Panksepp, 1998). For example, in rodents, gentle massage, stroking and handling have been shown to trigger central OT release and is associated with increased social motivation as well as reduced physiological and behavioral reactivity to stressors (Uvnas-Moberg et al 1996; Lund et al 1999; Okabe et al 2015;). Similarly in humans, skin to skin contact between mother and infant induces OT release, reduces physiological arousal and increases social interaction (Uvnas-Moberg et al 2015). In non-human primates social grooming has been linked with endorphin release, with administration of opioid antagonist naloxone significantly increasing grooming solicitation (Keverne et al 1989). Clinically, Bender et al (2007) reported that a spinal manipulation procedure, compared with fictitious manipulation, produced a significant increase in plasma levels of beta-endorphin. The release was rapid occurring from as early as the 5th minute of manipulation.

As stated earlier, OMT as with other manual therapies by definition requires the practitioner to touch the body and here we ask "what it is about touch that correlates with so many observations down the centuries of its therapeutic value"?

Most people understand the sense of touch as a discriminative sense, enabling us to detect for example a fly landing on our face, or the texture of a surface being manipulated. This primacy of touch has been reflected in the focus of research with most investigations of skin mechanoreceptors being conducted in either the glabrous skin of the hands or to a lesser extent the perioral regions of the face, possibly reflecting the importance of hand-to-mouth actions in feeding and the initial exploratory behaviors in infants. This property of touch relies on a 'fast' conducting system of myelinated nerves, as is required for activities such as manipulation of tools or detecting body contact, and is linked to motor control systems that need to function with millisecond neural processing precision based on the afferent sensory information received from the 'fast' mechanoreceptors. However, there is a relatively recently discovered (in humans) 'slow' touch system that is dependent on a class of unmyelinated low threshold mechanosensitive c-fibres called c-tactile (CT) afferents, which cannot provide any useful discriminative information due to the slow conduction velocity of c-fibres. (Fig 1 depicts the two types of touch and how a 'grip-like' touch and a gentle stroking touch selectively activate the 1st or 2nd touch systems respectively). CTs have only been found in the hairy skin of the body i.e. all skin other than the glabrous skin of the palms and soles, and are hypothesized to code for pleasant and affiliative properties of touch (Nordin, 1990; Vallbo et al, 1993; Vallbo et al, 1999; McGlone et al, 2012; McGlone et al, 2014). Here we propose that a neurobiological mechanism driving the therapeutic effects of touch-based therapeutic procedures such as OMT relies to a greater or lesser extent upon CTs.

[Insert Figure 1 about here]

5. A Putative Role for CTs in OMT

The presence of unmyelinated 'slow' mechanosensitive nerves in the skin – as opposed to the myelinated 'fast' mechanosensitive nerves that are generally seen as sub serving the sense of touch – was first discovered in the cat by Zotterman in the 1930s (Zotterman, 1939). These c-tactile afferents (CTs) have subsequently been found in all mammals so far studied, but had not, until very recently, joined the 'somatosensory lexicon' which has traditionally recognised only 4 sub-modalities of cutaneous sensitivity; touch, temperature, pain and itch. Of these, touch has been seen as solely dependent on large fast conducting myelinated A-beta nerves, whereas the thinly myelinated A-delta and unmyelinated c-fibres were seen as coding for nociception, pruriception and thermoception. The discovery of CTs that respond optimally to low velocity stroking movements such as gentle brushing has added a fifth sub modality to somatosensation that is now growing in acceptance (Vallbo et al, 1999; McGlone et al, 2014). Their response is also temperature sensitive, discharging preferentially to a skin temperature stimulus over warmer or cooler stimuli (Ackerley et al 2014). Specific to the CT system, the slow velocity and low force stimuli that maximally activate the primary afferent nerve when recorded during microneurography studies are just those velocities and forces that are reported as most pleasant during psychophysical studies of affective touch (Essick et al, 1999; Essick et al, 2008; Loken et al, 2009), and cause reduced autonomic arousal (Fairhurst et al 2014). Fig 2 shows the relationship between the firing frequency of CTs in response to stroking touch at different velocities and the subjective response to liking – note the similar inverted-U response functions.

[Insert Figure 2 about here]

Interestingly, touch-based therapies such as used in osteopathy, which is by most of us considered to be a rather pleasant intervention, utilises in the broadest sense many of these CT-appropriate stimuli. Of relevance to the clinical efficacy of OMT, the potency of CT-touch may well correlate with the body site being touched as well as the type of touch (dynamic, static, high/low force). Based on a rodent genetic visualisation study, CLTMS (the rodent CT) are densely distributed on the dorsal thoracic surface, the head and ears, and more sparsely in the distal limbs and, as also indicated by human psychophysical and neuroimaging studies, are absent from glabrous skin sites (Liu et al 2007; Li et al., 2011). Gentle stroking is associated with a sensation of pleasure, and is also seen in more complex social behaviors such as courtship, grooming and maternal care, but the neurobiological mechanism regulating the response *in vivo* has only recently been investigated. Using mice, Vrontou et al (2013) found that gentle stroking activated a population of MRGPRB4+ neurons that only innervated hairy skin and that activating these neurons using a genetically encoded drug-sensitive receptor acted as a positive reinforcer in a conditioned place-preference test. A recent psychophysical study, in which participants watched video clips of a person being touched (with CT or non-CT touch), rating how pleasant they thought the touch was for the person receiving it, found higher ratings of liking when observing CT-preferred velocity touch compared to static or faster speeds (Walker & McGlone 2014). Furthermore, in agreement with the rodent findings, liking was topographically dependent, with higher ratings for touch on proximal body sites (back and shoulder) than touch to more distal sites (forearm & palm). In line with the somatosensory homunculus (Penfield and Bowldrey, 1937 Fig 3A), which anatomically represents the innervation density of fast conducting low threshold mechanoreceptors, and in accordance with the projection of CTs to dorsal posterior insular cortex, a paralimbic part of the emotional brain, we have proposed an 'affective' homunculus in insular cortex that maps the hedonic properties of gentle touch, based on the inferred increase in innervation density of CTs in more proximal body sites (Fig 3B).

A key property of c-fibres as a class of somatosensory afferents is their influence on affect and emotion, as is well recognised for the c-fibres more commonly described that code for pain and itch. Thus, CTs are posited to signal information of an affective nature to the CNS, providing the neurobiological substrate for the positive hedonic aspects of gentle touch (Olausson et al, 2008; McGlone eta al, 2014). Neuroimaging studies in neuronopathy patients who have lost all 'fast' 1st touch nerves, and healthy controls, have shown that gentle stroking touch applied to hairy skin (where CTs are abundant), but not palmar skin (where CTs have not been found), reliably produces activation in posterior insular (interoceptive cortex) and orbitofrontal cortex (reward) as opposed to primary somatosensory cortex (McGlone et al 2012; Olausson et al 2002). Here, in common with other c-fibre mediated thermal, painful and pruritic inputs, they are thought to contribute to the central representation of the physical condition of the body (Craig, 2002; Craig, 2015; Bjornsdotter et al 2010). The rewarding benefit of gentle touch is seen as not just driving the affective state, but also a more body-centred psychophysiological benefit. In fact, in a recent paper D'alessandro et al (2016) hypothesised that the "interoceptive paradigm", a theoretical framework to explain how patient's clinical history and associated signs and symptoms can be mutually related in clinical practice, is mediated by CT afferents which can intercede with sensitisation states, at all levels, via interoceptive pathways

[Insert Figure 3 about here]

6. Future Research

Premature infants are exposed to an alien and potentially dangerous non-biological environment compared with the safety and protection provided by the uterus - and at a critical time in neurodevelopment when the brain is undergoing unprecedented exponential growth (see Silbereis et al 2016 for recent review). Although much is now done in neonatal intensive care units (NICU) to provide more natural environmental conditions for the preterm infant that are known to impact positively on brain maturation and neurobehavioral outcomes, there is still a lack of full appreciation and understanding of how important the continuing physical stimulation of the skin is to the infants' prognosis in terms of neurobehavioral outcomes in the short and long term (Meaney, 2001; Smith, 2012). Apart from the intentional therapeutic handling of preterm infants in the NICU, such as when being treated with OMT, the majority of the touch received is procedural, indeed very preterm infants (GA<30) often receive very little tactile stimulation of any type (Smith, 2012). Suomi (2011), in a study in which infant rhesus monkeys were separated from the mother with a transparent screen (a similar situation as with an infant incubator) thereby allowing them to see, hear and smell their mother but not touch her, reported a chronic activation of the HPA axis. It was only through the introduction of peer touch relationships that the infants were later able to develop normally. Another example of the costs of separating an infant from their mother was reported by Bystrova et al, (2009), who noted that separation of mother and baby after birth still persisted in many parts of the world. They carried out a study with 176 mother-infant pairs, randomized into four experimental groups: i) infants were placed skin-to-skin with their mothers after birth, ii) infants were dressed and placed in their mothers' arms after birth, iii) infants were kept in the nursery both after birth and while their mothers were in the maternity ward, and iv) infants were kept in the nursery after birth. Only the group that experienced skin-to-skin contact for 25 to 120 minutes after birth showed a positive influence on mother-infant interaction 1 year later, compared with the separation groups. The evidence is now overwhelming that touch is playing an important role in pre and post-term development, but for preterms, although the incubator keeps them alive, what is not fully recognized is the cost on brain development of the lack of 'appropriate' tactile stimulation (and we must not forget the olfactory, auditory, vestibular and gustatory stimuli the infant receives in the womb).

The incubator has not changed much since its invention in the 1870s by the physician Stéphane Tarnier who found that by keeping premature infants isolated under high levels of hygiene, appropriate feeding schedules, and a warm humid atmosphere mortality rates for infants weighing less than 2Kg were reduced from 98 percent to 23 percent. Focusing here on touch, and specifically CT directed touch, there is a need for NICU's globally to not only focus on keeping the physical body alive but to recognize that the mental status of the infant is equally important. In a study on preterm infants (<26 weeks) Johnson et al (2010) reported an increased risk for Autism Spectrum Disorders (ASD) in mid-childhood which may have been the result of abnormal brain development in this population. More recently Kuzniewicz et al (2014) found that ASD was approximately 3 times more prevalent in preterm infants <27 weeks, compared with term infants, commenting that each week of shorter normal gestation was associated with an increased risk of ASD. The putative link with CTs needs to be subjected to rigorous random controlled trials carried out in NICU's.

7. Conclusion

There is a long history in CAM that recognizes the therapeutic effects of touch, where it has been acknowledged as beneficial in many manipulative therapy interventions (Terry et al, 2012; Lanaro et al, 2016; Franke et al, 2015). As we have shown, the sense of touch plays a fundamental role in nurture and attachment during development and in many social and dyadic interactions in adulthood, with well documented positive impacts on health and well-being (House at al., 1988; Berscheid, 2003). Spitz's observations of the importance of nurturing touch in infancy (1945, 1946) noted that "at the beginning of our century one of the great foundling homes in Germany had a mortality rate of 71.5% in infants in the first year of life" (Spitz 1945 p.1). The children had 'all' their basic needs met, they were clean, well fed and warm, but what they lacked was physical touch, cuddling and stroking. Spitz concluded that it was the absence of nurturing touch that inhibited their ability to survive, impeding their physical and emotional development. Based upon reviewed evidence from a range of research studies and approaches, we would argue that OMT can putatively reduce the release of cytokines and sympathetic activity, creating a cascade of biological and neurological events that modulate the inflammatory and ANS mechanisms. Extrapolating from what we now know about the functional properties of CTs, we posit that the proven benefits of the kinds of gentle handling typically applied to pre-term infants during OMT will, in some part, be due to the selective stimulation of these cutaneous afferents and they are therefore likely to play a critical and significant role in perinatal care.

A robust understanding of the impact, the type and quality of touch has in clinical care will create opportunities for research and provision. It can be argued that the effectiveness of specific touch modalities are diverse and dependent on the age of the target population (very-, moderate- and late-preterm infants) or clinical condition. From a research perspective, we argue that investigating the role of different types of touch will shed light on the physiological effects of care on pre-term infants' brain function and development, nerve conduction velocity, biomarker variation and pain modulation. The results from this research could open avenues for multimodal care of pre-term infants, considering slow-stroking CT-based touch as part of usual medical care. The current underdeveloped knowledge on the underpinning correlates of touch-based osteopathic care can be theoretically fulfilled by emerging evidence in the field of neuroscience. However, robust research is necessary to fully understand the biological and clinical effects of osteopathic care in the field of neonatology.

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Figure Legends

Figure 1. There are two types of mechanosensory – touch – nerves innervating the skin of the body that transmit tactile stimuli to the brain at markedly different speeds. The fast response myelinated nerves process information in the somatosensory cortex within tens of milliseconds, enabling decisions to be made about where the body was touched and e.g. the use of tools. The slow response nerves however cannot provide such discriminative information as unmyelinated nerves take thousands of milliseconds to transmit a mechanical stimulus to the brain. These nerves respond optimally to slow gentle caressing types of touch and project to brain regions – the insular cortex – that process the affective properties of touch.

Figure 2. Brush Stimulation and Nerve Recordings (A and C). Dots show average discharge rates during brush stroking for two types of mechano-afferents across a range of stimulus velocities (A. CT, n = 16: C. Slowly Adapting type I (SAI), n = 8). Note the scaling on the y axis differs for CT & myelinated afferents. B. Average ratings of perceived pleasantness in response to soft brush stroking. Data are from ten subjects. Error bars indicate SEM. Open circles = 0.2N Force, Closed circles = 0.4N Force. Figure is adapted from Löken et al (2009).

Figure 3. A. the classic Penfield somatosensory homunculus showing the disproportionate representation of the body surface in primary somatosensory cortex, reflecting the innervation density of fast conducting low threshold mechanoreceptors to body parts sub serving discriminative touch e.g. the hands and lips. B. The proposed affective homunculus, based on the same interpretation re innervation density, but this time of c-tactile afferents, which project to dorsal posterior insular cortex and are inferred to be more densely represented in more proximal body parts e.g. the upper arms and back.